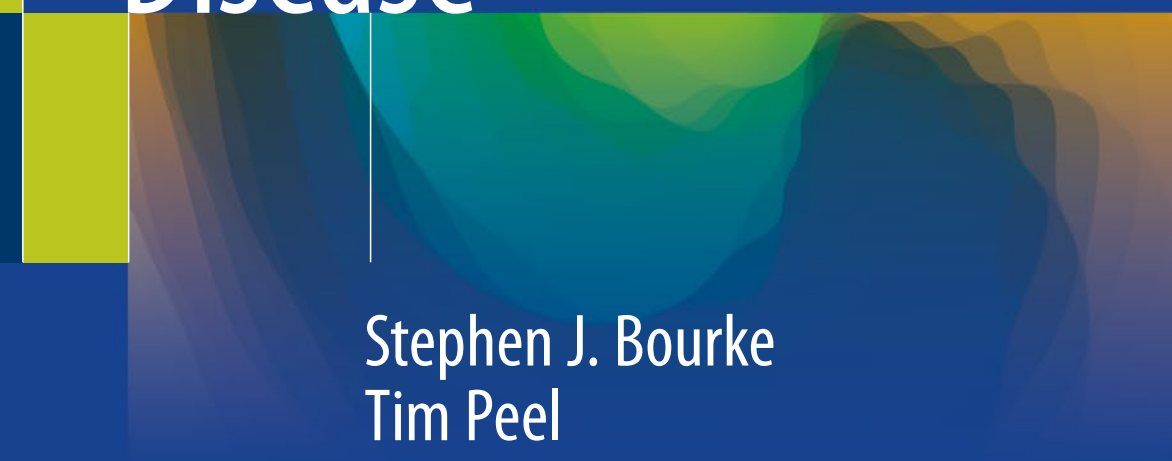
Integrated Palliative Care of Respiratory Disease



Stephen J. Bourke
Tim Peel
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Second Edition

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Editors
Stephen J. Bourke
Department of Respiratory Medicine
Royal Victoria Infirmary
Newcastle Upon Tyne
UK

Tim Peel
Policy, Ethics and Life Sciences
Newcastle University
Newcastle Upon Tyne
UK

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Preface

One of the major successes of modern medicine has been the integration of the ethos, knowledge and skills of palliative care into the standard care of patients with progressive disease. Substantial improvements have been made in the specialty of Respiratory Medicine in recent years such that many patients are now treated by multidisciplinary teams focused on support, symptom control, restorative care, rehabilitation and psychological interventions throughout the course of the illness, in parallel with disease-modifying therapies. Palliative care of respiratory disease is often complex because of the high level of symptoms experienced by these patients and the variable and sometimes unpredictable trajectories of these diseases. Sudden death is a feature of catastrophic illnesses such as severe pneumonia or acute lung injury. The end-of-life phase may be short and is likely to be in the setting of an intensive care unit (ICU), with very little time for the patient and family to adjust to the circumstances. They need to be supported in coping with a trajectory that moves quickly from good health to death and bereavement. More commonly patients are living their lives with chronic progressive lung diseases such as chronic obstructive pulmonary disease, fibrotic lung disease, neuromuscular disease or cystic fibrosis. They often show considerable resilience and fortitude in coping with the disability and distress of life-limiting conditions. These diseases tend to progress, but often over a period of many years, and are characterized by acute exacerbations. Often treatment will reverse the exacerbation and restore health but an acute exacerbation may be the start of the dying phase of the disease, and it is important to recognize when this is happening. Admission to hospital may be the best way of bringing comfort and control to a patient experiencing severe distress because of an acute exacerbation or a complication such as pneumothorax, infection or hemoptysis. Urgent assessment is required before deciding with the patient and family on the best course of action. A transplant trajectory is a particular feature for some lung diseases such as cystic fibrosis or idiopathic pulmonary fibrosis. The patient is seriously ill, has distressing symptoms and may die but is hoping for a rescue lung transplant which can transform the trajectory of the disease. It is clear that a traditional model of palliative care, based on a cancer trajectory which sometimes artificially divides care into a disease-modifying phase and a palliative phase, is usually not appropriate for patients with chronic progressive lung disease. As more treatments and interventions become possible, a key issue is less about ‘what can we do?’, but more about ‘what should we do?’ This is a concept of ‘Realistic Medicine’

which embodies a personalized approach to healthcare that encourages clinicians to find out what matters most to patients so that their care fits their needs and situation. It is important that the general public does not develop erroneous concepts of death in hospital being an undignified struggle with high-technology interventions being applied inappropriately. Advance Care Planning and Treatment Escalation Plans, developed in partnership between patients and clinicians, can restore control to the patient in the face of progressive disease and define their 'priorities for care'. Death is a natural end to life rather than necessarily a failure of medicine, and improving the quality of end-of-life care is a key priority in healthcare planning. Care must be organized in such a way that disease-modifying treatments, supportive care, emergency care, palliative care and end-of-life care all run in parallel. Flexibility is required to meet the needs of patients, and good quality care must be achieved in a variety of settings including the patient's home, care homes, clinics, emergency departments, medical wards and ICUs.

This book brings together the knowledge and skills of specialists in both Respiratory Medicine and Palliative Medicine in an integrated approach to the care of patients with severe lung disease. We have much to learn from each other, and from our patients, who have much to gain from integrated collaborative models of palliative care.

Newcastle Upon Tyne, UK — Stephen J. Bourke
Newcastle Upon Tyne, UK — Tim Peel

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Contents

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Contributors

Anne-Marie Bourke, MBBS, MRCP, MA Department of Palliative Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust and Marie Curie Hospice, Newcastle Upon Tyne, UK

Stephen J. Bourke, MD, FRCP, FRCPI, DCH Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Graham P. Burns, BSc, MBBS, FRCP, DipMedSci, PhD Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

Alexa Clark, BMedSci, BM, BS Department of Palliative Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

Stephen C. Clark, BMedSci, BM, BS, DM, FRCP, FRCS Department of Cardiothoracic Surgery, Freeman Hospital, Newcastle Upon Tyne, UK

David Cooper, MBBS, FRCP Department of Respiratory Medicine, North Tyneside General Hospital, Tyne and Wear, UK

Ian Forrest, BSc, MBChB, PhD, FRCP Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

Katherine E. Frew, MBChB, MRCP, PhD Department of Palliative Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK

Eleanor Grogan, BSc, MBBS, MA, FRCP Department of Palliative Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK

Bernard Higgins, MBChB (Hons), MD, FRCP Department of Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne, UK

Maria McKenna, MBBS, MRCP, MClinEd Department of Palliative Medicine, Freeman Hospital, Newcastle Upon Tyne, UK

Alice Melville, MBBS, FRCP Department of Respiratory Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK

Ben Messer, BMBCh, MA, MRCP, FFICM Department of Critical Care Medicine and North East Assisted Ventilation Service, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

Paula Mulvenna, MBBS, FRCP, FRCR Northern Centre for Cancer Care, Freeman Hospital, Newcastle Upon Tyne, UK

Paul Paes, MBBS, MSc, MMedEd, FRCP Department of Palliative Care, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, Tyne and Wear, UK

Newcastle University, Newcastle upon Tyne, UK

Tim Peel, MBBS, BSc, FRCP Policy, Ethics and Life Sciences, Newcastle University, Newcastle Upon Tyne, UK

Rachel Quibell, MBBS, FRCP Department of Palliative Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

David Snell, MBBS, MRCP, FRCA Department of Critical Care Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK

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Part I

Palliative Care Principles

Palliative Care of Respiratory Disease

1

Stephen J. Bourke and Paul Paes

One of the major successes of modern medicine has been the development of palliative medicine as a specialty in its own right and the dissemination of the knowledge, skills, and ethos of palliative care to clinical teams in all areas of medical practice [1]. This is particularly the case in respiratory medicine where considerable progress has been made in supporting patients living their lives with chronic lung disease, in relieving symptoms at all stages of a disease process, and in providing end-of-life care to patients facing death [2, 3].

The modern era of palliative medicine started in the second half of the twentieth century with an initial focus on the degree of distress suffered by patients dying of cancer. Key pioneers were Dame Cicely Saunders who founded St Christopher's Hospice, London, in 1967, and Elisabeth Kübler-Ross who conducted interviews with patients who were dying, leading to her seminal publication *On Death and Dying* in 1970 [1, 4]. These pioneers of palliative care built on the earlier successes of previous hospices such as Our Lady's Hospice in Dublin which was established in 1879 and St. Joseph's Hospice in East London, established in 1902. Care of patients in their own homes was a feature of the hospice movement from the start with a philosophy that hospice care was a concept rather than merely a place of care. Early developments were the extension of home care and the establishment of hospital care teams, visiting patients across all specialties to bring the skills of palliative care to seriously ill hospitalized patients. Palliative medicine gained formal recognition as a specialty in 1987 in the United Kingdom (UK), Australia, and New

S. J. Bourke (✉)
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle upon Tyne, UK
e-mail: stephen.bourke@nuth.nhs.uk

P. Paes
Department of Palliative Care, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, Tyne and Wear, UK

Newcastle University, Newcastle upon Tyne, UK
e-mail: paul.paes@northumbria-healthcare.nhs.uk

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Zealand, and subsequently in the United States (USA) in 2007. This led to the establishment of formal training programs, the expansion of clinical services, and the development of research in all areas of palliative care.

Initially the focus was on patients dying of cancer but it rapidly became clear that those dying from other chronic diseases also had considerable palliative care needs. Furthermore there was an important role in the relief of symptoms and the provision of support at all stages of serious illness, not merely in those approaching death. The World Health Organization (WHO) defined palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness [5]. Key elements of palliative care include the relief of symptoms and distress, a team approach in addressing the needs of patients and their families, the enhancement of life, the mitigation of suffering, and the recognition of dying as a normal process bringing life to a natural end.

Clinicians are in a privileged position in dealing with death as it is part of everyday practice in medicine. One of the more recent initiatives in palliative care has been a mission to overcome the taboo of death and to improve public understanding of death and dying. How society views death and dying is a crucial aspect of resilience in the face of illness and disease. Several individual authors have sought to improve everyone's understanding of concepts of disease, curative treatment, illness, living well, death, and dying. Foremost amongst these have been recent books such as Atul Gwande's *Being Mortal*, Kathryn Mannix's *With the End in Mind*, and Paul Kalanithi's *When Breath Becomes Air* which have served to improve understanding and open debate on these issues, so that people can be better prepared for living well and dying well [6–8]. They also challenge the approach taken to medical treatments of life-threatening illnesses. As more treatments and interventions become possible, the key question for society is less about "what can we do?" but more about "what should we do?." This question reflects a growing movement towards the idea of "realistic medicine," a personalized approach to healthcare that requires clinicians to find out what matters most to patients so that care of their condition fits their needs and situation. This concept is a shift from a purely evidence-based, protocol-driven decision-making process to one that balances the evidence with the individual's circumstances and values [9].

Palliative medicine has developed rapidly over recent years to become one of the fastest growing specialties in economically developed regions such as the UK, the USA, Europe, and Australia, but there are huge unmet needs in many other parts of the world [10–13]. There has been a substantial expansion of palliative care services in the USA and a greater emphasis on meeting the challenge of delivering comprehensive care to patients with progressive lung diseases, such as chronic obstructive pulmonary disease (COPD) [13]. In Europe there has been increasing focus on giving patients access to integrated holistic care as part of their standard care and access to specialist palliative care when needed [11]. At the same time as specialist palliative care services are developing, the major medical specialties have become more holistic in managing the impact a disease process can

have on the patient's quality of life, and recognizing the importance of patient-reported outcomes of treatments. Thus within respiratory medicine, many diseases are now treated by multidisciplinary teams focusing on support, symptom control, restorative care, rehabilitation, and psychological interventions in parallel with deploying new disease-modifying therapies. To some extent the ethos of palliative supportive care is becoming embedded into standard clinical practice [14, 15]. In 2008 the American Thoracic Society endorsed the concept that palliative care should be available to patients at all stages of illness and that clinicians who care for patients with chronic or advanced respiratory disease should have training and competencies in palliative care and access to consultations with palliative care specialists and services [3]. This is mirrored in primary care in the UK where there has been much greater emphasis on organizing care for patients who have long-term conditions or are approaching the last year of life through the use of patient registers and toolkits to help deliver care [16]. Governmental policies and healthcare planning have also focused on palliative and end-of-life care, providing a context for improvement of professional practice [10]. Traditionally healthcare outcomes have mainly been measured by mortality rates for various conditions, procedures, and treatments, and these remain key outcome measures. However this has tended to construe death as an unacceptable failure of medicine rather than a natural end to life. There is now increasing focus and scrutiny of the patient's experience of care, patient-reported outcomes, and quality-of-life outcomes, particularly around end-of-life care. In the UK the Department of Health published its strategy for end-of-life care in 2008 and the National Institute for Health and Clinical Excellence published its quality standards for end-of-life care in 2017 [16, 17]. More recently a national framework has been published as *Ambitions for Palliative and End of Life Care 2015–2020*, which sets end-of-life care as a major priority and as an indicator of overall quality of care [11]. While death should not necessarily be seen as a failure, poor end-of-life care is, and improving the quality of end-of-life care is now a key priority. For example, in the UK the Royal College of Physicians national care-of-the-dying audit for hospitals reported the views of 800 bereaved carers [18]. Although outcomes were generally good, this was not universally so, and there was a recognition that clinicians needed further support in developing services and commissioners needed to invest in services to improve care further. The audit report calls for appropriate training of all staff caring for patients at the end of their lives and for specialist palliative care teams to extend their working so as to be available every day of the week. It highlighted the need for improved decision-making, documentation, and communication with patients and relatives. It recommended appropriate accountability at board level of hospitals for quality of end-of-life care. The quality of end-of-life care is now assessed as part of the scrutiny of hospital outcomes. At the same time the specialty of palliative medicine is adapting to current patient needs, moving upstream from the last illness to earlier involvement in care, and extending from care of patients with cancer to patients with any serious progressive condition.

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Extent of Respiratory Disease

Respiratory disease is a major cause of suffering and death throughout the world, accounting for about four million deaths each year [19–21]. For some diseases the prevalence and mortality are rising. In the USA, for example, the death rate from COPD doubled over a 40-year period [19]. In Europe there are about 410,000 new cases of lung cancer each year and it is the major cause of cancer death [20]. In the UK about 20% of all deaths are due to lung disease, amounting to approximately 115,000 deaths each year, and about 12 million people have been diagnosed with lung disease. Lung disease accounts for over 700,000 hospital admissions and over 6.1 million hospital bed days each year in the UK [21]. The top causes of respiratory deaths are lung cancer, COPD, and pneumonia. There are about 35,500 deaths from lung cancer, 30,000 deaths from COPD, 29,000 deaths from pneumonia, 5300 deaths from idiopathic pulmonary fibrosis, and 2500 deaths from occupational lung diseases such as mesothelioma and pneumoconiosis [21].

There is a broad range of respiratory diseases from acute illnesses such as pneumonia, asthma, and acute lung injury to chronic progressive diseases such as COPD, fibrotic lung disease, cystic fibrosis, and neuromuscular disease. About 10% of all patients in hospital suffer from a respiratory illness. About 6% of the UK population is living their lives with a long-term respiratory disease, rising to about 10% of those over the age of 65 years [21].

Symptoms of Respiratory Disease

Patients with lung disease often have a high level of severe symptoms such as breathlessness, cough, respiratory secretions, and pain [2, 3]. For many patients with chronic lung disease breathlessness is a dominant symptom which is difficult to relieve. Optimal disease-modifying measures, pulmonary rehabilitation, and appropriate use of oxygen may all improve breathlessness but reduced exercise capacity with associated breathlessness is often an inherent feature of lung diseases such as idiopathic pulmonary fibrosis and COPD. Opioid and benzodiazepine medications may help reduce the sensation of breathlessness and associated anxiety but in many patients it is not possible to fully relieve this symptom, and patients are likely to need additional measures to support them in coping with activities of daily living. They have substantial disability which often leads to a vicious cycle of breathlessness, reduced physical activities, and deconditioning of muscles with secondary problems of social isolation, loss of autonomy, depression, and anxiety. They often have a complex range of emotional responses to their illness such as frustration, anxiety, panic, and fear of the future. The emotional and psychological impact of chronic lung disease can be as severe as the physical symptoms. Many patients with lung disease have to cope with complex and intrusive treatments which may include multiple drug treatments, nebulized medications, physiotherapy, oxygen therapy, and in some cases noninvasive ventilation (NIV) and nutritional support. Patients are often living their lives in the knowledge of having a chronic life-limiting disease. As a disease progresses it is

often necessary to intensify treatments but an ever-increasing treatment burden can further impair the quality of life. The concept of "realistic medicine" advocates a framework of five questions for patients to consider with their clinical teams: Is this test, treatment, or procedure really needed? What are the benefits and downsides? What are the possible side effects? Are there simpler or safer options? What would happen if I did nothing? [9]. Skills from several disciplines are needed in treating these patients and a multidisciplinary integrated approach is essential. Typically this currently involves doctors, specialist nurses, physiotherapists, and social workers and may increasingly involve palliative care clinicians, particularly as the focus changes in the course of the disease from chronic disease management to end-of-life care. End-of-life care includes the last phase of an illness, often extending over the last 6–12 months of life, rather than being confined to the terminal hours or days. In addition to expert treatment directed against the disease process, patients often benefit from supportive measures to enable them to live in their own home, pulmonary rehabilitation to improve the quality of life, and psychological therapies such as cognitive behavioral therapy to help them cope with and adjust to living with a chronic progressive lung disease. Many patients with chronic lung disease are elderly and suffer from general frailty and additional comorbid conditions, such that several disease processes may be present in an individual patient.

Respiratory Disease Trajectories (Fig. 1.1)

Predicting the prognosis of lung disease is often difficult and it is sometimes necessary for the patient and the clinical team to accept uncertainty. The rate at which a disease progresses—the disease trajectory—is often highly variable in chronic lung disease and patients follow their own unique clinical course [22, 23]. Sudden death is a feature of catastrophic illnesses such as acute asthma, severe pneumonia, or acute lung injury. The end-of-life phase may be short, often over a few hours, and is likely to be in the setting of an intensive care unit (ICU). Under these circumstances patients and families have very little time to prepare and they have to be supported in coming to terms with a trajectory that moves quickly from good health to death and bereavement. This poses particular challenges for the healthcare team. In contrast, patients with lung cancer often follow the "cancer trajectory" where there is an initial phase of disease-modifying treatments such as chemotherapy and radiotherapy, followed by a phase of progression of the cancer and declining health, evolving into a clearer palliative phase culminating in end-of-life care which may be in a hospice or in the patient's home, for example. However even in the lung cancer trajectory it has been shown that early palliative care from the time of diagnosis leads to significant improvements in quality of life, and also results in less aggressive care at end of life but longer overall survival [24]. The traditional cancer trajectory often does not fit well with chronic lung disease, where the clinical course is more variable. Patients live their lives with the disability and distress of a chronic illness which cannot be cured and in the knowledge that this is a life-limiting condition. However a patient's life span after diagnosis can be decades. In most cases

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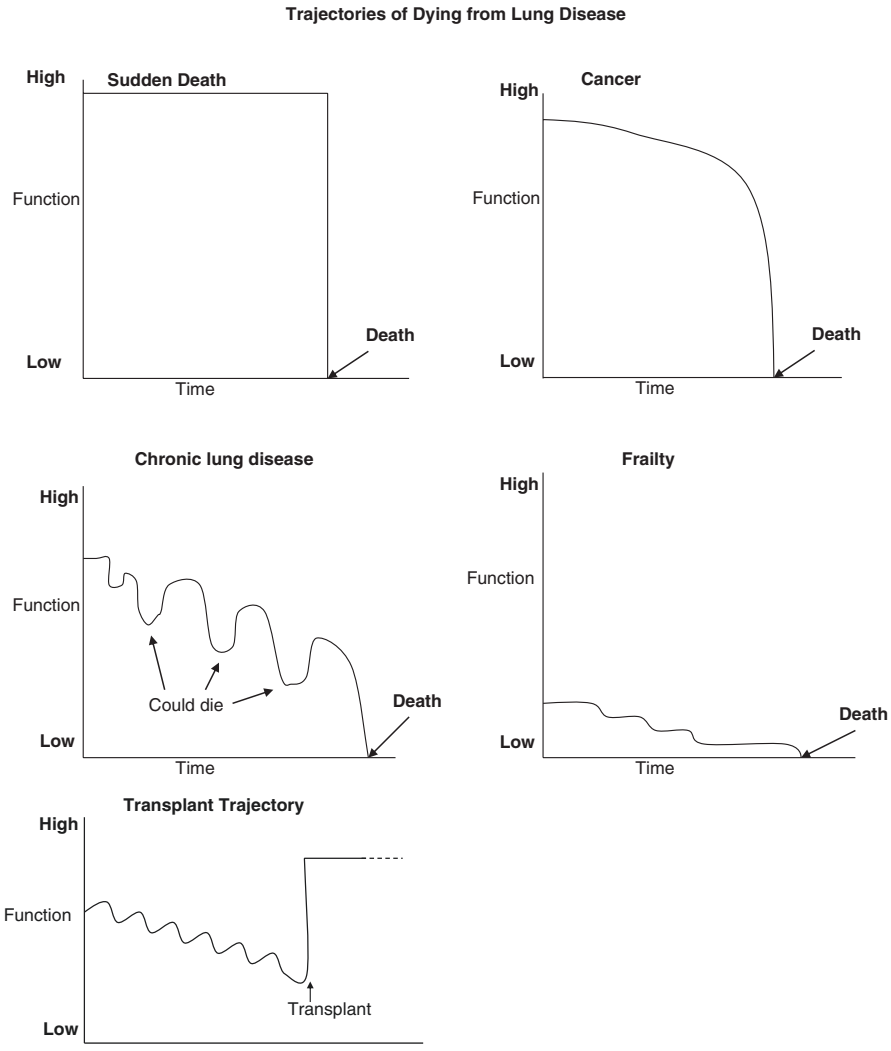

Fig. 1.1 Trajectories of dying from lung disease. The rate at which lung diseases progress is highly variable. Sudden death is a feature of catastrophic illnesses such as severe pneumonia. Lung cancer often follows a typical cancer trajectory. Chronic lung diseases such as COPD are characterized by gradual progression with intermittent exacerbations. Many patients with COPD are elderly with progressive frailty. A transplant trajectory is a particular feature of some lung diseases such as cystic fibrosis

palliative care runs in parallel with disease-modifying treatments, supportive care, and measures aimed at improving quality of life [22]. Many chronic lung diseases are characterized by acute exacerbations which can be reversed by acute treatments, which often involve admission to hospital. It is important to appreciate that acute exacerbations usually cause severe symptoms such as breathlessness, cough, pain,

and distress which require emergency treatment. Such treatments not only reverse the underlying disease process but are also the most effective way of relieving symptoms. Thus a course of intravenous antibiotics, with oxygen and sputum clearance physiotherapy, is the most effective way of relieving symptoms in a patient with an exacerbation of cystic fibrosis lung disease. Patients may suffer acute complications in the course of chronic lung disease, such as pneumothorax, pneumonia, or major hemoptysis, which cause an acute crisis with severe distress that can be relieved by prompt diagnosis and expert interventions. Such complications are more likely to occur in advanced-stage disease, and can be very difficult to manage well if an artificial model is followed, whereby palliative care is separated from active disease-modifying care. Such models of care provision are usually inappropriate for patients with progressive lung disease. It is usually better to organize care in such a way that disease-modifying treatments, emergency interventions for any acute crisis, and palliative and supportive measures run in parallel [25].

Patients with COPD typically have a trajectory of gradual decline punctuated by episodes of acute deterioration and recovery with treatment. The patient recovers from all exacerbations except the final one, and death can then be somewhat unexpected. This is sometimes referred to as "acute crisis/recovery trajectory." There are typically two phases in this trajectory: a phase of management of advanced disease which is often prolonged and a phase of end-of-life care of the dying patient which is often short. This trajectory may be inherent to the clinical course of some progressive lung diseases, and it needs to be acknowledged and managed accordingly. Many patients with chronic lung disease are elderly and frail with comorbid conditions such that they may follow a "frailty trajectory" [23]. They may experience dwindling health with increasing difficulties in coping at home even with intensive support, such that they may decide to live in a care home, which provides a high level of nursing and supportive care. Such patients may be following a chronic lung disease trajectory, but death may occur from other causes such as a myocardial infarction or stroke.

A "transplant trajectory" is a particular feature for some lung diseases such as cystic fibrosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension, or emphysema due to alpha-1 antitrypsin deficiency, for example. The patient is seriously ill, has a high level of symptoms, and may die but is hoping for a rescue lung transplant which can transform the trajectory of the disease dramatically [25].

Other trajectories may apply to specific aspects of a disease. For example emotional distress tends to peak at the time of diagnosis of a serious disease, such as lung cancer, at times of deterioration or relapse, and as death approaches. At the time of diagnosis the patient has to cope with receiving bad news and has to adjust to living with a serious life-limiting disease. There are elements of grief and loss at this time. The trajectory of symptoms may escalate as the disease progresses and death approaches [26]. This is particularly the case for breathlessness in progressive respiratory diseases. Patients with fibrotic lung disease or COPD often experience severe breathlessness, which can dominate all activities of living as the disease progresses. They may have severe hypoxia requiring high levels of supplemental oxygen. Respiratory distress escalates in the last days of life even in patients with

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non-respiratory diseases such as dementia and cancer. Pneumonia is a common complication at the end of life across diagnoses and may cause breathlessness. Respiratory teams in hospitals are frequently involved with end-of-life care for patients with progressive diseases such as dementia, frailty, Parkinson's disease, and cerebrovascular and neuromuscular diseases, as aspiration pneumonia may be a recurrent feature in advanced disease and is often the factor precipitating death. Delirium and impaired consciousness may reduce the patient's ability to report symptoms, which could lead to under-recognition and undertreatment [26].

There are substantial limitations to predicting the disease trajectory in patients with lung disease but there may be some advantage in predicting that a patient is likely to die within "months rather than years" or within 6 months, as this may avoid "prognostic paralysis" and may allow access to some additional support services. In some healthcare systems particular services or financial support is made available to patients who are unlikely to survive more than 6 months. For some diseases, such as lung cancer or progressive idiopathic pulmonary fibrosis, the disease trajectory is generally more predictable, and this facilitates discussion of prognosis, care, and end-of-life planning. For other patients, such as those with COPD or cystic fibrosis, it is necessary to acknowledge uncertainty. The prognosis and future plans can be discussed in terms of what is likely to happen over a period of time. Emergency health care plans under these circumstances are likely to involve admission to hospital for disease-modifying treatments, alongside parallel palliative interventions and exploration of the patient's goals and wishes. Precise planning is often unhelpful as patients often outlive predicted survival projections, and plans need to be adaptable to deal with events.

Integrating Palliative Care into Respiratory Care

Palliative care of respiratory disease is complex and no one model of care will suit all patients. Different countries organize their palliative care services in different ways but good-quality care must be achieved in a variety of settings including the patient's home, care homes, clinics, emergency departments, specialist respiratory wards, and ICUs. Delivery of care will depend on the patient's needs, the skills of the clinical team, and the availability of specialist palliative services. It is now widely recognized that palliative care principles apply at all stages of serious disease and that all doctors and clinical teams should be able to recognize the patient's needs and to deliver general palliative care, including elements of symptom control, support, communication, and discussion of future care planning. Specialists in palliative medicine have a crucial role in providing education and support to these clinical teams, with collaborative working across traditional boundaries.

There are substantial differences in the use of specialist palliative care services between patients with cancer and patients with other chronic lung diseases [27, 28]. Only a minority of patients dying with chronic lung disease have input from specialist palliative care services. This could be due to many factors including the clinical course of the disease, a failure to refer patients to palliative services, a

reluctance of palliative services to be involved with such a large number of patients, or a reluctance of the patients to consider palliative care. These are complex issues and the best way of providing palliative care to these patients has not yet been established. Many of these patients have long-standing relationships with a multidisciplinary respiratory team which endeavors to provide holistic care. Patients often value this continuity of care and it isn't clear that their needs are best met by a transfer of care from respiratory services to palliative services, especially when disease-modifying therapies, emergency treatments, and palliative care need to run in parallel. This is particularly the case in specialist areas such as cystic fibrosis, fibrotic lung disease, pulmonary hypertension, and neuromuscular disease where management is coordinated by the specialist respiratory team. It is often more appropriate to integrate palliative care and specialist respiratory care, with members of the palliative care team working alongside the respiratory multidisciplinary team [29–31]. As such patients enter advanced-stage disease particular palliative care skills may be needed in relieving complex symptoms and in addressing end-of-life issues. Health professionals trained in both respiratory and palliative care roles offer a further model of continuity, as do teams able to work across the hospital/community boundary. Specialist palliative care services may be able to facilitate a patient's wish to be at home when dying or to give access to hospice care if appropriate. Primary care teams form a crucial role in this especially in a large-volume condition such as COPD where the management of patients may be shared or coordinated in primary care. Primary care physicians and their teams are well placed to access community resources and to work closely with palliative care teams to manage people in their own home. Community-based palliative care teams are increasingly able to provide high-intensity palliative care in the patient's home [32, 33]. In this integrated model of collaborative working it is easier to manage any acute crises or complications which may arise in advanced lung disease. Integrated palliative care also encourages a focus on symptom management, support, communication, and quality-of-life issues at an earlier stage in the disease process [34]. Respiratory teams may be reluctant to discuss prognosis and future planning in detail but some studies suggest that patients want to make plans for their future care and would like their clinical teams to start such discussions. Palliative care clinicians can facilitate such discussions. Sometimes a question such as "what worries you most about the future?" can be a useful way of approaching the subject. There may be key events which should trigger these discussions such as an admission to hospital with an exacerbation of COPD, an episode of respiratory failure requiring noninvasive ventilation, or a deterioration in lung function in a progressive respiratory disease. Some patients have particular fears which can be addressed and alleviated. For example, patients who have problems with respiratory secretions may fear that they will choke to death and breathless patients may fear that death will be painful with them struggling to breathe [25]. They can be reassured that such symptoms can be controlled.

Around half of all deaths in England occur in hospitals, and death in hospital is even more common for patients with progressive lung disease [15]. In a large study Higginson et al. showed that 67% of COPD and 70% of patients with fibrotic

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lung disease died in hospital and only 0.9% and 2.9%, respectively, died in a hospice [35]. End-of-life care is therefore a core responsibility for hospitals in order to deliver high-quality care for patients in their final days of life, with appropriate support for their families, carers, and those close to them. These patients often need emergency assessment and management during an acute crisis and hospital is often the best place to achieve this, and should not be denied to the patient [36]. It is particularly important that palliative care has a high profile in certain areas such as ICU, emergency departments, and acute medicine wards. Because acute exacerbations and complications often occur in advanced lung disease these patients require access to emergency services. Prompt assessment is required to identify the problem and urgent specific treatment is needed to deal with complications such as infection, hemoptysis, and pneumothorax. In many cases accurate diagnosis and specific treatment will relieve symptoms and lead to recovery from the acute crisis. However an acute crisis may be the start of the dying process for these patients. If disease-modifying treatments are failing and the patient is progressively deteriorating it is important to recognize when the patient is dying and when escalation of treatments such as invasive ventilation may be futile and not in the patient's best interests. It is crucial that patients, their relatives, and the general public have confidence in the ability of emergency services to provide urgent palliation and that the general public does not develop erroneous concepts of death in hospital being an undignified, painful struggle with high-technology-intrusive treatments being applied inappropriately. One of the major successes in recent times has been the emphasis on providing good-quality end-of-life care in hospitals [15–17, 37].

Some patients wish to be at home when dying and the "preferred place of care" and "preferred place of death" have been key parameters for palliative care services. There are initiatives to facilitate patients in achieving their preferred place of death, although it is important that there is an option to make the decision in the circumstances at the time. Although patients might express a preference for home care futuristically, when an acute crisis occurs which is potentially reversible they and their families often opt for hospital care. When people are dying their focus is less on place of care and more on the quality of care [38]. "Preferred priorities for care" may be a more useful concept in advance care planning for these patients, identifying key issues such as symptom relief, maximizing comfort, achieving a peaceful death, avoiding distress to their family, and avoiding futile intrusive interventions such as cardiopulmonary resuscitation. Often disease-modifying therapies bring substantial improvement in symptoms and quality of life even in advanced lung disease and particular attention is needed when acute crises develop such as pulmonary embolism, pneumothorax, pneumonia, or exacerbations in the course of progressive lung disease: parallel disease-focused and palliative treatments go hand in hand. For diseases characterized by exacerbations and recovery respiratory physicians, palliative care specialists, patients, and families are unlikely to decide on forgoing acute medical management of potentially reversible disease, when this may often also be the best way of gaining control over symptoms and distress. Emergency healthcare plans, developed by clinicians with the patient, will usually

emphasize the need for rapid assessment and trials of treatment (e.g., NIV, antibiotics, corticosteroids, oxygen), although the patient's advance care plan and escalation plans may well state that invasive ventilation on ICU or cardiopulmonary resuscitation would not be appropriate. Often it is only after a few days of medical treatment that it becomes apparent that the patient is now dying.

Models of Palliative Care

Early integration of palliative specialists into the standard care of patients with advanced progressive lung disease is increasingly common. Thus several services for patients with COPD, interstitial lung disease, and cystic fibrosis now have a palliative care nurse or physician as part of the multidisciplinary team working alongside each other in a truly integrated fashion [29]. Pulmonary rehabilitation programs for patients with COPD now often also include information and education on future care plans to give the patient a positive approach to improving the situation and regaining control of future care plans in the face of progressive lung disease. This could be delivered by respiratory nurse specialists, for example, or by palliative nurse specialists working alongside the respiratory team. For those with advanced lung disease and a high burden of symptoms multidisciplinary clinics, such as "breathlessness support services," also have a role [12].

Particular consideration is needed in deciding how to organize urgent care for individual patients when a crisis occurs in their advanced-stage disease. An acute crisis in the course of chronic lung disease often causes acute severe breathlessness which is very distressing for patients and their families. Ideally admission to hospital should be directly to the clinical team which knows them well. Thus a patient with cystic fibrosis or neuromuscular disease for example develops a crisis and contacts their specialist team who arranges urgent assessment, diagnoses the problem, and decides with the patient on the best course of action. This can result in rapid control of a situation in which the patient and family are very distressed. It is more difficult to organize such a level of care for diseases such as COPD where there are large numbers of patients.

Table 1.1 Models of care at the end of life

• Transfer of care from respiratory to palliative medicine team.
• Transfer of care from respiratory to community teams for patients to have end-of-life care at home.
• Transfer of care to hospice.
• Transfer of care to a care home.
• Continuity of care by respiratory team with general palliative skills.
• Consultation by specialist palliative team.
• Integrated care jointly by respiratory and palliative teams.
• Hospital palliative care units.
• Hospital to home services.

For patients requiring admission to hospital the development of palliative care units within acute hospital services offers an innovative model of palliative care [37]. These units are designed to provide individualized, compassionate clinical care for hospital in-patients with the most complex, high-dependency palliative and end-of-life care needs, and their families. The "environment of care" is important at the end of life and palliative care units can be designed to provide a quiet comforting environment with open-access visiting, and facilities for family members to stay if needed. "Hospital to home" services can allow patients to return to their own home to die by providing intensive support to the patient and family in the home.

Patients with lung cancer often follow a more traditional palliative care trajectory, and it may be more appropriate to transfer their care from an oncology team to a palliative care team as the disease progresses and as death approaches. Nevertheless in the UK and many other countries, these patients often have continuity of care provided by a respiratory physician or by their primary care general practitioner. Considerable flexibility is needed in providing palliative care to these patients (Table 1.1).

Terminology and Definitions

There are some terms and phrases which are commonly used to describe the interventions and approaches to the care of patients with progressive disease.

Palliative care: Many patients, families, and healthcare professionals have difficulties with the term "palliative care," as involving perceived negative concepts, such as "nothing more can be done" and applicable only to someone who is dying. This may be a barrier to the integration of palliative care into standard care at an earlier stage [39]. Some palliative medicine specialists have themselves suggested avoiding, or reframing, the term and using other terms such as "supportive care" or "holistic care." However raising awareness of palliative care is a key component of the public health approach, and explaining that palliative care is not just about dying but also about living well to the end. The American Thoracic Society and the British Lung Foundation have produced useful patient education and information documents which emphasize that palliative care can be provided at the same time that the person is receiving medical treatments [40, 41]. This may be provided by their usual healthcare provider or involve referral to a specialist palliative care team, to address the symptoms and feelings of stress related to their illness, and to explore their values, goals, and preferences for medical care. This normalizes palliative care as part of standard care and encourages people with respiratory disease or critical illness to ask their healthcare providers about palliative care in their treatment plan. The WHO defines palliative care as an approach that focuses on the total care of the patient and family who are facing life-threatening illness [5]. It embraces symptom control and psychological, social, and spiritual support and aims to optimize quality of life in those with an incurable illness. This type of care should be offered by all healthcare professionals.

Specialist palliative care is care provided by clinicians who have specialist training and skills in palliative medicine, working within specialist multidisciplinary teams.

Supportive care is a broader concept which includes the provision of support and palliation to patients at an earlier stage of their illness when outcomes, such as cure, are still possible.

Disease-modifying treatment refers to treatments focused on the underlying condition that may halt or slow the disease process. In terms of an ultimately fatal disease such as mesothelioma chemotherapy might be expected to prolong survival as well as improve symptoms. Disease modification may be achieved with drugs, lifestyle changes such as smoking cessation in COPD, and nondrug interventions such as radiotherapy in lung cancer.

Active treatment includes both disease-modifying treatments and a range of possible interventions for potential complications which may arise. Examples might include antibiotics for infections or mucoactive drugs and physiotherapy for sputum clearance. Active treatment and palliative care are not mutually exclusive.

Ceilings of treatment (escalation plans) are terms used to describe what treatment options might be appropriate and desirable depending on the circumstances which might arise when an outcome of an illness is unpredictable. These are management plans by the clinical team, taking into account the wishes of the patient and family. Sometimes called treatment escalation plans, examples of ceilings of treatment options include at one end of the spectrum whether to use antibiotics for an infection, and at the other whether a patient should be transferred to the ICU for endotracheal ventilation for respiratory failure. Examples of ceilings of intervention include:

- Lung transplantation
- Cardiopulmonary resuscitation and invasive ventilation
- Noninvasive ventilation
- Clinically assisted nutrition
- Clinically assisted hydration
- Surgery if otherwise indicated, such as for an acute abdominal condition
- Intravenous antibiotics
- Oral antibiotics
- Disease-modifying drugs
- Symptom-controlling measures only

In the context of advanced respiratory disease it is important to stress that however actively the disease is to be managed, palliative treatments should still be offered if necessary. Similarly palliative care does not imply withdrawal of disease-modifying treatment. Guidance has been published by the General Medical Council in the UK on decision-making at the end of life [42]. Patients may refuse a proposed treatment if they have the capacity to make the decision or if they have made an advanced directive to refuse treatment. If a patient lacks capacity and has already appointed a legal proxy, then that person can refuse the proposed treatment on behalf of the patient. If the patient requests a treatment which the doctor, after due

consideration, does not think is clinically appropriate, the doctor is not beholden to provide that treatment but is advised to seek consensus, to discuss the reasons for the decision, and to offer a second opinion.

Prescribing in Palliative Care

Licensed, Unlicensed, and Off-Label Drugs

In the UK drugs can be licensed either through the European Medicines Agency (EMA) or the Medicines and Healthcare Products Regulatory Agency (MRHA). Drugs are licensed for a specific indication and administration route (for example oral or subcutaneous injection). Most drugs are therefore prescribed according to license (indication and route), for example morphine sulfate-modified release tablets orally for pain. There are also some unlicensed preparations available, such as cyclizine suppositories for nausea and vomiting. Finally, and most commonly seen in palliative medicine practice, is the use of a licensed drug for an indication outside the license, or given by an unlicensed route. This is commonly referred to as off-label or off-license prescribing. Appendix A at the end of this book lists some unlicensed drugs and off-license prescribing. The General Medical Council gives guidance on unlicensed and off-license prescribing [43]. Both are permissible if the prescriber is satisfied that the drug would serve the patient's needs better than licensed preparations, that there is sufficient evidence of efficacy and safety, and that the prescriber will oversee the patient's care and document the reasons for the prescription. This should also be discussed with the patient.

Opioid Prescribing Issues

Opioid dose conversions: It is often necessary to change one opioid drug to another, either because of adverse effects or due to lack of benefit. Recommended conversion ratios used in this book are based on recent European Association for Palliative Care guidelines, and are in line with other guidance [44, 45]. In two cases these differ from the manufacturer's suggestions (morphine-oxycodone and morphine-fentanyl conversions). It is important to appreciate that there is significant individual variation in the pharmacokinetics of these drugs between patients such that conversion ratios are approximations and may not be equianalgesic, and further titration may be necessary.

Rescue doses: When prescribing a regular modified-release opioid, it is important also to prescribe rescue (as necessary) analgesia for any breakthrough pain or breathlessness. This is usually prescribed hourly in hospices or hospitals and 4 hourly in the community (where there may be less ability to monitor toxicity). This is calculated by determining the total 24 hourly modified-release dose and multiplying it by 1/10–1/6 to obtain the rescue dose of immediate-release medication. The range allows doses in "round numbers."

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Dose escalation: Opioids are used to manage both pain and breathlessness. The dose required to manage breathlessness is usually lower than for pain and there is usually no benefit from increasing the dose significantly. When pain is uncontrolled and the opioids are being escalated day by day, it is usual to increase the regular daily dose by the amount of extra doses of rescue opioid being used or by 1/3–1/2 each time. The range allows calculation of doses in whole numbers. When the regular drug is increased the rescue dose must also be increased. This is discussed further in Chap. 5.

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Part II

Respiratory Symptoms

Breathlessness

2

Tim Peel and Graham P. Burns

Definition

Breathlessness, also known as dyspnea, is a symptom unique to the patient. Definitions stress the combination of unpleasant physical sensations with adverse emotions, such as anxiety, panic, or low mood [1]. The sensation of dyspnea arises as a result of complex synthesis of afferent signals to the brain, influenced by psychological and emotional factors and interpreted subconsciously based on a benchmarking of past experience. Because of the close association between physical and emotional inputs, it is often difficult to separate cause and effect in the anxious breathless patient.

Breathlessness is not the same as:

- *Tachypnea*: An increased rate of breathing.
- *Hyperventilation*: "Overventilation" (of the alveoli) beyond the level needed to maintain a normal pCO_2. Many doctors tend to use the term loosely to mean "anxiety-driven hyperventilation." It should be noted that anxiety is far from the only cause of a diminished pCO_2. Care is needed so that causes such as pulmonary embolism, acute severe asthma, and metabolic acidosis are not mistaken for "mere anxiety."

T. Peel (✉)
Policy, Ethics and Life Sciences, Newcastle University, Newcastle Upon Tyne, UK
e-mail: e.t.peel2@newcastle.ac.uk

G. P. Burns
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: Graham.Burns@nuth.nhs.uk

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Control of Breathing

For most people, in health, breathing is an automatic function, controlled by the autonomic nervous system, and does not impact consciousness. If we deliberately turn our attention to it, however, it can be readily perceived. The four respiratory centers are located in the brainstem (medulla and pons). They receive information from a number of central and peripheral receptors. Central chemoreceptors are located in the medulla and respond to changes in pCO_2 and therefore pH. Peripheral chemoreceptors are in the carotid and aortic bodies and respond to changes in pO_2. There are also stretch receptors in the chest wall muscles, mechanoreceptors in the airways and lung parenchyma, and also temperature receptors in the airways. These all transmit afferent messages to the respiratory centers where ventilation is controlled. This dictates the necessary ventilatory rate and depth via the common efferent pathway.

When the respiratory motor center sends an efferent signal to the respiratory muscles, it sends a copy of the signal (corollary discharge) [2] to perceptual areas in higher centers. The brain thus knows "what has been asked" of the ventilatory system. This information is compared with information returning from the respiratory muscles and other afferent signals on what is being achieved in terms of ventilation. When these two match, no red flags are raised, and breathing continues automatically, essentially unnoticed. When a mismatch occurs, when the return on effort is not what it should be the individual experiences an uncomfortable sense of inappropriate respiratory effort, more usually described as "breathlessness." Mismatch could be due to a number of mechanisms impeding the ventilatory response to its neurological command: obstruction to airflow, increased load on respiratory muscles (including hyperinflation see below), or respiratory muscle weakness.

Descending pathways, either via the thalamus or directly to the respiratory muscles, are the means whereby we can, to some extent, voluntarily alter our pattern of breathing.

Most of the drugs that are used for purely symptomatic relief of dyspnea act at the higher centers.

Causes

There are many causes of breathlessness, both acute and chronic. Some of these are primarily due to underlying respiratory disease, whilst others are a manifestation of pulmonary vascular, cardiac, psychological, or other diseases. The causes are summarized in Table 2.1. The medical treatment of many of these underlying conditions (i.e., disease modification) is not within the scope of this chapter. When describing management options for dyspnea, it is assumed that all appropriate medical treatments for the underlying cause have been offered.

Table 2.1 Breathlessness: causes

Respiratory		
Chronic	COPD/asthma	
	Sepsis	Bronchiectasis
		Cystic fibrosis
	Cancer	Lung cancer
		Mesothelioma
		Intrathoracic metastases
	Fibrosis	
	Neuromuscular	Motor neuron disease
		Muscular dystrophies
	Skeletal	Chest wall abnormalities
Acute	Pneumonia	
	Emphysema	
	Pneumothorax	
Pulmonary vascular	Pulmonary thromboembolism: acute and chronic (recurrent)	
	Pulmonary hypertension: primary and secondary	
Cardiac		
Chronic	Heart failure (right, left, or congestive)	
	Arrhythmias (particularly atrial fibrillation)	
Acute	Coronary events	
Psychological	Anxiety, depression, hyperventilation	
Other causes		
Anemia		
Cachexia Metabolic acidosis		

Mechanisms of Dyspnea in Chronic Lung Disease

Hyperinflation

Certain lung conditions, such as asthma and chronic obstructive pulmonary disease (COPD), cause generalized narrowing of the airways. This narrowing implies increased airway resistance which necessitates an increase in the effort of breathing. Further, premature complete closure of some small airways leads to gas trapping within the lungs, poor ventilation in general, and inefficiency in the function of the lungs.

In an attempt to obviate the degree of airway narrowing, patients with asthma or COPD tend to breathe at a higher lung volume, closer to total lung capacity (TLC) than usual (Fig. 2.1). By doing so, the lungs in general are stretched and the airways, that are embedded within lung tissue, experience increased retractile force on their outer walls and are, to some extent, widened. In that sense the strategy works. There is, of course, no conscious or deliberate decision to breathe at a higher lung volume. Patients are not even aware they are doing so. It is an automatic, unconscious maneuver. However, as well as alleviating, to some degree, the airway narrowing,

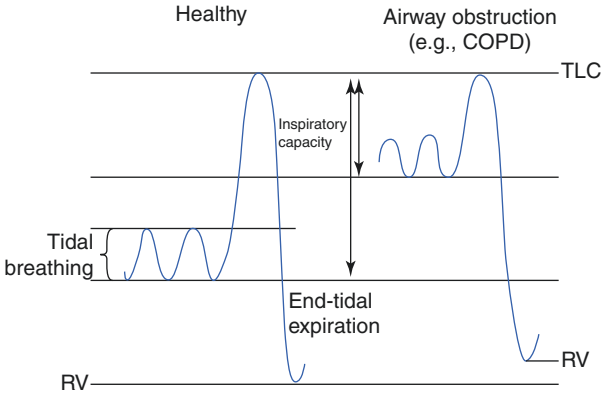

Fig. 2.1 Graph of lung volumes against time in a healthy subject and a patient with airway obstruction (e.g., COPD). In the context of COPD, tidal breathing occurs at a higher lung volume; this helps to support the airway open but has a number of other consequences (see text). Note that the inspiratory capacity (the gap between the lung volume at the end of a tidal expiration and the total lung capacity) is reduced in airway obstruction. *TLC* total lung capacity, *RV* residual volume

there are a number of other consequences to this adaptation which can give rise to specific symptoms.

Reduced Inspiratory Capacity

As can be seen, breathing at a higher lung volume implies that the inspiratory capacity is diminished. At this increased lung volume, following a conscious attempt to take a deep (full) breath in, TLC, the absolute limit to inspiration, is reached relatively quickly. In a patient who would be unaware that their inspiratory maneuver had begun at a higher lung volume and unaware that they were already at TLC, the absolute limitation to further inspiration would be perceived as an "inability to get a full breath in," an unpleasant sensation often reported by patients.

Increased Work of Breathing and Increased Dyspnea

In healthy subjects at the end of a normal tidal expiration, the intrinsic tendency for the lungs to contract is just counterbalanced by the natural tendency for the chest wall to "spring outward." No muscular effort (no work) is required to hold this "neutral" position. Breathing close to this lung volume is therefore quite effort efficient, like gently stretching and releasing a spring that has no baseline tension. As lung volume increases, lung tissue is stretched, and like the spring it tends to resist further stretch. In fact, unlike the perfect spring of Hooke's law, the greater the stretch, the greater the force that is required to further expand the lung. When, as in airway obstruction, tidal breathing occurs at a higher lung volume, the muscular effort needed simply to move the chest wall (*the work of breathing*) is hugely increased, like attempting to stretch and relax a spring that is already under considerable tension. Therefore for a given degree of ventilation, much greater effort is needed. This "mismatch" between the ventilation achieved and the greater than expected work

needed to achieve it contributes to the sensation of breathlessness and is another price paid for airway dilatation achieved by hyperinflation.

To gain some appreciation yourself of how important a factor this is in the perception of breathlessness try it. From a normal lung volume, take a breath in, about halfway to full capacity. Then spend just a minute trying to breathe normally, at this hyperinflated position. A minute will seem like a long time. Remember that those with airway obstruction are breathing at this high lung volume all the time.

Hypoxia

The link between hypoxia and breathlessness is weak. To the lay person, the reason we breathe is to take in oxygen. Whilst this is of course an important imperative, the first priority of the respiratory system is to maintain a normal pH. It is not possible to survive for long with a pH outside of the normal range. Control is achieved by adjustments in pCO_2 (pH and pCO_2 are intimately linked). So, if for example a metabolic alkalosis were to arise (e.g., after vomiting), to correct the high pH, ventilation would be reduced and CO_2 would accumulate. By reducing ventilation however pO_2 would also fall. Fortunately (within limits) this has no detrimental effect. The level of oxygenation we normally maintain (pO_2 11–14 kPa) is far above what is required to sustain life, even in the long term. A modest fall in oxygenation would not normally be perceived by the individual as breathlessness and it would not, per se, drive up ventilation. Only at a much lower level (pO_2 around 8 kPa) does the center in the brain stem responsible for protecting us from hypoxia wake up and start to take action.

Prevalence of Breathlessness in Advanced Respiratory Diseases

Studies of symptom prevalence in advanced diseases show wide variation. This variation is dependent on the symptom, disease, and stage of the disease. A systematic review [3] reported the prevalence of breathlessness in cancer studies at 10–70% (10,029 patients) and in advanced COPD studies at 90–95% (372 patients). In one cancer study [4], the incidence of dyspnea was 84% in lung cancer and the next most frequent was 58% in lymphoma. In this study, they also assessed severity of breathlessness by a dyspnea score. The most severe dyspnea was observed in lung cancer.

Idiopathic pulmonary fibrosis (IPF) is characterized by dyspnea. Kozu et al. [5] studied 65 stable IPF patients and correlated their Medical Research Council (MRC) Dyspnea Grade [6] with exercise capacity and lung function. The percentage of subjects in MRC Grades 2, 3, 4, and 5 was 25, 26, 26, and 23%, respectively. The MRC Grade correlated positively with 6-min walking distance (6MWD) and with the transfer factor for carbon monoxide gas transfer (TLCO).

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Assessment of the Breathless Patient

Apart from understanding the underlying cause for dyspnea, it is also important to assess the impact that the symptom has on the patient. This applies both to the individual practitioner managing a particular patient and to the researcher investigating new interventions. Such assessments may include qualitative descriptors of the experience, quantitative measures of the symptom and its influence on quality of life, and functional assessments such as exercise tests. It is obvious that the choice of application of these will depend on the status of the patient and his/her wishes. An extensive literature on assessment tools already exists [7, 8].

Attempts to identify the underlying cause of breathlessness by studying the words or phrases used to describe the experience have largely been unsuccessful [9]. Although there do seem to be clusters of descriptors in specific conditions, such as the inspiratory effort needed in COPD, their usefulness in the assessment of the breathless patient is limited.

Quantification of the symptom is more relevant and supported by a greater body of evidence [7]. The Medical Research Council Dyspnea Score (MRCD) [6] is well validated and simple to apply, and has been used for other respiratory conditions too [5]. Another simple scoring scale of severity is the Numerical Rating Scale (NRS) [10]. This is a scale from 0 to 10 (no breathlessness up to the worst possible).

Apart from the actual symptom, there are a number of other concomitant symptoms that the breathless patient may experience at the same time, such as fatigue, mood changes, and loss of control. These are captured in the Chronic Respiratory Disease Questionnaire (CRQ) [11]. In the CRQ, the patient chooses those situations most important in terms of impact of dyspnea on his/her life. The questionnaire may then be self or healthcare professional administered. Four domains are identified: dyspnea, fatigue, emotional, and mastery.

In the palliative context, it is rarely necessary to demonstrate or measure functional impairment objectively. If it is felt necessary, then exertional dyspnea can be simply assessed with the 6-min walking test (6MWT) [12]. Breathlessness at rest can be quantified by counting numbers [13]. This simple test involves the patient reading out aloud randomly generated two-digit numbers over a 1-min period. From this the observer measures the total number of numbers and also the number of breaths taken. Thus the number of numbers per breath is calculated.

Management of the Breathless Patient

General Principles

The first stage after an assessment of the underlying cause of dyspnea will be to offer disease-modifying treatment in an attempt to reverse the process. Mostly this will be drug treatment, but, particularly in cancer-related dyspnea, radiotherapy or physical interventions may also be employed. These will be discussed in the lung cancer or mesothelioma chapters.

Purely symptomatic strategies for breathlessness management include:

1. Pharmacological management
2. Non-pharmacological management
3. Oxygen

Pharmacological Management of Dyspnea

Of the drugs that have been tried for the symptomatic relief of breathlessness, only opioids and benzodiazepines are widely used.

Opioids

A systematic review [14] explored randomized controlled trials comparing any opioid drug with placebo or any other intervention for the relief of breathlessness in patients with a variety of conditions, including COPD, lung cancer, heart failure, and interstitial lung disease. The conclusions were that there was low-quality evidence to support the use of oral and parenteral opioids, but none for the nebulized route. Most of the evidence came from studies in COPD patients, with less evidence for cancer and interstitial lung disease. Two studies [15, 16] have explored the use of sustained-release morphine and attempted to define a starting dose. In the more recent study [16], it was reported that 10 mg sustained-release oral morphine gave a beneficial response rate of 62%, which was not improved by further dose incrementation. There were no episodes of respiratory depression in the 83 COPD patients involved in that study.

There are no studies looking at dosing of opioids for dyspnea in patients already taking them for pain.

Suggested Dosing Schedules for Opioids for Breathlessness

In opioid-naïve patients, the options include a weak opioid such as codeine phosphate, immediate-release (IR) oral morphine suspension, or modified-release (MR) morphine. One breathlessness service describes weekly up-titration of morphine, starting at 1 mg IR morphine daily, to a maximum of 5 mg MR morphine 12 hourly [17]. The usual morphine adverse effects (constipation, initial drowsiness, and nausea) may well be encountered. Parenteral opioids are usually reserved for the end of life when the oral route is not appropriate. If the dose is started low and escalation appropriate, then respiratory depression should not be a problem in stable COPD, but intercurrent infection or other causes of exacerbations may interfere with this.

In patients already on morphine for pain, it is conventional to use short-acting morphine at the appropriate rescue dose for dyspnea as well. Towards the end of life, the equivalent subcutaneous dose is used.

Benzodiazepines

The use of benzodiazepines for the palliation of dyspnea is widespread, perhaps justified by the presence of accompanying fear or panic. A Cochrane review [18]

described eight randomized studies involving 214 patients with COPD or advanced cancer comparing benzodiazepines with placebo or other drugs. They concluded that there was no evidence for the beneficial effect of these drugs for either relief of breathlessness or prevention of episodic dyspnea in these conditions.

Despite this, review articles do suggest the use of benzodiazepines as a second-line option, particularly in the presence of distress and anxiety [17, 18].

Dosing schedules suggested as follows:

1. Dyspnea associated with panic, requiring rapid palliation: lorazepam 500 μg–1 mg sublingually or midazolam 2.5 mg subcutaneous.
2. End-of-life respiratory palliation: midazolam 5–10 mg/24-h continuous subcutaneous infusion titrated upward as necessary.

Non-pharmacological Management of Breathlessness

Introduction

Non-pharmacological strategies are very varied in nature. Some are techniques taught by the professional to encourage self-management by the patient, for example breathing retraining. Others require direct input from the therapist, such as acupuncture. A third group are those where a piece of equipment provides the therapy, such as handheld fans, which are self-administered, or applied by the practitioner, such as chest wall vibration. The other variable is whether the intervention involves an exercise component. The non-exercise interventions are well evaluated in a Cochrane review from 2009 [19]. In this review, they are grouped as single- (stand-alone) or multicomponent.

Single-Component Interventions

These include acupuncture, distraction with music, and relaxation with pre-recorded tapes, which includes progressive muscle relaxation. Although these are widely used in the palliative care setting, the evidence for their efficacy is limited.

The use and benefit of walking aids as are prescribed by physiotherapists have been studied in COPD patients. These include walking sticks, frames, wheeled walkers, or a vehicle to carry things. Four out of six studies showed significant improvements in breathlessness.

Two more complex interventions are chest wall vibration (CWV) and neuromuscular electrical stimulation (NMES). CWV involves the application of vibrators bilaterally to the chest wall or an inflatable vest connected to an air pulse generator for 3–5 min. It was concluded that there was evidence of benefit in the COPD patients studied, but not those with motor neuron disease [19]. The problem with this approach is the complexity of the technique, need for expensive equipment, and lack of evidence of longer term benefit. In NMES, a portable NME stimulator is applied to the leg muscles (quadriceps, hamstring, and calf) and they are stimulated for 15–30 min/day for 3–5 days/week for 6 weeks. The studies demonstrated an improvement in quadriceps strength, symptoms, and walking distance in the COPD

patients included at the end of the treatment period [20]. The intervention was well tolerated. Whether NMES is a practical option for those patients unable to undertake conventional exercise programs as in pulmonary rehabilitation remains to be seen.

The beneficial effect of cool air blowing across the face has been known to COPD and other breathless patients for a long time. The mechanism is thought to be stimulation of the nasal and oral mucosa by cold air. Many patients will describe the need to stand by an open window or door or have discovered the benefit of fans themselves. A study with a handheld fan held close to the face [21] showed a significant improvement in breathlessness as measured by a visual analogue scale over control (fan directed at the leg). The authors state: "The use of a handheld fan is an inexpensive, non-invasive, patient-directed, safe, practical technique for managing breathlessness in any setting."

Anxiety is an important symptom that warrants attention in its own right. Anxiety is however so intimately intertwined with the sensation of breathlessness that it should also be considered in the management of the breathless patient. Not being able to breathe is just about the most terrifying sensation a human being can experience. Acute severe breathlessness can trigger a very real sense of imminent death. The link between the sudden realization that "I can't breathe" and "panic" is hardwired in the human brain. When describing previous episodes patients will offer reports such as "I thought I was breathing my last."

Though anxiety is a normal and entirely understandable response to severe breathlessness, it is never helpful. Breathlessness leads to anxiety, anxiety leads to an abnormal breathing pattern (breathing becomes more rapid and more shallow and occurs at a higher lung volume), and this abnormal pattern serves to heighten the sensation of breathlessness, which fuels further anxiety; very quickly a vicious circle ensues. On occasions this spirals out of control into a full-blown "panic attack." Controlling anxiety is therefore an important component of managing the breathlessness. Psychological interventions, such as cognitive behavioral therapy, may be very effective in this context [22].

Multicomponent Interventions

Multicomponent interventions can be subdivided into those that contain an exercise component and those that do not. The best documented example of the former is pulmonary rehabilitation, which is a central component in the management of COPD. Exercise programs have also been used in other chronic lung diseases and chronic heart disease. Although exercise is not a component of the type of multicomponent intervention described by Corner [23], there is no reason why patients with cancer-related dyspnea who are able to undertake the type of exercise in pulmonary rehabilitation should not do so.

Multicomponent Interventions: Without Exercise

The interventions included in these programs are listed below. Different programs will include different combinations of them [20]. The supervision may be by a nurse, physiotherapist, or multi-professional.

- Assessment involves understanding the cause of the breathlessness and the factors that make it better or worse.
- Counseling and support are difficult to define. It should include attention to physical and emotional issues, and advice may be verbal or written. The interaction may be in the clinic or the patient's home.
- Breathing retraining encourages diaphragmatic breathing and other techniques to ensure breathing at a lower functional residual capacity (more efficient).
- Energy conservation, goal setting, and lifestyle adaptation.
- Relaxation and stress management.
- Psychotherapy.

Corner's program was nurse led and included weekly sessions over 3–6 weeks. Sessions included counseling, breathing retraining, relaxation, and coping and adaptation strategies. Twenty lung cancer patients were randomized to either receive the program or follow up as a control group. There were improvements in median scores for breathlessness, distress due to breathlessness, functional capacity, and ability to perform activities of daily living in the treatment group compared with the control. These improvements were seen at 4 and 12 weeks after entry to the study. No improvement in anxiety or depression was seen. This led to a multicenter study of a similar nurse-led intervention [24]. One-hundred and nineteen patients were randomized; there were significant improvements at 8 weeks in breathlessness at best, WHO performance status, levels of depression and distress, and breathlessness from the Rotterdam symptom checklist.

These early studies of Corner [23] and Bredin [24] have led to the development of multicomponent lung cancer dyspnea programs in many centers. It has been observed however that not all patients need all of the components of the program [25]. It is suggested therefore that the program needs to be tailored to the individual and his/her needs.

One of the problems of such studies is that most of the patients have a poor prognosis and many symptoms will be deteriorating from week to week so there will be a considerable dropout rate, making quantitative assessment of benefit difficult. An alternative approach is a qualitative assessment by semi-structured interview and analysis of common key themes. Wood [26] performed such a study in nine patients with advanced intrathoracic malignancy (six mesothelioma and three lung cancer). The major themes identified were:

1. Recognition of need but mixed expectations
2. A personally tailored program
3. The personal touch and attributes of the therapist
4. Specific changes in coping achieved
5. The global impact of the program
6. Difficulties and barriers to achieving change
7. Facing the uncertainties of the future beyond the program

The improvements in breathing control and activity management along with the qualities of the therapist led to improved functional capacity, coping strategies, and self-control.

Pulmonary Rehabilitation

Pulmonary rehabilitation is "a multi-disciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize each patient's physical and social performance and autonomy. It is widely used for patients with COPD" [27]. The program will include incremental exercise (walking, treadmill, or cycle ergometer), arm and shoulder exercises, respiratory muscle training, breathing retraining, education, psychological and social support, and nutritional advice [28]. Pulmonary rehabilitation can take place in a variety of settings such as inpatient, outpatients, or in the community. A meta-analysis [29] showed significant improvements in the dyspnea, mastery, fatigue, and emotional function domains of the CRQ. The authors conclude: "rehabilitation relieves dyspnea and fatigue, improves emotional function and enhances patients' sense of control over their condition. These improvements are moderately large and clinically significant."

In summary, pulmonary rehabilitation is a well-researched and -documented intervention for the management of breathlessness in patients with chronic lung disease. It should be offered to all patients well enough to participate. More work needs to be done to assess the role of exercise in the management of cancer-related dyspnea.

Oxygen

Rational and safe use of oxygen is discussed in detail in the COPD chapter. However, oxygen is widely used in the palliative setting for the relief of dyspnea without an assessment of the oxygen saturation (SpO_2) or partial pressure of oxygen in arterial blood (PaO_2). In a double-blind trial [30], Abernethy compared breathlessness, measured on a numerical rating scale, in dyspneic patients with chronic lung disease (predominantly COPD). They were randomized to receive either oxygen or air by nasal cannula at 2 L/min for at least 15 h/day for 7 days. Breathlessness scores were repeated morning and evening throughout. There was no difference in the symptomatic benefit reported between the two groups. The important fact was that the mean PaO_2 of the oxygen group was 10.3 kPa and the air group, 10.1 kPa. In other words, the patients were not significantly hypoxemic. This confirms the long-held belief that supplemental oxygen does not benefit patients who are breathless but not hypoxic. In practice, we do not measure arterial blood gases, but rely on measuring SpO_2 by pulse oximetry. It is recommended that oxygen should not be offered to those patients whose SpO_2 is 90% or greater.

Carers and Their Needs

Whilst dyspnea causes considerable physical and emotional distress to the patient, it can also have a significant impact on the carers. This has been the subject of a qualitative study of ten lung cancer patients and ten COPD patients and their carers [31]. The authors commented that the patients developed stoical, philosophical coping strategies for living with their symptoms. Carers, on the other hand, felt anxious, preoccupied, and helpless in their role and needed support. Mostly this came from their general practitioner, or in the case of COPD patients the respiratory clinical nurse specialist.

Approach to the Breathless Patient

The next question is the timing of applying the various strategies for managing dyspnea that have been described. In general terms, the first step would be by treating the underlying cause (i.e., disease modification). If the patient is capable of it, then non-pharmacological interventions should be offered, including exercise-based programs if feasible. When the patient is not capable of exertion, or is breathless at rest, pharmacological treatment becomes more relevant. The problem with both opioids and benzodiazepines is that whilst they reduce the symptom and its emotional concomitants, the sedating side effects tend to reduce the desire for physical activity. Many components of the non-exercise programs are relevant at this time too. These include breathing control, energy conservation, stress management and relaxation, as well as use of fans. Oxygen may also be relevant.

As the end of life approaches, there will be increasing reliance on drug treatment with opioids and benzodiazepines, but fans may also still be relevant. Table 2.2 summarizes an approach to dyspnea management.

The American Thoracic Society statement on dyspnea [32] stresses the importance of detecting and relieving the underlying cause first, and then if possible addressing associated cardiovascular deconditioning (with exercise) before the physical and pharmacological interventions described above.

Breathlessness as a Prognosticator

One of the key components of the Gold Standards Framework is the identification of patients in the last 6–12 months of their life so that their palliative care needs can be identified and met, and indeed prognostic indicator guidance has been published [33]. Of the commoner respiratory diseases, COPD has proved one of the most difficult to predict. The severity of dyspnea is one of the components of most assessment tools [30, 31]. Sadly, the end-of-life trajectory for COPD is unpredictable and these tools are of limited practical use. Even when combined with other independent predictors of survival (body mass index, FEV_1, and exercise capacity), patients in the lowest quartile had a median survival of over 3 years [34].

Table 2.2 Outline of breathlessness management

1.	Identify mechanism and cause
2.	Treat (modify) underlying disease process as appropriate. This should be continued throughout until it is felt to be inappropriate
3.	Check SpO_2 at rest and exertion if relevant
4.	Exertion-related dyspnea: consider exercise-based program such as pulmonary rehabilitation
5.	Exertion-related dyspnea: unable to do exercise program, consider non-pharmacological multi-component program, not all components of the program may be needed
6.	Other options for exertional dyspnea:
	Walking aids
	Handheld fan
	Ambulatory oxygen if SpO_2 drops below 90% on exertion Codeine phosphate 15 mg twice daily
7.	Rest dyspnea, but stable Non-pharmacological multicomponent program, or parts of it
	Cognitive behavioral therapy if appropriate Fan: static or handheld
	Oxygen if SpO_2 less than 90%
	Escalating opioids and/or benzodiazepines as previously described
8.	End of life
	Fan
	Oxygen if SpO_2 less than 90%
	Sublingual lorazepam or subcutaneous midazolam
	Subcutaneous opioids

In cancer, a systematic review [35] identified a number of independent predictors of reduced survival in a total of 7089 patients. These were poor performance status, cognitive impairment, weight loss, dysphagia, anorexia, and dyspnea. The median survival of the patients in these studies ranged between 1.8 and 11 weeks.

Despite this, clinical experience suggests that as death approaches the symptom becomes less troublesome. This observation was confirmed in study of the prevalence of dyspnea in patients dying from cancer [36]. They found that as death approached the prevalence fell from 39% at referral to the palliative care team to 23% in the last week of life.

In summary, in chronic lung disease, whilst there is some correlation between severity of dyspnea and survival, its presence or severity cannot usefully be used to determine the approach of the end of life. However, palliation of a symptom should not be limited to the last year of life anyway.

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Hemoptysis

3

Bernard Higgins

Hemoptysis is an alarming symptom, and one which usually prompts the patient to seek medical attention. The majority of cases which a healthcare professional sees will therefore tend to be of small-volume hemoptysis and, while investigation to determine the cause is clearly appropriate, the symptom itself does not usually require immediate treatment other than reassurance.

This is not always the case. Some people find hemoptysis distressing even if the volume of blood loss is small. Furthermore, in a small but important number of cases, bleeding from intrapulmonary lesions can be more substantial. It is not possible to define a precise cutoff point at which hemoptysis definitely requires treatment since this depends on several factors including the respiratory and circulatory response of the patient, but the volume of blood loss may itself suggest a need for action. There is no universally accepted definition of major or massive hemoptysis, but many articles refer to a volume of >200 mL in 24 h. At this level treatment of the symptom in its own right is clearly appropriate.

In general terms hemoptysis is best treated by addressing the underlying cause. A huge variety of diseases can lead to hemoptysis. A small amount of blood in the sputum is not uncommon during the course of a simple respiratory tract infection, and other diseases which will be seen frequently in both primary care and by respiratory specialists will involve hemoptysis, including cardiac disease and bronchial carcinomas. However, hemoptysis can also be associated with a number of far less common conditions and the management of these varies hugely; for example, the approach to a patient bleeding from an arteriovenous malformation of the lung is very different to the management of a patient with

B. Higgins (✉)
Department of Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne, UK
e-mail: Bernard.Higgins@nuth.nhs.uk

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diffuse alveolar hemorrhage secondary to a vasculitic disease. It is clearly outside the scope of this chapter to list all these situations, still less to attempt to cover their specific management. The focus here is on those situations where it is necessary, for palliative reasons, to control significant hemoptysis with direct treatment to its source.

Blood Supply to the Lung

The pulmonary circulation is well described and familiar to most doctors. The main pulmonary artery arises from the right ventricle and divides below the aortic arch into right and left branches. Each of these then divides into upper and lower branches, and thereafter further subdivision follows a much more variable pattern. There are a further 15–20 orders of branching before the vessels become pulmonary arterioles which ultimately break up into the pulmonary capillaries which envelop the alveoli. In health, and in most diseases causing hemoptysis, this is a low-pressure circulation in comparison to the systemic arteries arising from the left ventricle. The pulmonary artery pressure may, however, be elevated in the context of chronic hypoxic lung disease. It is estimated that only 5% of clinically evident hemoptysis arises from the pulmonary circulation [1].

The more frequent anatomical source of significant hemoptysis is the bronchial arterial circulation. The right and left bronchial arteries usually arise from the descending aorta just below the left subclavian artery. The most common pattern sees two left-sided bronchial arteries and one common trunk on the right, but it is not unusual to find this situation in reverse, or a single stem on both sides, or two arteries on both sides [2]. Moreover the arteries can originate further down the descending aorta. To add to this variation, in a minority of healthy people the bronchial supply arises from arteries other than the aorta; aberrant vessels might arise directly from intercostal arteries, the internal mammary artery, or the brachiocephalic or the left subclavian arteries.

In any of these cases the bronchial arteries usually produce branches which follow the major airways with frequent smaller branches coming off the main vessels to create an anatomical vascular plexus in the adventitia of the bronchi, from which arterioles pass through the muscular layer and break up into capillaries in the submucosa. One particularly important aspect of the anatomical variation described above is that in some people the anterior spinal artery takes part of its supply from the bronchial arteries. This is important if clinicians are contemplating arresting bronchial bleeding by embolization of such a vessel since there is the risk of causing significant spinal cord damage. In a small number of cases hemoptysis is from neither the bronchial nor the pulmonary circulation as delineated above. When hemoptysis is associated with a pulmonary sequestration a totally aberrant arterial supply is to be expected. In addition, in cases of diffuse pulmonary hemorrhage, as in systemic vasculitis, blood loss is not associated with any particular anatomical site.

Management of Major Hemoptysis

Investigation

In the palliative setting the cause of large-volume bleeding will often be apparent since it is relatively unusual for massive hemoptysis to be the first presenting symptom in any disease process. When the relevant disease is known to be localized to a particular pulmonary lobe as, for example, in most lung tumors, management can move forward based on the reasonably safe assumption that the bleeding is from this site. However, in diseases such as bronchiectasis and cystic fibrosis where multiple areas of lung are involved, each of which may be the source of the hemoptysis, further investigation will be required to establish the site of bleeding. In the relatively small number of cases in which large-volume hemoptysis is the first presenting feature, the most useful investigation is usually computed tomography (CT). A review of 208 consecutive cases showed that CT alone established a likely diagnosis in 67% of cases [3]. The addition of fiber-optic bronchoscopy increased the yield to over 90%.

CT and bronchoscopy will also be of benefit in cases with diffuse disease in which it is necessary to localize the site of bleeding. A CT scan will show alveolar filling in cases of significant bleeding, and this will usually be more obvious in one segment of lung than another indicating that this is the likely source. Profuse hemorrhage can lead to shadowing scattered over several segments, but this is less typical. Bronchoscopy can also localize bleeding to a degree and even if it does not pinpoint a source due to profuse bleeding and obscured vision, it is often possible to at least identify the side responsible which is important if a procedure such as embolization is being considered [4].

Treatment

The sections which follow this deal with specific treatment modalities which might be used in cases of major hemoptysis, but it is pertinent to consider also the small number of patients with a truly massive, life-threatening hemorrhage who require immediate resuscitation and stabilization. Such patients are relatively rare even in large referral centers, and because of this, and because of the virtual impossibility of conducting trials in such extremely ill people, there is little formal evidence on which to base advice. Indeed, even consensus guidance is difficult because each case has unique features, and because comorbidity and overall prognosis determine what can, and what should, be done.

When a major blood vessel is eroded, bleeding may be catastrophic and rapidly fatal, and there is little to be done except to ensure that the patient is given medication such as benzodiazepines and opioids to relieve acute anxiety and breathlessness. If the patient survives the initial bleed, resuscitation is directed at maintaining the airway and circulatory volume. If there has been sufficient blood loss to produce

hypotension, fluid resuscitation and blood transfusion may be appropriate. Because these cases are infrequent we do not have the depth of experience available to our colleagues in gastrointestinal medicine who will see many patients with major upper gastrointestinal bleeding each year. Experience there is that overenthusiastic transfusion is deleterious and, while extrapolation from one disease system to another is not necessarily correct, it seems sensible to exercise similar caution in cases of hemoptysis. Administration of supplemental oxygen is sensible when required, aiming to treat to a target oxygenation value [5].

In centers with the available expertise, it may be possible to provide beneficial treatment via a rigid bronchoscope. Such centers will usually be those with cardiothoracic surgery on site. The technique of inserting ice-cold saline into the segment responsible for blood loss with a bronchoscope inserted as tightly as possible into the segmental bronchial orifice has been described, as has the use of bronchial balloon tamponade [6, 7]. Balloon tamponade has also been described via a fiber-optic bronchoscope but the poorer direct vision and the relatively restricted aspiration abilities of the fiber-optic scope make this far less attractive, and generally speaking attempts to staunch bleeding via the fiber-optic bronchoscope are unlikely to succeed in a truly massive hemoptysis [8]. Where the relevant anesthetic expertise is available it may also be possible to control bleeding, or to buy time by maintaining oxygenation, by using selective endotracheal intubation of the right or left main bronchus.

The ultimate treatment when all else fails is to remove the segment from which the bleeding emanates. This may be a suitable option in a patient with a good overall prognosis, but is rarely appropriate in the palliative care setting of advanced lung disease. The majority of patients presenting with massive hemoptysis will not be suitable for such invasive management. A treatment decision in this group of patients will clearly be easier when the person is previously known to the clinical team, but in all cases it is important at as early a stage as possible to agree what ceiling of treatment should be applied. In many cases sedation with intravenous opioids or benzodiazepines is more appropriate than taking an aggressive surgical route.

Specific Therapy for Hemoptysis

Radiotherapy

External beam radiotherapy is long established as a useful mode of treatment in lung cancer. The overall value of radiotherapy in the treatment of lung cancer is dealt with in Chap. 7. Most studies which have assessed the palliative benefits of radiotherapy have reported the combined benefit on a range of symptoms. However, where the individual response rate of specific symptoms has been given, hemoptysis is usually seen to be one of those which respond most readily. This has been the case in older studies such as the Medical Research Council study in 1991, and is still seen in more recent publications of large case series [9, 10]. It is not clear within these studies whether there is any systematic difference in response rates between

tumor types, nor whether the initial severity of hemoptysis predicts the response. Intuitively one would expect cases with brisker bleeding to show benefit less readily, but moderately large-volume hemoptysis can respond completely to a course of radiotherapy. Treating patients in whom hemoptysis is the predominant symptom has been shown to be of benefit in terms of improving the overall quality of life [11].

Different radiotherapy regimens have been compared. The generally accepted principle in palliative work for lung cancer is to aim for the fewest fractions possible since this appears to be no less beneficial, reduces the risks of side effects, and reduces the time that patients with a limited life expectancy need to spend on hospital visits [12]. Although radiotherapy is essentially employed as a treatment of malignant conditions, there are a small number of case reports of its use in other circumstances. Cases of hemoptysis due to mycetoma and mediastinal fibrosis have been treated successfully with radiotherapy [13–15]. Of note, these patients were described as having life-threatening hemoptysis, not simply small-volume self-limiting bleeding.

Brachytherapy

The term "radiotherapy" is usually applied to radiation treatment administered via an external source. Treatment can also be given by positioning a radioactive source inside a body cavity close to the tumor, which in the case of the lung involves placing a source within the affected bronchus. This is known as intraluminal radiotherapy or brachytherapy. Brachytherapy is carried out as part of an extended fiber-optic bronchoscopy procedure. Under light sedation a flexible catheter with a closed distal end is inserted through the biopsy channel of the bronchoscope, and is advanced across the area of tumor. A radio-opaque marker is threaded down this catheter which is held in position while the bronchoscope is removed. A chest radiograph is then taken and the marker used to calculate the precise length of the catheter tube over which radiation can impact the tumor. The marker is then withdrawn, and a small, highly radioactive source of iridium-192 welded to the end of a steel cable is passed down the catheter to deliver the radiation dose. It is shielded for most of its journey but is controlled by a computerized after-loader which exposes the source when it is in the appropriate position along the catheter. Because the strength of the source is known, its "dwell time" can be programmed over each 5 mm of the exposed area to allow precisely calculated doses of radiation to be delivered to the tumor.

There was initial hope that this elegant procedure might provide the benefits of radiotherapy treatment with fewer side effects. Unfortunately this does not seem to be the case. Although trials are not entirely consistent, external radiotherapy appears to provide better symptom control [16]. However, control of symptoms including hemoptysis can be achieved with brachytherapy, and one systematic review suggested that palliation with brachytherapy plus external beam treatment is superior to external beam radiation alone although this conclusion was not specific to hemoptysis [17]. Another reason that brachytherapy is not commonly employed is that

there is a measurable incidence of massive hemoptysis, including fatality, after brachytherapy and probably caused by it. It is thought that this is mostly likely when the radioactive source has been lying directly against the bronchial mucosa or when an area close to a major blood vessel has been treated [18].

Because of these factors intraluminal radiotherapy is not widely used in treating lung cancer but it does have one noteworthy advantage. Brachytherapy can be used in previously irradiated patients who have recurrence of symptoms including hemoptysis in situations where further conventional radiotherapy is not feasible because of dose thresholds. In one study of 270 patients with recurrent endobronchial disease after primary treatment, their response rate to brachytherapy for those with hemoptysis was 92% [19]. Brachytherapy may therefore be of particular value in this "second-line" role.

Bronchoscopic Therapy

There are a number of treatment modalities which can be deployed directly via a bronchoscope to treat hemoptysis when the symptom is caused by endobronchial disease. In general these have been applied in the lung to malignant lesions, and their use has been restricted to a few centers.

- Bronchoscopically visible tumor causing hemoptysis has been successfully treated using the Nd:YAG laser (neodymium:yttrium aluminum garnet laser). An Australian study of 110 patients demonstrated beneficial effects on a number of symptoms, and once again the effect on hemoptysis was particularly marked with a 94% response rate [20]. However, symptom response was generally better if laser therapy was combined with other forms of treatment.
- Coagulation using jets of ionized argon gas (argon plasma coagulation, APC) has also been described [21]. APC is widely used in gastrointestinal work to control bleeding lesions. Its disadvantage is that it can only treat to a depth of a few millimeters.
- There are occasional reports of successful treatment of hemoptysis by placing silicone stents to effect tamponade of the bleeding site, but this is rarely feasible [22].
- Although cryotherapy has been used to treat bronchial tumors, I am not aware of any reported series in which it has been used for the treatment for hemoptysis.

Bronchial Artery Embolization

Whereas the techniques considered so far have involved attempts to stop bleeding via a bronchial approach, bronchial artery embolization attacks the problem by obstructing the vascular supply to the area of blood loss (Fig. 3.1). The procedure requires location of the bleeding vessel, and the variable origins of the bronchial

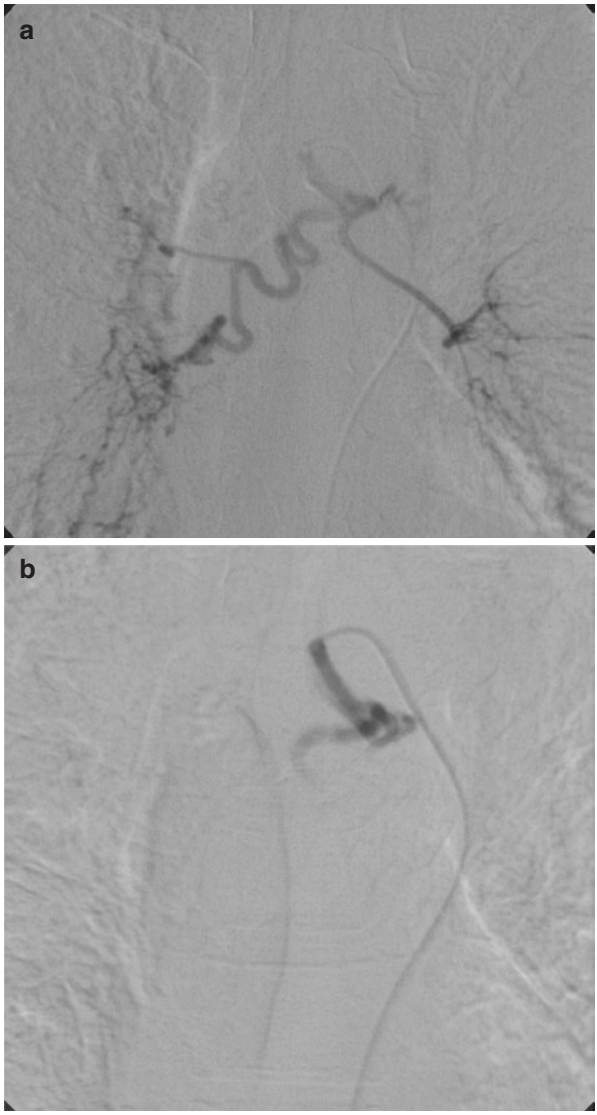

Fig. 3.1 Bronchial artery embolization. Bronchial arteriography showing an abnormal dilated bronchial artery (**a**) which was the source of massive hemoptysis. The bleeding was stopped by bronchial artery embolization which occluded the vessel (**b**)

arteries from the aorta can make this difficult, but an experienced operator can usually identify these reasonably swiftly. Once this has been done a bronchial arteriogram is performed. The expectation is not that this will allow direct visualization of bleeding with extravasation of contrast medium, as this is unusual. Rather, the operator hopes to identify an abnormal circulation such as a hypertrophied or tortuous vessel, or neovascularization of an area, any of which implies that this is the likely source of bleeding. The confidence in this conclusion is enhanced by the prior radiological or bronchoscopic identification of the likely responsible area.

AL GRAWANY

If the bronchial arteries have been identified and do not appear suspicious, a search must be made for another vascular supply. While the bronchial arteries themselves can arise from sites other than the aorta, areas of lung disease can also acquire a separate systemic, non-bronchial blood supply. These feeder vessels may arise from various sites including intercostal arteries, internal mammary, subclavian, or even axillary arteries. Once an abnormal circulation has been identified an embolic material is introduced via the catheter. Various materials are used including gelatine sponge, metal coils, liquid "glues" such as *N*-butyl cyanoacrylate, or polyvinyl alcohol particles. The choice will depend to some extent on the nature of the vessel to be occluded, but also to a large extent on the familiarity of the operator. There are no controlled comparisons of the available agents.

Several series have been published to demonstrate the effectiveness of embolization in managing major hemoptysis [23]. The case mix generally includes patients with cystic fibrosis, non-CF bronchiectasis, lung cancer (both primary and metastatic), aspergillomas, and, in series from some countries, patients with active tuberculosis. The immediate success rate is good, varying from 70 to 99%. However, most series also report a substantial recurrence rate varying with the duration of follow-up. For example, one Korean study of 108 patients, predominantly with non-malignant conditions, showed an immediate success rate of 97.2% but a decline in freedom from recurrence over time; non-recurrence rates were 91.4% at 1 month, 83.4% at 1 year, and 56.8% at 5 years [24]. Recurrence may be due to incomplete embolization, but more commonly to recanalization or to revascularization of the diseased area. The latter is more likely if the underlying disease cannot be controlled [25].

Hemoptysis can occasionally be a major problem in patients with cystic fibrosis, and several reports have focused on this group. Unsurprisingly the occurrence of major hemoptysis is associated with more severe disease, with a high incidence of multidrug-resistant bacterial cultures [26, 27]. The success rate of initial embolization was over 90% in these series, although some patients needed more than one procedure, perhaps because of a high rate of bleeding from non-bronchial systemic vessels [26]. However recurrence rates are also high and the prognosis of these patients with massive hemoptysis, without intervention via lung transplantation, is poor [26, 28].

The success rate of embolization has also been reported in an exclusively oncological population, most of whom had substantial blood loss (43% of the group had over 300 mL blood loss in 24 h) [29]. Hemoptysis could be controlled in most; 89% had either a cessation or a definite decrease in the degree of hemoptysis. However, the cohort had a poor overall prognosis with a 30-day mortality of 30%.

Although immediate success rates from bronchial artery embolization are good, the procedure can have adverse effects. There may be bruising at the arterial puncture site. Chest pain is a common complication, presumed to be due to ischemia of the chest wall because of involvement of the intercostal arterial supply; this is almost always short lived. Dysphagia has also been reported because of involvement of esophageal branches, and again it is transient and self-limiting. The complication of greatest concern is spinal cord ischemia. The incidence of this varies

between series but is generally low [30]. Visualization of the anterior spinal artery at the preliminary arteriogram should preclude embolization of that vessel.

Antifibrinolytic Agents

Tranexamic acid is a synthetic derivative of lysine and acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin. It is used to treat menorrhagia and its efficacy in treating trauma victims has also been demonstrated. It is widely used in an attempt to reduce major hemoptysis, particularly while other measures are being organized. However, although this has been common practice for years, there is surprisingly little formal evidence of benefit. The only formal trial of oral tranexamic acid of which I am aware randomized just 46 patients with hemoptysis of variable cause to either tranexamic acid or placebo and failed to demonstrate any benefit in terms of reducing blood loss or shortening the duration of hemoptysis [31]. However, this trial can be criticized in a number of ways, and in particular the patient group were atypical of those in whom tranexamic acid would usually be employed in that the degree of hemoptysis was modest in many of them. Moreover, in a significant proportion of those studied no underlying lung disease was identified (although investigation was not extensive). A recent double-blind, randomized controlled trial looked at nebulized tranexamic acid and showed that bleeding had stopped within 5 days in more subjects than in the placebo (nebulized saline) arm [32]. Nebulized tranexamic acid is not widely available, and it should be noted that this study excluded people with massive hemoptysis.

Anecdotally most physicians who deal frequently with hemoptysis believe that tranexamic acid has a role and will remember patients whose hemoptysis has recurred and improved in timing with the cessation and reintroduction of tranexamic acid. Despite the lack of firm evidence the use of tranexamic acid can be recommended as a holding procedure in cases of major hemoptysis. The usual dose used is 1 g three times daily orally or 500 mg–1 g by slow intravenous injection (over 5–10 min) three time daily or 25–50 mg/kg by intravenous infusion over 24 h. Etamsylate, 500 mg four times daily orally, is an alternative agent with an unknown mechanism of action, although it is believed to work by altering the permeability of the capillary wall and possibly by promoting platelet aggregation. There is even less evidence for its benefit in hemoptysis than there is for tranexamic acid.

Reversal of Abnormal Coagulation

Occasionally hemoptysis is caused or significantly exacerbated by abnormalities of the coagulation system. In the palliative care context this is not common, but will be seen in a proportion of patients who require treatment with warfarin for some other condition. In patients with persistent low- or modest-volume hemoptysis, the question of whether anticoagulation should be stopped will depend on an individual risk assessment which must take into account the reason for starting anticoagulation.

When hemoptysis is more substantial, and certainly when life threatening, it is undoubtedly appropriate to stop anticoagulation and even to consider the use of prothrombin complex concentrates. The use of fresh frozen plasma may also be appropriate.

Patients receiving chemotherapy may present with significant hemoptysis and low platelet counts. If bleeding cannot be controlled and platelet count is below 50×10^9/L, it may be necessary to offer platelet transfusion. Among the commonest pharmaceutical agents used by patients with hemoptysis is some form of antiplatelet therapy, such as aspirin or clopidogrel, since these are in widespread use for primary and secondary prevention of atherosclerotic diseases. Again, decisions about stopping these drugs are based on an individual assessment of risk. There are no clinical trials to guide the decision in patients with hemoptysis, although one interesting study in patients with upper gastrointestinal bleeding showed an increase in mortality if antiplatelet agents were stopped beyond the immediate period in which treatment to the bleeding source was carried out [33]. These patients were taking aspirin for secondary prevention of known cardiovascular disease. This is clearly indirect evidence, but it would be reasonable to stop antiplatelet agents briefly in cases of major hemoptysis and to restart them once the bleeding is controlled, where there is a good indication for their use.

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Cough and Respiratory Secretions

4

Rachel Quibell and Stephen J. Bourke

Cough is a normal physiological response to airway irritation. It plays a fundamental role in protecting the lungs from inhaled materials and in clearing airway secretions. Cough is also a troublesome symptom which is very common in advanced lung disease. It may be productive of secretions and therefore of physiological benefit to the patient, or nonproductive in which case it serves no physiological purpose. In palliative care management of cough involves balancing the positive effects of cough in clearing secretions and the negative effects of the distress persistent coughing can cause. In the circumstances of a productive cough the goal of treatment is usually to increase the effectiveness of the cough in clearing secretions. This is particularly the case in chronic suppurative lung diseases such as bronchiectasis, cystic fibrosis, and advanced chronic obstructive pulmonary disease (COPD). In neuromuscular disease failure to clear secretions results in distressing symptoms with a sensation of congestion, rattle, or choking, and predisposes to pneumonia and respiratory failure. Techniques which enhance the clearing of secretions can provide symptom relief and reduce the risk of complications. In patients with a dry nonproductive cough, suppression of the cough is desirable as persistent coughing has a substantial negative impact on health, daily activities, and quality of life, and can give rise to secondary symptoms such as retching, pain, headache, sleep disturbance, urinary incontinence, and exhaustion. Each situation requires careful assessment and specific treatment targeted at the particular circumstances of the individual patient.

R. Quibell
Department of Palliative Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

S. J. Bourke (✉)
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: stephen.bourke@nuth.nhs.uk

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Mechanisms of Cough

Direct stimulation of the larynx provokes an immediate expiratory effort as an "expiration reflex," which acts to expel an inhaled foreign body. This reflex does not include an inspiratory phase which would tend to suck material into the lungs. For example, inserting a bronchoscope through the vocal cords in a conscious patient provokes this expiration reflex which can be ameliorated by numbing the sensory pathways by applying lidocaine to the vocal cords. The expiration reflex is a true reflex which is not amenable to voluntary control. In contrast classic cough involves a complex reflex arc usually initiated by stimulation of airway receptors transmitting signals via an afferent sensory pathway in the vagus nerve to a "cough center" in the medulla oblongata, with motor efferent pathways to the muscles of respiration [1, 2]. However this reflex is also subject to significant central control from higher cerebral centers such that a cough can be initiated when a patient is asked to cough and can also to some extent be suppressed by volition. A classic cough begins with an inspiratory phase before a forced expiratory maneuver, initially against a closed glottis, followed by expulsion of air on glottic opening. An effective cough generates a column of expired air moving rapidly through the bronchial tree dislodging mucus and material from the bronchial mucosa and propelling it outwards from the lungs. The first phase is a full inspiration to a high lung volume. The second is a compressive phase and this occurs when the glottis closes for about 0.2 s, during which there is contraction of the thoracic and abdominal muscles against a fixed diaphragm with rising intrathoracic and intra-abdominal pressure. The third phase is an expiratory phase with rapid expulsion of air when the glottis opens. During vigorous coughing intrathoracic pressures of up to 300 mmHg and expiratory velocities of up to 500 miles/h may be generated. Cough acts to clear the airway when there are large amounts of mucus due to excessive secretions or impaired mucociliary clearance. The removal of secretions is dependent on the shearing force produced by the airstream and the viscosity of the mucus. An ineffective cough predisposes to aspiration pneumonia and the accumulation of secretions in the airways can also cause breathlessness, rattle, and a sensation of chest tightness and congestion. The effectiveness of cough depends on several factors, including the patency of the airways, bronchial collapsibility, lung volumes, glottic closure mechanisms, respiratory muscle strength, and amount and viscosity of mucus. Patients with neuromuscular disease, such as motor neuron disease/amyotrophic lateral sclerosis or muscular dystrophy, who have inspiratory muscle weakness, will inhale only a small volume of air, but inspiratory muscle weakness must be severe before it affects cough. In contrast, expiratory muscle weakness may have a more profound effect as mild to moderate degrees of expiratory muscle weakness affect the expiratory pressures, airflow, and cough effectiveness. Paralysis of a vocal cord such as occurs in recurrent laryngeal nerve palsy results in a "bovine cough" with hoarseness. The inability to adduct the vocal cords during the compressive phase of the cough mechanism limits the expulsive effect resulting in a weak nonexplosive cough, giving a prolonged wheezing effect like that of a cow, since bovine vocal folds lack elasticity compared to humans.

The anatomy and neurophysiology of cough are complex and incompletely understood. Studies have mainly been performed in animals and results may not always be transferable to humans. Cough is usually triggered by physical and chemical stimuli which activate receptors in the upper and lower airways, pleura, pericardium, and esophagus [1]. The sensory impulses are then carried centrally to the brain stem via the vagus nerve. In some people cough can also be provoked by stimulation of the posteroinferior area of the auditory canal and tympanic membrane, which is innervated by the auricular branch of the vagus nerve (Arnold nerve). This is referred to as the "ear-cough" reflex or Arnold nerve reflex, and is present in about 25% of adults with chronic cough and about 2% of healthy adults [3]. Motor impulses are transmitted to the effector muscles which include the diaphragm, abdominal, intercostal, back, and laryngeal muscles. It is thought that rapidly adapting "stretch" or "irritant" receptors and C-fiber receptors are important, and the type 1 vanilloid receptor may be the primary sensory mechanism in cough in humans [4]. Receptor responses can be augmented by inflammatory mediators, including histamine, prostaglandin E2, and cysteinyl leukotrienes. Angiotensin-converting enzyme inhibitor drugs, such as lisinopril, often increase cough sensitivity as they reduce the degradation of protussive inflammatory mediators. Cortical input from higher centers can initiate or suppress cough. There may be different patterns of cough from different stimuli arising in different parts of the respiratory tract. A better understanding of the receptors and mechanisms involved in cough might lead to new improved treatments.

The compressive and expiratory phases of cough are a modified Valsalva maneuver and the high pressures generated can be transmitted throughout the body and give rise to additional problems such as urinary incontinence, rib fractures, musculoskeletal pain, pneumothorax, cough syncope, headaches, arterial hypotension, cardiac arrhythmias, and subconjunctival hemorrhage. Persistent coughing can be exhausting.

Cough Hypersensitivity

The concept of "cough hypersensitivity" has developed as a clinically useful paradigm which particularly applies to patients with a chronic dry, nonproductive cough which persists despite treatment of any inciting cause or underlying disease [5–9]. It is a disorder characterized by troublesome coughing triggered by low levels of thermal, mechanical, or chemical exposures which wouldn't normally provoke cough. It is thought to be an enhanced somatosensory response arising from hypersensitivity of airway sensory nerves. Patients report a sensation of an irritation in the throat with an urge to cough, and cough is triggered by minor exposures to environmental irritants, temperature changes, perfume odors, talking, or laughing, and with swallowing dry crumbly food for example [8]. The hyperexcitability of the neuronal pathways can be measured by challenge testing with inhaled irritants such as capsaicin. These patients demonstrate a heightened cough response and a reduced ability to voluntarily suppress cough. It is thought that there may be mechanisms of

neuronal activation, sensitization, and dysfunction which may be common to several different underlying conditions. Evidence from animal studies and some clinical research in humans shows that peripheral inflammation lowers the threshold of sensory cough fibers in the airways and increases sensitivity to stimuli. Inflammatory mediators for this sensory neuropathy include prostanoids, leukotrienes, oxidants, and adenosine triphosphate derived from immune cells or from epithelial damage. Some of these mediators act on ion channels in cough receptors such as the transient receptor potential (TRP) family of channels and voltage-gated sodium channels [9]. Mediators, such as neurotrophin nerve growth factor and brain-derived neurotrophic factor, can induce changes in sensory neurons driving cough hypersensitivity. Dysregulation of sensory nerves may also be accompanied by augmented central processing. There are similarities in the neurobiology of cough and pain, where it is recognized that patients may experience excessive pain from minor painful stimuli (hyperalgesia) and from non-painful stimuli (allodynia). Patients with cough hypersensitivity similarly demonstrate an excessive cough response to tussive stimuli (capsaicin, odors, smoke) as "hypertussia" and to non-tussive stimuli such as talking or laughing as "allotussia." Recent functional magnetic resonance imaging studies have also shown increased activation in the cortical and brain stem centers of patients with cough and these may be important in the control of the descending motor pathways that promote or inhibit cough [6].

Measurement of Cough

A variety of validated techniques have been developed to measure different aspects of cough such as cough frequency, severity, sensitivity, and impact [10]. Electronic acoustic or video recording devices can measure the frequency of cough. Visual analogue scales can be useful as a patient-reported outcome to define the patient's perception of the severity of cough. The Leicester cough questionnaire and cough-specific quality-of-life questionnaires can measure the impact cough is having on the patient's life [11]. The cough response to inhalation challenges with capsaicin or citric acid measures cough hypersensitivity. The multidimensional nature of the impact of cough may manifest as anxiety and depression which can be measured using scales such as the hospital anxiety and depression scale (HADS). The different tools measure different aspects of cough and provide a comprehensive overall measurement of the problem. They have mainly been used in clinical research studies but may also be helpful in the assessment of patients with troublesome cough and in the evaluation of the response to treatment.

Cough in Lung Disease

Acute cough is one of the most common respiratory symptoms presenting to general practice [12]. It often occurs after an upper respiratory tract infection and is self-limiting and does not require treatment. Exclusion of more serious disease,

such as pneumonia or lung cancer, and reassurance are all that is needed. Chronic cough can occur with almost any lung disease and assessment and management of the specific disease are essential. An isolated chronic cough in the absence of apparent intrinsic lung disease is most often attributed to gastroesophageal reflux, rhinosinusitis (upper airway cough syndrome), and asthma or eosinophilic bronchitis. Chronic cough under these circumstances can be distressing and can have a significant impact on quality of life. Treatment is directed at the likely cause of the chronic cough with therapeutic trials of proton pump inhibitors for gastroesophageal reflux, antihistamines and nasal corticosteroid inhalers for rhinosinusitis, and inhaled corticosteroids for asthma or eosinophilic bronchitis.

In the palliative care of advanced respiratory disease cough is a common symptom but its significance may be masked by the dominance of other symptoms. In patients with lung cancer a study of the pattern of symptoms and the efficacy of symptom relief showed that almost 80% of patients had cough at presentation, and in half of these the cough was graded as moderate or severe [13, 14]. Throughout the palliative course of the disease cough persisted and was not fully suppressed by palliative treatments. In these patients symptoms such as hemoptysis and chest pain were relatively well palliated whereas cough and breathlessness were more difficult to control. Radiotherapy can be particularly effective in improving cough in patients with endobronchial tumors where this treatment is appropriate. Bronchorrhea, in which there is hypersecretion of very large volumes of clear sputum, is a rare manifestation of multifocal lepidic adenocarcinoma (bronchioloalveolar carcinoma), and may respond to specific treatment with tyrosine kinase inhibitors such as gefitinib or erlotinib [15]. Although breathlessness is the dominant symptom in patients with idiopathic pulmonary fibrosis these patients often have cough with a markedly enhanced cough responsiveness to capsaicin challenge, although the precise mechanisms involved are uncertain [16]. Similar results are found in patients with lung fibrosis due to systemic sclerosis [17]. Chronic cough is one of the most common symptoms in patients with COPD, and these patients also have increased responsiveness to capsaicin challenge [18].

Chronic cough is an important symptom which has a substantial adverse effect on the quality of life [5]. It results in substantial physical and psychological morbidity. Quantitative assessment of cough in patients with cystic fibrosis using an ambulatory recording device showed that they had a median of 643 coughs per day (range 324–1569). The cough rate was substantially higher when awake than when asleep [19]. Even though patients were studied in a stable phase many had unremitting cough when awake, sometimes having more than 100 coughs/h. This level of coughing is distressing for patients and has an adverse effect on their daily activities, social interactions, and quality of life. It makes them avoid theaters, cinemas, lecture theaters, and other situations where their cough is embarrassing for them and irritating to others.

Chronic cough gives rise to secondary symptoms such as headaches, retching, vomiting, musculoskeletal pain, sleep disturbance, exhaustion, and urinary incontinence. Depression is common in patients with chronic cough and improvements in cough with treatment correlate significantly with improvement in depression scores

[20]. The mechanisms provoking cough in each of these diseases are very different and require a specific approach to treatment.

Clearance of Secretions (Table 4.1)

In the palliative care of many advanced respiratory diseases clearance of airway secretions is an important aspect of treatment. This is particularly the case in patients with cystic fibrosis and diffuse bronchiectasis, and in some patients with advanced COPD, where large volumes of sputum may overwhelm the mucociliary clearance mechanisms. Patients with ineffective cough due to neuromuscular diseases, such as motor neuron disease/amyotrophic lateral sclerosis or muscular dystrophy, are particularly vulnerable to retained airway secretions and pneumonia. Cough suppressants are not usually appropriate in these patients although they may be used at night in the palliative phases of the disease if cough is disturbing sleep.

In patients with copious sputum production and an effective cough the initial approach is to reverse or ameliorate the cause by use of specific treatments. In patients with cystic fibrosis or diffuse bronchiectasis a prolonged course of intravenous antibiotics is often the most effective measure in relieving symptoms even in end-stage disease, and may remain an appropriate treatment even in patients approaching death [21]. A number of mucolytic or mucokinetic drugs are used in specific diseases [22]. Nebulized 0.9% sodium chloride is sometimes used in patients with COPD or other lung diseases in an attempt to improve expectoration, although its effect is modest. Hypertonic 6–7% sodium chloride has been shown to be effective in patients with cystic fibrosis and diffuse bronchiectasis of other causes [22]. It improves hydration of the airway surface liquid and enhances sputum

Table 4.1 Nondrug interventions for cough and secretions

Airway clearance techniques
Forced expiratory technique (“huffing”)
Autogenic drainage
Active cycle of breathing
Postural drainage
Positive expiratory pressure devices
Chest wall oscillation devices
Cough assistance technique
Glossopharyngeal (“frog”) breathing
Manual cough assist (“thrust”)
In-exsufflation devices
Removal of secretions
Oropharyngeal suctioning
Patient positioning
Suppression of cough hypersensitivity
Speech and language therapy interventions
Physiotherapy exercises
Psychological and educational counselling

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clearance but it can provoke coughing which may be distressing and exhausting for patients with advanced disease. Hypertonic sodium chloride sometimes provokes bronchospasm so that patients may benefit from prior use of a bronchodilator drug such as salbutamol or terbutaline. Inhaled mannitol also improves mucociliary clearance in patients with bronchiectasis or cystic fibrosis [23]. It acts as an osmotic agent, drawing water into the airway mucosa. Dornase alfa (rhDNase) is widely used in all stages of cystic fibrosis but is not effective in bronchiectasis of other causes. The sputum of patients with cystic fibrosis is very viscous as a result of a high content of DNA derived from decaying neutrophils in the airway. DNase is an enzyme which cleaves this DNA, thereby reducing the viscosity of the sputum making it easier to expectorate [22]. Stopping smoking improves the symptom of cough in patients with chronic bronchitis and COPD [24]. Carbocisteine is a mucolytic drug which reduces the frequency of exacerbations in patients with COPD who have a chronic productive cough. Inhaled anticholinergic drugs such as ipratropium, tiotropium, glycopyrronium, or aclidinium may reduce mucus production although their effect on cough is not consistent.

In patients with suppurative lung disease clearance of secretions can be enhanced by a variety of specialist physiotherapy techniques and devices [25]. Cough is the natural mechanism for airway clearance. However in disease states collapse of the airways may occur during the high intrathoracic pressure phase of coughing, impairing the clearance of secretions. The forced expiratory technique ('huffing') consists of forced expirations without closure of the glottis, starting from mid-lung to low-lung volumes. It can be particularly effective in patients with bronchiectasis or cystic fibrosis as an alternative to coughing. Patients can be taught the forced expiratory technique to enhance clearance without excessive effort. Physiotherapy is an integral part of the long-term management of these patients. Airway clearance treatments aim to enhance removal of secretions, reduce the risk of bacterial infections, slow the progression of the disease, and also reduce symptoms such as cough and breathlessness. Some techniques such as chest wall percussion and vibration require the assistance of a caregiver while other techniques can be performed without assistance, giving patients independence in performing their own airway clearance. Autogenic drainage is a technique that uses controlled expiratory airflow during tidal breathing to mobilize secretions from the peripheral airways. The active cycle of breathing technique involves a cycle of breathing control, thoracic expansion exercises, and forced expiratory technique. A number of mechanical devices can assist in sputum clearance. These include positive expiratory pressure (PEP) masks, and oscillating PEP devices such as flutter, Acapella® or cornet devices, as well as high-frequency chest wall oscillation vests [25]. The acceptability of airway clearance techniques is crucial and patient preference must be taken into account. The amount of time and effort involved can infringe on daily activities and can add to the overall burden of treatment in patients with advanced lung disease. Specialist physiotherapist input is invaluable in devising an airway clearance regimen that suits the individual patient's needs.

In patients with neuromuscular disease cough becomes less effective as muscle weakness progresses. An effective cough requires a full inspiration, followed by

glottic closure and adequate expiratory muscle strength to generate a high intrathoracic pressure and high peak expiratory flow. Physiotherapy techniques for improving the effectiveness of cough in clearing secretions are crucial in the management of these patients [26, 27]. The inspiratory phase of cough normally fills the lungs to a high lung volume which optimizes the length-tension properties of the expiratory muscles and increases the lung elastic recoil pressure. In neuromuscular disease a poor inspiratory effort results in only a small volume of air being inhaled. Patients can be trained in techniques which increase lung inflation and augment cough effectiveness. Glossopharyngeal breathing ("frog breathing") involves the patient using the glottis and mouth muscles to gulp air into the pharynx and then propel it into the lungs. This technique relies on glottic closure or use of a one-way valve to "hold in" sequential breaths. Breath-stacking is a technique whereby the patient takes 2–3 consecutive breaths without exhaling. A mechanical ventilator or resuscitation bag can also be used to augment spontaneous breaths. These techniques increase lung inflation and therefore subsequent expiratory flow. Weakness of the expiratory muscles results in paradoxical outward motion of the abdomen with reduced expiratory flow during coughing. Manual compression of the upper abdomen and lower thorax ("manual thrust") can enhance cough flow rates and effectiveness. Mechanical means of assisting cough include insufflation-exsufflation devices. These deliver deep positive pressure insufflations followed immediately by application of a negative pressure to the airway opening during exsufflation. This enhances both the inspiratory phase of cough by increasing lung inflation and the expiratory phase by augmenting expiratory flow. However in patients with neuromuscular disease with bulbar palsy there is often a loss of coordination of the cough mechanism of inspiration, laryngeal opening, glottic closure, and expiration. Laryngoscopy studies have shown that these patients often demonstrate adduction of the aryepiglottic folds on insufflation and constriction of the hypopharynx during exsufflation. This limits the effectiveness of treatment and may be distressing for patients. Careful titration of pressures and settings may be helpful, starting with low insufflation pressures and longer insufflation times with gradual increase in the settings to tolerance and efficacy [28].

Cough Suppression (Table 4.2)

When a patient continues to have a distressing cough despite treatment of the underlying disease, a combination of pharmacological and non-pharmacological interventions can ameliorate cough severity, cough frequency, and impact of cough on quality of life. Of the drug treatments opioids and gabapentin are the most effective but can be associated with undesirable adverse effects [29, 30]. Codeine, 15–30 mg 3–4 times daily, is a weak opioid which has some cough-suppressant effect [24]. It is widely used in clinical practice but results are often disappointing and adverse effects such as constipation are common. Pholcodine, 10 mg 3–4 times daily, has similar efficacy but may be less constipating. Strong opioids such as morphine, methadone, oxycodone, and fentanyl all suppress cough but their use can be limited

Table 4.2 Drugs for cough and secretions

Cough enhancement
Nebulized 0.9% sodium chloride 5 mL 4 times daily
Nebulized hypertonic (6–7%) sodium chloride twice daily (bronchiectasis/cystic fibrosis)
Nebulized dornase alfa (rhDNase) 2.5 mg once daily (cystic fibrosis only)
Carbocisteine (capsules or suspension) 750 mg orally 3 times daily
Central cough suppressants
Codeine linctus 15 mg (5 mL) orally 4 times daily
Morphine oral solution 2.5–5 mg 4 hourly
Methadone linctus 2 mg (5 mL) orally 12 hourly
Gabapentin 300 mg daily, increasing to 900 mg twice daily
Peripheral cough suppressants
Simple linctus 5 mL orally 4 times daily
Removal of secretions
Glycopyrronium bromide 200 μg 4–8 hourly
Hyoscine hydrobromide 150–300 μg orally 3 times daily
Hyoscine hydrobromide transdermal patch 1 mg/72 h
Death rattle
Hyoscine butylbromide 20 mg subcutaneously 4–8 hourly or subcutaneous infusion 60–120 mg/24 h
Hyoscine hydrobromide 400 μg 4–8 hourly subcutaneously or subcutaneous infusion 1.2–2.4 mg/24 h
Glycopyrronium bromide 200 μg subcutaneously 4 hourly or subcutaneous infusion 600–1200 μg/24 h

by adverse effects of sedation and constipation. A randomized double-blind placebo control study of morphine sulfate in patients with isolated chronic cough without apparent lung disease showed a significant benefit [29]. Patients were started on morphine sulfate 5 mg twice daily, and the dose was increased to 10 mg twice daily if cough control was not adequate. This low dose of morphine was effective in suppressing cough and was well tolerated. No patient had to discontinue treatment although 40% developed constipation and 25% drowsiness, which was usually transient. Methadone is sometimes used to suppress cough at night because of its long duration of action but there is a risk of accumulation of the drug because of its long half-life. In the advanced stage of many respiratory diseases patients may already be receiving opioids for other symptoms such as pain or breathlessness. Opioids act centrally in the brain stem in suppressing cough although some studies in animals suggest that inhibition of peripheral cough receptors in the airways may also occur [31]. Centrally acting neuromodulators, including gabapentin, pregabalin, amitriptyline, and baclofen, also act on the heightened neural sensitization that is involved in cough [5, 30]. Gabapentin is usually started at a dose of 300 mg daily, and gradually increased to a maximum of 900 mg twice daily, if well tolerated.

Many proprietary medicines are sold for the treatment of cough [32]. These contain a number of agents including demulcents, eucalyptus oil, moguisteine, benzonatate, and menthol, which may have a peripheral mechanism of action on cough

receptors in the airways [14, 24]. Menthol has been shown to reduce cough in normal subjects undergoing a cough challenge study. Benzonatate is chemically related to anesthetic agents and acts peripherally by anesthetizing the stretch receptors in the airways. There are reports of its benefit in some patients but it is not licensed for use in the UK. Simple linctus 5 mL 3–4 times daily is a commonly used demulcent which some patients find soothing for a dry irritating cough. In general the evidence of the effectiveness of proprietary medicines for cough is weak. In the palliative care of advanced-stage disease a number of other drugs have occasionally been used in an attempt to suppress intractable cough. Nebulized 2% lidocaine 5 mL may be effective in patients with severe cough near the end of life but should be used with caution as it can cause bronchospasm or impair swallow [33]. Inhaled sodium cromoglycate has been shown to reduce cough in patients with lung cancer and idiopathic pulmonary fibrosis [34].

Although the evidence is judged to be weak, expert guidance recommends a combined stepwise approach to treating cough, starting with disease-directed treatment first; cessation of drugs which can exacerbate cough (for example, angiotensin-converting enzyme inhibitors); management of coexisting causes of cough such as asthma, rhinitis, and gastroesophageal reflux; then use of cough suppressants such as simple linctus; and then trials of sodium cromoglycate, opioids or gabapentin, before considering experimental options such as carbamazepine, thalidomide, or nebulized lidocaine [14, 35]. Cough-suppressant drugs can be combined with non-pharmacological multidisciplinary adjunctive therapies and vocal cord hygiene techniques.

Most current cough-suppressant drugs have limited efficacy and undesirable adverse effects and there is a need for new agents. Research into better treatments is focused on an understanding of the receptors and neuronal pathways involved in cough, using voltage-gated sodium channel blockers, transient receptor potential channel blockers, neurokinin antagonists, and purinergic antagonists [9]. However the mechanisms underlying cough are complex and incompletely understood. Translating preclinical animal studies to effective clinical treatments has so far been disappointing.

Non-pharmacological Suppression of Cough

A behavioral approach involving multidisciplinary input by physiotherapists and speech and language therapists may be helpful in modulating cough. This involves education about the nature of cough, the lack of physiological benefit of a dry cough, and the nature of cough hypersensitivity. Patients are encouraged to exert some voluntary control of cough [36]. They are taught to recognize their cough triggers and to use cough suppression or distraction techniques to reduce the urge to cough. They can substitute a forced swallow or sip water or suck on sweets to sooth the urge to cough. Attention is paid to laryngeal hygiene and hydration. Breathing

exercises encourage nasal, rather than mouth, breathing and promote a relaxed abdominal breathing pattern or pursed lip breathing to control cough. Mindfulness meditation has also been shown to reduce cough reflex hypersensitivity [37]. This involves teaching the patient to develop a moment-to-moment awareness of thoughts, feelings, and sensations with stress reduction and integration of coping strategies to reduce the urge to cough. Psychology counselling can also help promote behavior modification to reduce the over-awareness of the need to cough, and to manage any associated anxiety or depression. In some diseases cough can be accompanied by the fear that as the disease progresses patients may experience choking, and that they may choke to death at the end of life, and patients may need reassurance and support in coping with such fears. These multidisciplinary approaches to cough suppression have mainly been used in patients with chronic idiopathic cough but may be applicable as part of cough management in respiratory conditions. Such a non-pharmacological intervention has been applied in patients with a cluster of symptoms, including cough, from lung cancer, and has been feasible and applicable in this situation [38].

Death Rattle

Death rattle is the noise made by breathing through accumulated fluid in the upper airway in the dying patient [39]. This fluid may be due to bronchial secretions, saliva, pulmonary edema, or gastric reflux. The prevalence of death rattle is estimated at 35% of patients in the last days of life as patients are often too weak to expectorate or to swallow this fluid. It can be distressing for those at the bedside but it is unclear how distressing it is, if at all, for the patient. Explanation and reassurance for staff and relatives are important. It can be managed with non-pharmacological approaches, such as repositioning or rarely gentle oropharyngeal suction in an unconscious patient, or with pharmacological approaches. Treatment of pulmonary edema, gastric reflux, or infection should be considered for symptom management if suspected as the underlying cause even in the last days of life. Airway secretions are synthesized in the salivary glands and bronchial mucosa, which are innervated by cholinergic nerves. Anticholinergic drugs which block muscarinic receptors are the mainstay of treatment. These agents can cause dryness of the mouth, blurred vision, palpitations, constipation, urinary retention, confusion, and delirium. Hyoscine butylbromide and glycopyrronium are non-sedating and may be useful in the conscious patient. Hyoscine hydrobromide (scopolamine), 400 μg subcutaneously every 4–8 h, is more sedating as it crosses the blood–brain barrier and can rarely cause paradoxical agitation. It should be avoided in renal impairment. There is no evidence that one anticholinergic is more effective than another or that they are better than placebo; however, it is acknowledged that with heightened emotions surrounding imminent death it is difficult for staff not to intervene [40, 41].

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Pain in Respiratory Disease

5

Alice Melville and Eleanor Grogan

Pain is a common and distressing symptom in respiratory disease and can be caused by a wide range of conditions other than malignancy. For example pleuritic pain is experienced in patients with pulmonary emboli, sarcoidosis, pneumonia, and pneumothorax as well as from mesothelioma, lung cancer, or other malignant infiltration of the pleura. Bone pain is the cardinal symptom of those with rib fractures, which can be pathological from underlying bone metastases, or traumatic in origin. Pain in respiratory disease can be an exacerbation of a preexisting pain, e.g., worsening bone metastases, pleural pain from mesothelioma, neuralgic pain from a Pancoast tumor invading the brachial plexus, or from a separate cause such as pleuritic pain from pneumonia. Management of the underlying condition alongside pain control is essential. Chronic respiratory disease as it advances not infrequently culminates in the development of respiratory failure. Chronic obstructive pulmonary disease (COPD) is a very common cause of this and with many patients living longer due to the increasing use of noninvasive ventilation for hypercapnic respiratory failure with acidosis, there can be a delicate balance between managing pain effectively and not exacerbating respiratory depression [1].

A. Melville
Department of Respiratory Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK

E. Grogan (✉)
Department of Palliative Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK
e-mail: eleanor.grogan@nhct.nhs.uk

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Pain Classification

Usually pain occurs when the body receives a stimulus that is perceived as painful. Impulses are transmitted via the spinothalamic tract, an ascending pathway which relays sensory information about pain and temperature, upwards from the peripheries to the thalamus and onto the cerebral cortex. Other sensory modalities, such as light touch and proprioception, are transmitted via other ascending pathways.

Damage to these ascending pathways or other parts of the pain pathway due to disease or treatment may lead to patients experiencing pain in the absence of a painful stimulus.

Patients can experience multiple pains at the same time so it is essential to ask the patient if they have pain and how many sites they have pain in and then explore each in turn as they may have different etiologies, have different types of pain, and require different treatments.

Types of Pain

Most people experience occasional pain (such as headaches) and this is termed functional pain. Organic pain is pathological and in some way related to a disease process.

Nociceptive Pain

Nociceptive pain is an organic pain. Nociceptors are sensory receptors at the nerve ending which are sensitive to noxious stimuli. They respond to stimuli by sending a signal via the spinothalamic tract to the brain. They are found in skin, bone, muscle, connective tissue, and thoracic, abdominal, and pelvic viscera.

Visceral pain is nociceptive pain caused by viscera being infiltrated, compressed, distended, or stretched by an underlying disease process. Patients often describe a deep aching pain which they struggle to localize and may be referred to unusual sites; for example patients with lung cancer and liver metastases may experience shoulder pain resulting from diaphragmatic irritation by the liver metastases.

Neuropathic Pain

Neuropathic pain is also an organic pain. It results from damage to the peripheral or central nervous system. Central neuropathic pain is less common than peripheral pain and may arise due to damage within the cerebral cortex, brain stem, or spinal cord.

Peripheral pain can directly relate to disease (such as damage from a tumor), damage secondary to surgery (such as peripheral nerves in the skin being cut during

surgery), chemotherapy (including some used to treat cancer and some antituberculosis treatments), and radiotherapy.

Patients typically describe neuropathic pain as a background ache with superimposed shooting or stabbing pains. Sometimes they use more unusual descriptions including sandpaper-like pain, an unpleasant sensation of running water, and pain like an electric shock. If a patient has an unpleasant pain that they are struggling to describe, or if they have pain in an otherwise numb area, it is likely to be neuropathic pain.

Neuropathic pain can arise from damage to sympathetic nerves. As well as neuropathic pain, the patient may experience symptoms relating to activation of the sympathetic nervous system such as redness and sweating over the affected area.

Total Pain

Many factors can influence pain and the way that it is perceived, in both positive and negative ways. The concept of total pain describes how social, spiritual, psychological, and physical factors interact to result in the experience of pain: physical reasons may be only one factor contributing to a patient's pain. Nonphysical factors can be as significant a contributory factor to pain as physical factors but unless they are addressed the patient's pain is unlikely to be resolved. Pain may be perceived as being worse if a patient is upset, agitated, bored, depressed, and lacking in sleep or if they do not understand what is happening to them. Conversely, patients may feel that their pain is decreased when they are relaxed and their mind is occupied by pleasant distractions (such as visitors, reading, enjoyable activities).

Regular and Breakthrough Pain

Not all pain is present all the time. If it is present most of the time it is termed "regular" or "background" pain and usually requires regular analgesia. Many patients experience breakthrough pain despite good usual pain control.

Breakthrough pain is common, occasional, may or may not be at the site of the usual pain, and may or may not occur in response to a specific trigger. Some breakthrough pain may be predictable. For example a patient may be pain-free when sitting down but on standing experiences a pain down their leg. Other breakthrough pain is less predictable and can occur for no obvious reason.

Successful treatment of breakthrough pain is multifactorial, like all pains. If a patient is requiring several doses of quick-acting analgesia a day for unpredictable pain he/she would usually benefit from starting or increasing regular analgesia.

However, if a patient is requiring several doses of quick-acting analgesia a day for a predictable pain and is pain-free the rest of the time, the analgesia regimen will

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require careful consideration: if regular analgesia is started, the patient will have analgesia in their system all the time to treat a few short painful episodes in the day. As with all pain, consideration should be given to eliminating triggers for the pain, practical nondrug measures, or medication that is unlikely to cause adverse effects when the pain is well controlled.

Pain Assessment

Pain is a complex, multifactorial symptom that we all perceive in different ways. When assessing pain it is important to remember that pain is what the patient says it is and that many patients have more than one pain. It is therefore important not just to ask if they have pain, but to also ask how many. The location and nature of each pain then need clarification so that each can be appropriately treated. Effectively treating pain may require an accurate diagnosis of the cause of the pain. This may involve radiological imaging or other investigations, but a careful and detailed history taken from the patient may provide much of the same information.

Pain Management

There are many different types of pain and different classes of analgesic drugs, as well as multiple nondrug treatments. Not all treatments will work for all pains, which is why a detailed history of the pain is crucial.

Nondrug Treatment

Patients often need reassurance about their pain as they may worry that it indicates a worsening of their disease. This may be true for some, but it will not be the case for all patients. An explanation of what is causing their pain and the opportunity to discuss this with a healthcare professional are often helpful to patients.

The right environment is critical to successfully managing a patient's pain. Imagine having persistent pain and being in the middle of a busy, noisy hospital environment where you are unable to sleep properly at night. You would be tired, less able to manage the pain, and may perceive the pain as being worse. If, on the other hand, you were in a quiet, calm environment where you were able to adequately rest and sleep, and people were available to reassure you about your pain and listen to your fears, you may be better able to manage the pain.

Pain can be all-consuming and patients may find it difficult to think of anything else. Distraction can therefore be a useful management strategy—perhaps a project to work on, someone to talk to, or questions and discussion about matters other than their pain. Simple measures such as repositioning the patient, supports, and heat should not be forgotten. Massage with or without aromatherapy may provide analgesic benefit to some patients, as well as provide distraction and relaxation [2].

Acupuncture may also provide analgesic benefit but currently there is insufficient evidence to support this [3].

Transcutaneous electrical nerve stimulation (TENS) is a further possible non-drug treatment that may provide pain relief. There is little evidence to support it but many patients report finding it helpful [4].

Treating the underlying cause of the pain, if appropriate and possible, should always be considered. For example, if a patient has lung cancer with bone metastases and they sustain a pathological fracture, this is likely to be painful. Treatments such as surgery or radiotherapy should be considered alongside analgesia as they may provide a more targeted and long-lasting pain benefit.

Non-opioid Analgesia

Paracetamol (Acetaminophen)

Paracetamol is a centrally acting synthetic non-opioid analgesic working at several enzyme pathways. There is synergy between paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) suggesting different analgesic mechanisms.

The evidence about whether or not paracetamol has a synergistic effect when used with strong opioids is contradictory [5, 6]. It therefore seems reasonable to use a trial of regular paracetamol, but to stop it if it provides no analgesic benefit after a few days.

Adverse effects: Paracetamol can commonly cause dyspepsia and elevated alanine aminotransferase, which is worth being mindful of in patients with progressive cancer as deranged liver function may otherwise have been attributed to cancer progression [7]. Other adverse effects are rare but paracetamol should be used with caution in severe hepatic impairment or severe active liver disease.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are anti-inflammatory and antipyretic. They inhibit cyclo-oxygenase (COX) and disrupt prostaglandin production, preventing its amplification of pain, although a recent Cochrane review found no high-quality evidence to prove that NSAIDs are useful in treating people with cancer pain [8].

Adverse effects: NSAIDs are effective painkillers, but have wide-ranging and potentially serious adverse effects including gastrointestinal toxicity (which may be reduced by co-prescription with a proton pump inhibitor) and cardiovascular toxicity.

Other adverse effects include acute and acute-on-chronic renal failure, and NSAID-induced asthma, even in patients with no previous history of atopy.

As with all medication, the risks and benefits for an individual patient should be weighed up and the NSAID be used for a few days as a trial. If it is not of benefit then, given the wide range of potential adverse effects, it would be sensible to stop it. In patients with advanced disease, the benefits usually outweigh the potential adverse effects.

Opioid Analgesia

Traditionally, the WHO analgesic ladder has been followed which divides opioids into weak and strong. However, weak opioids (such as codeine, tramadol) should not be used in patients with advanced cancer and pain. Low-dose morphine provides better and quicker analgesic benefit in cancer pain than weak opioids, with similar tolerability [9].

Opioid dose should be titrated according to the patient's pain and response. A common concern of prescribers, especially in patients with respiratory conditions, is that strong opioids may cause clinically significant respiratory depression. If opioids are used and titrated appropriately, this is unlikely to happen [10].

Morphine is usually the first-choice opioid; unless the patient has had significant adverse effects with morphine, an alternative route is needed, or the patient has relative contraindications, such as significant renal impairment. If the patient has not previously been taking an opioid, a low starting dose is used and the dose is titrated upwards according to benefit and adverse effects. When increasing the dose of morphine, the dose should be increased by a maximum one-third to one-half, no more often than every 24 h.

Morphine is available in long- and immediate-acting preparations. Patients should be given long-acting (modified release) morphine regularly. Most preparations are designed to last 12 h and therefore given twice a day, although some last for 24 h and are given once a day. Despite this, the patient may still experience some pain so they should also be prescribed immediate-release morphine as rescue analgesia for use when needed. The dose of this is calculated as 1/10–1/6 of the total daily dose of morphine. If the regular dose is increased, the rescue dose should also be increased to stay in proportion.

Adverse effects: Opioids share some common adverse effects. They are not experienced by all patients but it is prudent to warn patients of the common adverse effects to help compliance.

- Nausea and vomiting often occur when starting an opioid and usually settle within a few days. As this is quite predictable, the patient should be co-prescribed or offered an antiemetic such as haloperidol for the first week.
- Drowsiness/lightheadedness usually settle after the first few days. Patients should be warned of this and advised not to drive until these symptoms resolve.
- Constipation affects nearly all patients receiving opioids and this adverse effect persists. Patients should be warned of this and co-prescribed suitable laxatives.
- Dry mouth is often an ongoing adverse effect.

Routes of administration: Unless there is good reason not to, patients should be given opioids by mouth. Parenteral opioids are only needed if a patient is unable to absorb medication when taken orally, or if there are swallowing concerns. Parenteral opioids are not stronger than oral opioids, though they may work more quickly. In

advanced disease the choices of parenteral routes are typically subcutaneous or transdermal.

- The subcutaneous route is easier to manage than intravenous administration as it does not require an intravenous cannula and is a route that can be used at home; it is more practical than intramuscular administration as many patients with advanced disease have little muscle bulk. If regular subcutaneous medication is required it can be given via a continuous subcutaneous infusion using a syringe driver or syringe pump.
- Transdermal opioids are only suitable when pain is stable as it can take at least 24 h for the patient to feel the analgesic benefit; it can take a similar time for transdermal opioids to wash out of a patient on ceasing the medication. For these reasons transdermal opioids should not be started or stopped in the last few days of life, when managing unstable pain, or when rapidly titrating analgesia. In a patient already receiving transdermal analgesia who is in the last few days of life, their transdermal analgesia should be continued and a syringe pump added with additional analgesia, if required. Caution must be exercised regarding doses of transdermal patches—their strength is prescribed as micrograms/hour, whereas morphine and most other opioids are prescribed as milligrams. For this reason the dose may seem numerically smaller than it actually is. Opioid dose conversion charts should be consulted to see equivalent doses.

Alternative opioids: Most patients tolerate morphine and do not require an alternative opioid but there are several indications when it may be appropriate to try an alternative opioid.

Constipation: Most patients receiving regular opioids will experience constipation and should be co-prescribed laxative medication. Despite taking laxatives at high doses, some patients still struggle with constipation. These patients may benefit from a switch of opioids to one less constipating, such as fentanyl.

Neurotoxicity: Some patients experience significant neurotoxic problems such as delirium, hallucinations, myoclonus, and hyperalgesia. These symptoms may settle spontaneously after a few days. If they persist, and once other causes of neurotoxicity have been excluded, switching to a different opioid should be considered as they are chemically different, work on different opioid receptors, and hopefully do not cause the same adverse effects.

Compliance: Patients who have difficulty in adhering to an oral analgesic regimen may benefit from switching to a transdermal opioid. Fentanyl patches are changed every 3 days and buprenorphine every 3 or 7 days depending on the formulation.

Renal impairment: Most, but not all, opioids are excreted renally. If the renal impairment is mild, the prescriber should be aware of this and use morphine with caution, possibly starting at a lower dose than usual. In more significant renal impairment, morphine should be avoided and an alternative opioid used that is safe in renal impairment, such as fentanyl, alfentanyl, or methadone.

Adjuvant Analgesia

Adjuvant analgesia may often be needed in addition to opioids, for example with neuropathic or bone pain. They are often medications that have primary indications other than analgesia, but that work as well as analgesics. Commonly used examples include antidepressants, antiepileptics, corticosteroids, bisphosphonates, antispasmodics, and skeletal muscle relaxants.

Antidepressants and antiepileptics may be effective in the treatment of neuropathic pain that has not responded to an NSAID or morphine. They modulate pain in different ways so if a drug only provides partial benefit, it may be worth adding in a different one. First-line choices often include amitriptyline and gabapentin, but pregabalin, duloxetine, and nortriptyline can also be effective. As with many analgesics the chosen medication should be started at a low dose and slowly titrated upwards in an attempt to limit adverse effects. Amitriptyline is usually started at a dose of 10 mg at night, and gradually increased up to 75 mg/day, if tolerated and beneficial. Pregabalin is usually started at a dose of 75 mg twice daily and gradually increased to 150 mg twice daily and then 300 mg twice daily if tolerated and beneficial. Gabapentin is usually started at a dose of 300 mg at night increasing to 300 mg twice daily on day 2 and then 300 mg three times daily on day 3. The dose can then be further gradually increased until a maximum on 3600 mg/day, but many patients achieve adequate analgesia at doses lower than the maximum. If a dose increase causes adverse effects the patient should reduce to the previous dose and slow down the titration regimen. These doses should be increased not more often than every few days, or even more cautiously, particularly in frail patients or patients with renal impairment.

Corticosteroids can be used to reduce an area of edema that surrounds many tumors, so reducing the size of a mass that may be compressing or invading surrounding structures and causing pain. Reducing this edema often provides rapid and effective relief from pain, though these benefits are usually short lived so additional analgesia or more definitive treatment, such as radiotherapy, may need to be considered. If the patient does not experience benefit within a few days the steroids should be stopped to prevent the development of unnecessary adverse effects. These adverse effects may also arise if corticosteroids are used long term.

Bisphosphonates may provide relief from the pain arising from bone metastases that hasn't responded to usual analgesia. Benefit is usually seen within a couple of weeks and may persist for several months, though the patient may also benefit from a treatment such as radiotherapy [11].

Antispasmodics may help relieve pain secondary to smooth muscle spasm, such as that arising from constipation, bowel obstruction, or bladder spasm which may not respond to other analgesia. As with all pains, the underlying cause should be identified and treated where possible. Only after this should an antispasmodic medication be considered. Hyoscine butylbromide is commonly used, but is poorly absorbed orally so should be used parenterally, usually subcutaneously in the palliative care setting.

Skeletal muscle relaxants may help relieve pain associated with muscle spasm or cramp, although nondrug treatment is probably best for this type of pain—for example heat packs, massage, or relaxation therapies. If the pain is persistent and troublesome the patient may require medication. Skeletal muscle spasms rarely respond to other analgesia but may respond to quinine, baclofen, or benzodiazepines. Patients often report finding TENS machines helpful for skeletal muscle pain, although the evidence is inconclusive [12].

Complex Pain

Occasionally a patient has more complicated pain that does not respond to the analgesia discussed already. There are further options that can be considered including less commonly used, more complex analgesia (for example, ketamine methadone). Advice should be sought from specialist pain management services or anesthetists regarding nerve blocks or other anesthetic procedures that may help pain relief.

Case Studies

Example 1

Mrs. S has advanced COPD with a usual exercise tolerance of 10 m around the house. She develops acute worsening breathlessness and sharp left-sided chest pain, worse on inspiration and movement. A pulmonary embolus is confirmed in her left lower lobe pulmonary artery with distal lung infarction. Thrombolysis is not clinically indicated. The nociceptive chest pain described arises from irritation/stretching of the pleura from inflamed lung parenchyma. The pulmonary embolus is treated with subcutaneous low-molecular-weight heparin initially and later she is converted to oral apixaban. She is given 5 mg of intravenous morphine by the admitting doctor. This helps her pain but she becomes drowsy but rousable and is noted to be in decompensated hypercapnic respiratory failure with acidosis. This improves quickly with noninvasive ventilation (NIV). Reversal of the opiate with naloxone is considered but not given, due to the rapid clinical improvement. There is a difficult balance to be achieved here. Relative hypoventilation from pain may impede precarious oxygenation and worsen respiratory failure, but at the same time sedative effects of analgesics may cause clinically significant respiratory depression in those with little reserve, especially when titrated too quickly or a dose is given that is too large for the patient. Regular non-sedative analgesia is prescribed (paracetamol and NSAIDs with a proton pump inhibitor for gastric protection) but she continues to be in a lot of pain. She should be given a low dose of oral immediate-release morphine, such as 2.5 mg (as there is no indication to give it parenterally). If she finds it helpful and she needs several doses, she should be started on regular low-dose modified-release morphine, perhaps 5 mg twice a day, with the dose titrated gradually over several days according to analgesic response and side effects.

Example 2

Mrs. F presents with 2 months of weight loss, constant right axillary pain radiating down her lateral chest wall and medial aspect of her right arm, and right-hand weakness. She has a right Horner's syndrome and further investigation confirms a right apical non-small cell lung cancer. The "Pancoast" tumor is invading the brachial plexus, and first and second anterior ribs. Pancoast tumors often present challenging pain control issues. Pain is often nociceptive, bony, and neuropathic in origin with a combination of strategies often needing to be utilized for pain control including opioids, NSAIDs, adjuvant analgesics, and radiotherapy. She receives radiotherapy for pain control and subsequently chemotherapy.

Example 3

Mr. M has worsening pulmonary sarcoidosis for which he is on the active lung transplant waiting list. He takes prednisolone daily for the sarcoidosis. He has sarcoid-associated arthritis but reduced his analgesics recently as he thought it was better. In addition to his joint pain he has intermittent pleuritic pain and is anxious about whether he will ever receive a transplant. Restarting simple analgesics very effectively improves his pain control with his pain score reducing from 6/10 to 2/10. Further addressing his fears and anxieties reduces his symptom burden with his pain score reducing to 1/10.

Example 4

Mr. G worked as an electrician in the shipyards for 15 years during which time he was exposed heavily to asbestos. He develops breathlessness and right-sided pleuritic chest pain and is found to have a right pleural effusion. Thoracoscopic pleural biopsies prove mesothelioma to be the cause. He later requires insertion of an indwelling pleural catheter due to re-accumulation of the pleural effusion after drainage and talc pleurodesis. Although regular drainage by the community nursing team improves his breathlessness, chest pain remains a significant issue. He has constant neuropathic and pleuritic chest pain for which NSAIDs, gabapentin, and increasing doses of opioids initially provided some benefit but are no longer proving effective. He should be considered for more complex analgesia (such as methadone or ketamine) which would need to be initiated by a palliative medicine or pain specialist, possibly in the inpatient setting in a palliative care unit or hospice. Alternatively, he may benefit from interventional analgesia, such as a nerve block, intrathecal analgesia, or nerve ablation. Again, this would need consultation with an interventional pain expert.

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Part III

Respiratory Diseases

Lung Cancer

6

Bernard Higgins, Tim Peel, and Paula Mulvenna

More than 1 million people die from lung cancer every year making it the world's leading cause of cancer death [1, 2]. There is wide variation in both the incidence and death rate of lung cancer in different countries and regions depending on socio-economic factors and prevalence of smoking. In the UK in the year 2015 there were 46,388 new cases of lung cancer. Of these, approximately 47% occurred in women, and the proportion of women affected is steadily increasing [3]. Cure rates are low, with a 5-year survival of only 9.5%. The epidemic of lung cancer is beginning to wane in the Western world but is rising inexorably in other parts of the world.

There are well-established guidelines for the investigation and management of patients with lung cancer [4]. Unless there is a specific reason not to, it is recommended that histological or cytological confirmation should be sought, the disease should be staged using the current version of the TNM classification system, and the patient's performance status should be assessed. Lung cancer is broadly divided into non-small cell (NSCLC) carcinoma, the main types of which are squamous carcinoma, adenocarcinoma, and small-cell carcinoma (SCLC). In NSCLC cures are sought by either surgical excision or radical radiotherapy. Increasingly adjuvant chemotherapy is being used in an attempt to improve cure rates. In SCLC the very few cures are achieved in patients with limited-stage disease who have a complete response to chemotherapy and subsequent consolidation radiotherapy. Management of lung cancer involves a multidisciplinary approach with involvement of

B. Higgins (✉)
Department of Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne, UK
e-mail: Bernard.Higgins@nuth.nhs.uk

T. Peel
Policy, Ethics and Life Sciences, Newcastle University, Newcastle Upon Tyne, UK

P. Mulvenna
Northern Centre for Cancer Care, Freeman Hospital, Newcastle Upon Tyne, UK

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respiratory physicians, thoracic surgeons, medical and radiotherapy oncologists, pathologists, nurse specialists, and palliative care teams. Good communication of the diagnosis and discussion of the management options with the patient and family are crucial, and patients and their families need considerable support at the time of diagnosis and throughout the course of the disease [4].

Lung cancer management typically involves an initial phase of diagnosis during which the patient and their families experience considerable emotional distress in coming to terms with a life-threatening illness. This is usually followed by a phase of specific anticancer treatments (surgery, chemotherapy, or radiotherapy) which can themselves give rise to significant symptoms and adverse effects. Unfortunately in the majority of cases the tumor relapses and progresses leading to a palliative phase focused on relief of symptoms, followed by an end-of-life phase. This is typical of a "cancer trajectory" and it allows a planned approach to palliative care. The importance of palliative care was emphasized by a study in the United States (USA) in which patients with metastatic non-small cell lung cancer were randomized to receive either standard oncologic treatment alone or with added specialist palliative care input [5]. Those receiving palliative care had better quality-of-life scores and less depression and were less likely to receive aggressive care at the end of life. More surprisingly their median survival, at 11.6 months, was significantly longer than those who received oncologic care only (8.9 months). Palliative and supportive care are crucial components and must run in parallel with anticancer treatments throughout the course of the disease.

Presentation and Progression of Symptoms

Presentation

The commonest presentation of lung cancer is with local symptoms from the presence of the intrathoracic tumor or from local direct spread to involve adjacent organs. Symptoms from metastatic disease are the next most common, while rarer presentations result from various paraneoplastic phenomena. Lung cancer may also be discovered coincidentally on a chest X-ray done for some other purpose. A study in 1993 reported the symptoms at presentation in 289 unselected patients with non-small cell lung cancer [6]. They are listed in Table 6.1.

While most of these reflect local disease some, such as extra-thoracic pain, suggest distant metastatic spread, and malaise and anorexia are systemic manifestations of cancer and probably paraneoplastic in origin.

Another study examined the symptoms of lung cancer patients in their last year of life and compared them with those of patients with chronic obstructive pulmonary disease (COPD) [7]. While some local symptoms, such as cough, improved throughout the course of the disease others, such as pain, became more troublesome. Systemic symptoms and low mood were common in both advanced lung cancer and COPD (Table 6.1).

Table 6.1 Symptoms of lung cancer at presentation and later in the course of the disease [6, 7]

	% Presentation [6]	% Late [7]
Cough	79	40
Breathlessness	5	69
Pain	55	64
Anorexia	45	70
Malaise	47	
Hemoptysis	35	
Hoarseness	11	
Dysphagia	7	
Vomiting		25
Constipation		42
Mouth problems		46
Insomnia		40
Confusion		33
Low mood		49

Mechanism of Symptoms

Cough

Stimulation of the irritant receptors in the central airways causes a cough relatively early in patients with lung cancer. The problem is that most of these people will have been smokers and possibly have a chronic cough due to coexistent COPD. The change in the nature of the cough may be an important clue. Sputum production is not discriminating except in multifocal lepidic adenocarcinoma (bronchoalveolar cell carcinoma) which is sometimes characterized by excessive secretions (bronchorrhea).

Breathlessness

Breathlessness, like cough, is a common symptom in the patient group who develop lung cancer. The commonest underlying causes are collapse of a lobe or whole lung, and pleural effusion. Less common causes include pericardial effusion, lymphangitis carcinomatosa, superior vena cava obstruction (SVCO), tumor bulk, and mediastinal involvement causing a phrenic nerve palsy with diaphragmatic paralysis.

Stridor and Hoarseness

Stridor is a predominantly inspiratory wheezing sound due to either an intraluminal tumor narrowing a large airway or extrinsic compression of an airway by tumor mass or lymph nodes. The wheezing sound is from turbulent airflow through the narrowing. Hoarseness is usually due to left recurrent laryngeal nerve palsy from a tumor in the left upper mediastinum. This results in paralysis of the left vocal cord. In addition to a hoarse voice, such patients also develop a “bovine” cough as they are unable to completely adduct the vocal cords to generate adequate pressure for a normal cough. Rarely a tumor at the extreme right apex causes a right cord palsy.

Hemoptysis

This is an alarming symptom and therefore one likely to make the patient seek medical advice. It is usually due to mucosal disruption from a central tumor or from a peripheral tumor outgrowing its blood supply and cavitating. Major hemoptysis is uncommon at presentation but can occur in advanced disease if bronchial or pulmonary vessels are invaded by tumor.

Pain

There are no pain receptors in the airways or lung parenchyma, so pain generally implies disease extension to the surrounding pleura or mediastinal structures. Another explanation of pain is due to infection distal to an obstructing central tumor. Pleural and mediastinal pain are usually nociceptive and opioid sensitive. Unilateral facial pain due to mediastinal involvement has been described [8]. This is usually felt in or around the ear and is thought to be referred pain via the vagus nerve. It improved with palliative radiotherapy to the tumor. If a peripheral cancer invades the chest wall, it will cause nociceptive pain due to involvement of the pleura, muscle, ribs, or connective tissues, and neuropathic pain in the distribution of any intercostal nerve involved. At the apex of the lung, superior sulcus tumors, known as Pancoast tumors, can cause neuropathic pain if the brachial plexus is involved, sympathetically maintained pain if the subclavian sympathetic plexus is affected, and an ipsilateral Horner's syndrome of ptosis, meiosis, enophthalmos, and anhydrosis [9].

Metastatic Symptoms

Lung cancer can metastasize via the bloodstream to almost any organ. In practice the commonest sites for symptomatic metastatic spread are the brain, bones, liver, pleura, skin, and subcutaneous tissue. The lungs and adrenals are commonly also involved but tend not to give rise to new symptoms. Bone metastases present with bone pain, pathological fracture, or nerve compression symptoms such as spinal cord compression. Brain metastases can present with focal neurological symptoms due to the presence of a space-occupying lesion, with an epileptic fit, with symptoms of raised intracranial pressure or with personality change due to frontal lobe involvement. Liver metastases are characterized by pain due to stretching of the liver capsule or jaundice if the bile ducts are compressed. Pleural involvement results in breathlessness due to effusion or pleuritic pain.

Nonmetastatic Symptoms

Also known as paraneoplastic symptoms, these are thought to be caused by secretion of tumor products that act at sites separate from the tumor. Some symptom complexes are not confined to lung cancer, or indeed cancer in general, but occur in a variety of advanced diseases. Fatigue, anorexia, and cachexia are the most obvious examples of this and are found in chronic lung diseases such as COPD, chronic

Table 6.2 Summary of paraneoplastic syndromes in patients with lung cancer

Neurological
Peripheral neuropathy, Lambert-Eaton syndrome, encephalopathy, myelopathy, cerebellar degeneration, psychosis, dementia
Cutaneous
Clubbing, dermatomyositis, acanthosis nigricans, pruritus, sweating, erythema multiforme, hyperpigmentation, urticaria, scleroderma
Musculoskeletal
Hypertrophic pulmonary osteoarthropathy, polymyositis, myopathy, osteomalacia.
Blood disorders
Thrombocytosis, polycythemia, hemolytic anemia, red cell aplasia, dysproteinemia, leukemoid reaction, eosinophilia, thrombocytopenic purpura, hypercoagulable states
Endocrine
Cushing's, syndrome of inappropriate antidiuretic hormone (SIADH), hypercalcemia, carcinoid syndrome, hyper- and hypoglycemia, gynecomastia, galactorrhea, growth hormone excess, calcitonin secretion, thyroid-stimulating hormone
Vascular
Thrombophlebitis, arterial thrombosis, nonbacterial thrombotic endocarditis
Miscellaneous
Fatigue, anorexia/cachexia, nephrotic syndrome, hyperuricemia

suppurative lung diseases, and idiopathic pulmonary fibrosis (IPF). Secondly there are systemic symptoms that are more commonly associated with lung cancer and mesothelioma. These include sweats and generalized itching (without biochemical abnormality). Clubbing and its rarer companion hypertrophic pulmonary osteoarthropathy (HPOA) occur in lung cancer but also in chronic lung suppuration, IPF, and cyanotic congenital heart disease. The paraneoplastic syndromes variably associated with lung cancer are listed in Table 6.2 [10]. Some, such as hypercalcemia, associated with squamous lung cancer, and hyponatremia, associated with small-cell lung cancer, are relatively common and their management will be described. Others are much rarer and more exotic. They are more difficult to manage and may not improve even with successful treatment of the primary cancer.

Palliative Treatments

Chemotherapy

The value of chemotherapy in prolonging life in lung cancer patients was first demonstrated unequivocally in 1969 in a classic study of 2000 patients at the Veterans Administration Hospitals [11]. It was readily apparent even in those early days that the response rate was vastly superior in cases of small-cell cancer. At that time surgery was regarded as the standard treatment of choice for all lung cancer, but in 1973 Matthews and colleagues published their experience of patients who had died within a month of surgical resection of a small-cell tumor and showed that systemic

metastases were present even though there had been no sign of these at preoperative evaluation [12]. In the following years it became clear that small-cell tumors responded to a variety of drugs and that using these in combination produced better results than when these drugs were used as single agents alone [13]. Thus chemotherapy became established as the treatment of choice for small-cell cancer (SCLC).

The obvious problem with chemotherapy has been its toxicity; adverse effects are both frequent and potentially serious. Even in cases of small-cell cancer there has been some debate as to whether the incidence of side effects outweighed the survival benefit, particularly in extensive-stage disease. When considering the use of chemotherapy in non-small cell lung cancer this issue becomes central. The response rate is clearly less than in small-cell cancer and for years many physicians were reluctant to subject their patients to this treatment, but over time it has also become an acceptable option in non-small cell lung cancer (NSCLC), as a potential cure when used in combination with radiotherapy, or as a means of prolonging life and palliating symptoms by reducing tumor load. Moreover, in recent years a number of new agents have been developed with completely different modes of action than that of established cytotoxic chemotherapy, and which do not carry the same intrinsic risk of toxicity to tissues such as the bone marrow and gastrointestinal tract. Chemotherapy can therefore now be considered as a genuinely palliative option in NSCLC.

Small-Cell Lung Cancer

The concept of formally measuring quality of life was not properly appreciated when survival benefits of chemotherapy for small-cell lung cancer were first being demonstrated. The toxic effects of chemotherapy were, of course, readily apparent, most notably the effects of bone marrow suppression producing anemia, neutropenia with the risk of infection, and thrombocytopenia causing bleeding or bruising. The problems of nausea, vomiting, and hair loss were notorious. Nonetheless, patients with limited-stage small-cell cancer who had a measurable chance of cure with chemotherapy are generally prepared to accept these, although appreciative of any attempts to mitigate the toxicity.

Does Chemotherapy Improve Quality of Life?

Although chemotherapy can produce a range of adverse effects, this has to be set against its potential for shrinking or even curing the cancer, and thereby improving the symptoms produced by the malignant disease itself. Even in patients with relatively good performance status and prognosis, baseline symptoms are common. Thatcher and colleagues reported a cohort of 402 patients who were treated with standard chemotherapy regimens (doxorubicin, cyclophosphamide, and etoposide (ACE) or carboplatin-etoposide) or with more aggressive ICE-V (ifosfamide, carboplatin, etoposide, and vincristine) [14]. At baseline about one-quarter reported their overall quality of life as poor or extremely poor. Chemotherapy produced improvements in both groups. For ICE-V the percentage with poor or extremely poor quality of life fell from 25% to 13% at 3 months, and to 14% at 6 months, while for the standard regime the equivalent figures were 24%, 16%, and 15%.

Moreover many specific symptoms such as cough, dyspnea, and appetite improved after chemotherapy was started, although others such as general fatigue and levels of energy did not.

In a later study Quoix measured quality of life using the functional assessment of cancer therapy-lung (FACT-L) questionnaire, and also looked at individual symptoms. This was linked to a comparison of topotecan used with either cisplatin or etoposide. There was no difference in outcome between the two treatment groups, but it was noteworthy that all baseline symptoms improved with both treatment combinations, with the exception of hemoptysis [15].

The balance between prolongation of life and changes in the quality of life is perhaps most important in those patients with poor prognosis. Frustratingly there remains a paucity of good information on quality-of-life changes with chemotherapy in this group. A Cochrane review found only two small studies of first-line chemotherapy versus best supportive care in extensive-stage small-cell lung cancer, both conducted in the 1970s and therefore of diminishing relevance as optimal treatment has moved on in both of the comparators [16]. The review concluded that the impact of chemotherapy on quality of life in poor-prognosis small-cell cancer is uncertain. One subsequent large study in which patients with small-cell cancer of various stages were randomized to receive either paclitaxel, carboplatin, and etoposide or vincristine, carboplatin, and etoposide reported the results separately for the stage IV patients [17] and showed that the global quality-of-life parameters of the EORTC questionnaire improved. However, it is important to note that in this study patients were well enough to be randomized to receive potentially toxic systemic chemotherapy, and thus are not truly representative of the generality of patients with extensive-stage disease. It remains the case that the patients with most symptoms (i.e., who have most to gain from treatment) are also those least likely to be able to tolerate chemotherapy.

Non-small Cell Cancer

Cytotoxic Chemotherapy

It is now accepted that in patients with NSCLC and a good performance status, chemotherapy confers a survival benefit. However, the response rate remains poorer than in SCLC, and one might therefore have expected studies to have focused more intensely on the balance between extension and quality of life but formal data on quality of life are relatively sparse.

Where possible, NSCLC is treated by surgery, radical radiotherapy, or combination chemoradiotherapy with curative intent. Patients who are not suitable for surgery or radiotherapy are offered appropriate symptomatic treatment, but they may also wish to try palliative chemotherapy rather than making no attempt to reduce the tumor burden. Among those who are fit enough for chemotherapy there is no doubt that this improves survival. Meta-analysis has shown a reduction in the risk of death at 1 year from study entry of 11% in the groups receiving chemotherapy [18]. Although this meta-analysis included 16 randomized controlled trials and over 4000 patients there were insufficient data to formally assess the effects on quality of life.

Individual controlled trials have reported either improvement or no difference in quality of life in those randomized to chemotherapy compared to those given best supportive care [19–21]. It is disappointing that there is no clear evidence of symptomatic benefit given the modest survival benefit.

There has been considerable interest in the use of chemotherapy combined with surgery to improve survival in NSCLC. The earliest trials which used alkylating agents tended to show an adverse effect from the addition of chemotherapy, but more modern studies have suggested that this adjuvant therapy is beneficial whether the chemotherapy is given after surgery or preoperatively, and postoperative chemotherapy is now used routinely, dependent on the final pathological staging. However, once again the benefit in terms of quality of life has not been well documented [22].

As already noted, chemotherapy can also be used in combination with radiotherapy as primary treatment for NSCLC. The chemotherapy can be given at the same time as the radiotherapy (concurrent chemoradiotherapy) or one can follow the other (sequential chemoradiotherapy). Both approaches have been studied extensively although with different drug combinations. Concurrent chemoradiotherapy has been shown to be superior to radiotherapy alone in terms of overall survival and superior to sequential chemoradiotherapy [23]. However, for both comparisons the concurrent chemoradiotherapy also caused more symptoms, particularly esophagitis. Global measures of quality of life are lacking, once again.

The Emergence of Molecular Oncology

In the past 10 years there has been a huge step forward in the pharmacological management of lung cancer with the arrival of new therapies which target specific mutations within, or on the surface of, cancer cells. The range of these newer agents is still expanding and their precise role in management continues to evolve as further research is published. This is an exciting area of medicine, and it is already clear that there are major benefits, for example in lengthening the duration of progression-free survival [24, 25], but these considerations are beyond our remit here. From the point of view of palliation the interest lies in the potential of the newer agents to reduce tumor bulk and the associated symptoms without the adverse effects of standard cytotoxic chemotherapy.

At present there are three main groups of drug to consider (in the UK):

- Epidermal growth factor receptor (EGFR) inhibitors were the first of these drugs to be approved in the UK. It should be emphasized that they are not free from adverse effects, and indeed are more likely to cause skin rashes, stomatitis, and diarrhea than cytotoxic therapy, but they are less likely to produce nausea, constipation, fatigue, or bone marrow toxicity, the latter being particularly important. The likelihood of severe grades of toxicity is less when compared to cytotoxic agents [24, 26].
- ALK inhibitors target tumors with variants of the enzyme anaplastic lymphoma kinase. They can cause nausea, diarrhea, and visual disturbances, but their effects on quality of life are better than with cytotoxic drugs whether used as first-line treatment or when re-treating after a prior course of chemotherapy [25, 27, 28].

- PD-1/PDL-1 inhibitors block the linkage between the programmed cell death protein receptor and its ligand. Expression of these molecules is reasonably common in lung cancer, albeit in variable amounts, and this group of drugs therefore has potentially wide applicability. Several agents are available with differing adverse effect profiles, and although comparative data is not available for all of these, the indications are that they are associated with better quality of life than cytotoxic regimens [29, 30].

Radiotherapy

Radiotherapy is a valuable treatment which has been in use in various forms for around 100 years. The development of linear particle accelerators began 60–70 years ago and it has become possible to link this to computed tomography (CT) imaging to deliver the radiation in three dimensions, further enhancing the precision of therapy. This evolution continues with the advent of stereotactic radiotherapy techniques which aim to deliver radiotherapy more precisely and thus, hopefully, reduce the adverse effects which arise from normal structures being affected by the radiotherapy beam. While a lot of the relevant literature concentrates on cure and response rates, one large study has confirmed that stereotactic radiotherapy reduces the incidence of adverse effects.

Radiotherapy can be employed in a variety of ways. It can be used in an attempt to cure a lung cancer, when a high radiation dose is employed and the patient accepts the increased risk of adverse effects that this greater dose entails. Alternatively, lower doses can be used as palliative radiotherapy with a view to reducing tumor bulk and prolonging life but accepting that cure is not likely to be achieved and that the principal value of shrinking the tumor is to improve symptoms. Sometimes there is a particular symptom which the radiotherapy is intended to resolve, and indeed this may not necessarily be in the lung; for example, bone pain due to metastasis from a lung primary is often treated with radiotherapy. Finally, there are some other specific situations in which radiotherapy has been used, for example, cranial irradiation to prevent cerebral metastases after chemotherapy for small-cell lung cancer. Each of these situations will be covered in turn.

Radical Radiotherapy

Radical radiotherapy is usually given to patients who are not suitable for surgery because of comorbidity or poor respiratory function, or because they decline surgery. Dosing schedules vary, and this affects toxicity. As with chemotherapy, the benefits in terms of improvement of quality of life are hard to assess because of a paucity of data. One study which specifically aimed to look at this aspect of radical radiotherapy provided data from only 164 patients who received 60 Gy with curative intent, and recorded quality of life using the EORTC questionnaire before treatment and then five times posttreatment up to a 12-month time point. The response rate for improvement in global quality of life was 36% [31].

Palliative Radiotherapy

It is harder still to synthesize the symptomatic benefit from trials of palliative radiotherapy since the variation in treatment regimens is even greater, because it is not clear in some trials how bad symptoms were before treatment, because of variation in other patient characteristics, and because of variation in outcome measures. One interesting UK trial looked at patients with minimal thoracic symptoms who were unsuitable for resection or radical radiotherapy. These patients were randomized to receive radiotherapy to their thoracic tumor immediately, or to wait until specific symptoms developed. Two hundred and thirty patients were randomized of whom 42% in the delayed treatment group eventually received radiotherapy after a median wait of 125 days [32]. No difference was seen in symptoms, psychological distress, activity level, or survival, implying that treatment can wait until there is at least one specific symptom needing to be addressed.

Palliation of Specific Symptoms

Cough

An unpleasant persistent cough is a common problem in advanced lung cancer particularly with more central lesions as cough receptors are present in greater density in central airways. Radiotherapy is a potential treatment option, the benefit presumably relating to shrinkage of the tumor. The success rate for significant palliation of cough is a little over 50%, although this estimate is based on retrospective review [33]. One prospective evaluation using a standardized questionnaire found a disappointing response rate of 31% [31]. The technique of endobronchial radiotherapy (brachytherapy) has been described in Chap. 3. It is probably inferior to external beam radiotherapy for palliation of symptoms, but has the advantage of being potentially applicable in patients who have already had maximal dose of conventional radiotherapy, the limiting factor being that the lesion has to be accessible to the bronchoscope in order to position the treatment catheters. Brachytherapy has been used to treat patients with symptomatic tumor recurrence after primary treatment with high-dose radiotherapy and a surprisingly good response rate of 77% was seen for improvement of cough [34].

Hemoptysis

As with cough, hemoptysis secondary to lung cancer has long been treated with radiotherapy, and brachytherapy is again an option in those patients who have already received external beam therapy. Hemoptysis seems to respond well to radiotherapy. A prospective study using a validating questionnaire showed that the symptom disappeared or improved significantly in 83% of patients [31]. In a separate retrospective study the response to brachytherapy as second-line treatment of hemoptysis was 92% [33].

Breathlessness

Breathlessness can arise for several different reasons in lung cancer. When it is caused by the development of a pleural or pericardial effusion, or by anemia,

radiotherapy has no role, nor is it of any benefit when dyspnea is caused by lymphangitis carcinomatosa. However, when breathlessness has arisen because of mechanical obstruction of a large bronchus, with or without collapse of the distal lung, radiotherapy may be of value in shrinking the tumor and relieving the obstruction. Unfortunately, even if the tumor responds, re-expansion of collapsed lung is not guaranteed. Experience suggests that expansion is less likely the longer the lung remains in its non-aerated state, and treatment of dyspnea due to obstruction of tumor should consider the role of radiotherapy in conjunction with other treatments such as stents or laser therapy. Because tumor response in this situation does not necessarily lead to re-lung expansion, the response rates for breathlessness treated by radiotherapy tend to be poorer than those for symptoms such as hemoptysis. In a prospective study the response rate for dyspnea was 37% [31].

Pain

Lung cancer can produce pain by local invasion of the chest wall or through distant metastases, particularly to bone. The degree of discomfort and the likelihood of a worthwhile response to radiotherapy will differ a little with the extent of the invasion, but some relief is usually achieved. A response rate of 68% has been found in a prospective study [31]. For distant bone metastases, studies have shown that a single fraction of 8 Gy is as effective as higher dose multi-fraction therapy in relieving pain [35]. Response to radiotherapy is usually reasonably quick and treatment need not be withheld because a patient is judged to be within a few weeks of death: improvement of pain at 1 month is found in 70% of patients [36]. Treatment of bone metastases can be associated with further weakening of the bone, and this is particularly important in weight-bearing sites, such as the femur. Adequate palliation should involve orthopedic advice, and it may be necessary for patients to avoid weight bearing for a period of time or to undergo a surgical stabilization procedure.

Cerebral Metastasis

The brain is a relatively common site of metastases for both small-cell and non-small cell cancer. In the latter case the metastasis may be solitary and in that situation treatment via surgery or stereotactic radiotherapy with a view to cure may occasionally be appropriate.

Traditionally patients with symptomatic brain metastases from lung cancer have been treated with dexamethasone with a view to reducing cerebral edema. Some physicians would then proceed routinely to radiotherapy (usually whole-brain radiotherapy) whereas others believed that the chances of any worthwhile benefit were confined to those who had shown a satisfactory response to dexamethasone. The evidence for this differential approach is scant. The recent QUARTZ trial including 538 patients has shown no benefit in quality of life from routine whole-brain radiotherapy in the presence of metastases which are not suitable for surgical resection or stereotactic radiotherapy [37].

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Symptom Management

The management of the most common symptoms, namely cough, breathlessness, pain, and hemoptysis, is the subject of specific chapters. In this section the commoner paraneoplastic and systemic symptoms encountered in lung cancer and, to a lesser degree, other respiratory conditions are described. The commoner systemic symptoms include anorexia, cachexia, weight loss, and fatigue. Two others, less commonly seen but equally troublesome to those affected, are sweating and pruritus. The two common paraneoplastic syndromes of lung cancer that will be considered are hypercalcemia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Finally we consider the management of the consequences of intrathoracic spread in four circumstances, namely stridor, hoarseness, superior vena cava obstruction (SVCO), and spinal cord compression.

Anorexia, Cachexia, and Weight Loss

Anorexia (the loss of desire to eat), reduced food intake, and weight loss (of more than 10%) are common in a number of advanced respiratory diseases. These include mesothelioma, lung cancer, COPD, and lung infections such as occur in cystic fibrosis and bronchiectasis, lung abscess, and tuberculosis. There are in fact two separate entities that result in significant weight loss in these circumstances, anorexia and subsequent starvation, and the anorexia/cachexia syndrome. The mechanisms and response to treatment vary between the two.

Anorexia and Starvation

Anorexia occurs naturally with ageing, but more so with illness. Local symptoms that predispose to it include: dry or sore mouth, problems with teeth or dentures, altered or lost sense of taste, and swallowing difficulties. Other physical symptoms that reduce appetite are pain, nausea and vomiting, early satiety due to gastric stasis, and constipation or diarrhea. Depression and anxiety will also have a negative impact on the desire to eat. The result is reduced food and calorific intake followed by weight loss and ultimately starvation. Starvation is characterized by loss of fat initially with preservation of muscle. Subsequently there is protein loss, both skeletal and visceral. There is no systemic biochemical abnormality, such as a rise in acute-phase proteins. Management is focused on correction of the predisposing factors with appropriate nutritional support. This may be simply by improving the presentation, amount, and frequency of meals, or by nutritional supplements. These strategies should result in weight gain.

Anorexia/Cachexia Syndrome

Cancer cachexia is a syndrome defined by loss of skeletal muscle (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support [38]. In fact cachexia is not restricted to cancer but can also be associated with other chronic respiratory diseases. The key feature is that it includes a chronic systemic

inflammatory response characterized by increased synthesis of acute-phase proteins and mediated by cytokines [39]. The result is redistribution of body protein with muscle wasting, hepatomegaly, and increased resting energy expenditure. Nutritional supplementation alone does not reverse the metabolic consequences of anorexia/cachexia. Nonetheless nutritional support is clearly part of the overall management of these patients. Strategies to assist this include:

- Small frequent meals or snacks
- Attractive appearance, taste, and palatability of food
- Food fortification
- Oral nutritional supplementation
- Environmental issues (surroundings, social context of meals)

Various drugs have been studied in attempts to reverse the metabolic processes involved in this syndrome. Unfortunately none is entirely successful. These include:

- Corticosteroids
- Progestagens
- Omega-3 fatty acids
- Prokinetic drugs
- Nonsteroidal anti-inflammatory drugs
- Thalidomide

It is common practice to prescribe dexamethasone (2–4 mg daily) or prednisolone (5–10 mg daily) to improve appetite (and energy) in patients with cancer-related cachexia. However with continued use adverse effects become prominent. Proximal muscle wasting due to the steroids is observed after only a few weeks of treatment. The potential benefit therefore needs to be balanced with potential adverse effects and survival. Megestrol acetate (40–160 mg daily) has been used with variable benefit but adverse effects include edema, feminization, and increased risk of thromboembolism.

Eicosapentaenoic acid (EPA) is a long-chain polyunsaturated fatty acid in the omega-3 family which has been used in attempts to reverse cancer cachexia. A systematic review concluded that there was no clinical effect on weight, appetite, or quality of life [40]. Prokinetics such as metoclopramide and domperidone have been shown to improve the symptoms of early satiety and nausea, but do not improve appetite or weight.

Fatigue

Sometimes described as asthenia, fatigue is a very common symptom in many chronic diseases. In respiratory medicine it accompanies advanced COPD, cystic fibrosis, and other causes of chronic sepsis, lung fibrosis, and neuromuscular disorders as well as lung cancer and mesothelioma. Fatigue includes both a physical

(easy tiring and generalized weakness) and emotional component. The latter is characterized by poor concentration and memory with changes in mood. There are a number of potentially treatable causes to consider, before giving purely symptomatic management:

- Cachexia/malnutrition
- Chronic infection
- Anemia
- Chronic hypoxemia
- Emotional problems
- Insomnia
- Dehydration and electrolyte imbalance
- Other metabolic disturbance
- Drugs

In lung cancer and mesothelioma patients who do not have any of the above problems, fatigue may be presumed to be truly paraneoplastic. It is believed to be due to the production of tumor products such as cytokines.

Corticosteroids are the most widely used group of drugs for the management of fatigue in advanced disease. There is little controlled trial evidence to support their use. Dexamethasone (2–4 mg daily) and prednisolone (5–10 mg daily) are the drugs most commonly used. Certainly they do have an initial positive effect, on energy and well-being, as well as appetite. Unfortunately, as with their use in anorexia, the adverse effects become evident within a few weeks of treatment. The proximal muscle weakness, particularly quadriceps, then worsens the ability to walk and transfer. Steroids are therefore only recommended for fatigue for short-term use when anticipated survival is short. A Cochrane review has examined drug treatment for cancer-related fatigue [41]. Methylphenidate (10–20 mg daily) showed a small but statistically significant improvement in fatigue over placebo at the cost of some adverse effects. Hemopoietic growth factors such as erythropoietin and darbepoetin show significant benefit for fatigue in chronic renal failure only. There are concerns about the safety of these drugs and their use is not recommended for cancer-related fatigue. Neither progestational steroids such as megestrol acetate, nor antidepressants such as paroxetine, showed significant benefit.

Exercise programs may be helpful for patients with fatigue. A meta-analysis of 28 studies including 2083 cancer patients with fatigue concluded that exercise was beneficial for patients with cancer-related fatigue [42]. The nature of the exercise depends on the functional capacity of the patient and the stage of the disease, and if possible a physiotherapist should be involved as early as possible. In relatively early stages where it is hoped to restore function a program similar to pulmonary rehabilitation may be appropriate. In more advanced disease the aim is more supportive rather than restorative. This will involve low-intensity aerobic exercise. This can be achieved with walking, static cycle, dancing, recumbent cycle, or chair-based exercise. Some prefer individual activity, and some group work, aiming at enjoyable,

purposeful, and meaningful goals. As the end of life approaches the focus will be on conservation of energy for important activities.

Sweating

There are two types of sweat glands, apocrine, which develop at puberty and are found on the scalp, axillae, nipples, and anogenital area, and eccrine. The eccrine glands in turn are of two types, those on the palms, soles, and axillae and those over the rest of the body, which are under the control of the cholinergic postganglionic sympathetic chain [43]. It is this latter type which is involved in the excessive sweating associated with mesothelioma and other malignancies. This sweating may be due to a paraneoplastic phenomenon, in which case it will be generalized. Mechanisms for this include a response to pyrexia, the production of pyrogens by the tumor, or effects of tumor products on the hypothalamus. Tumor involvement of the thoracic sympathetic chain can result in ipsilateral sweating of the trunk. Some drugs such as morphine and antidepressants can also cause excessive sweating. Symptomatic treatment of sweats includes drug and nondrug approaches. The latter includes cooling fans, tepid sponging, and wearing lightweight cotton clothes, which will absorb the sweat.

There is no drug that has been proven to consistently alleviate sweats in mesothelioma. Those which have been reported to help include:

- Paracetamol or aspirin as an antipyretic
- Nonsteroidal anti-inflammatory drugs (ibuprofen 200–400 mg 8 hourly or naproxen 250–500 mg 12 hourly)
- Propantheline 15–30 mg 8–12-hourly
- Amitriptyline 25–50 mg at night
- H2 antagonists such as cimetidine, 400 mg twice daily
- Thalidomide 100–200 mg at night

Itch

Itch, also known as pruritus, occurs in a large number of cutaneous and systemic disorders including lung cancer.

Itch nerve endings are found in the superficial layers of the skin, mucous membranes, and conjunctivae. Impulses pass via the spinothalamic tract, thalamus, and internal capsule to the somatosensory cortex. The sensation of itch is aggravated by anxiety, depression, and boredom, and reduced by distraction and other sensory stimuli [44]. The nerve fibers in the epidermis contain neuropeptides, such as substance P, which is a sensory transmitter. These neuropeptides also stimulate the local release of inflammatory mediators such as interleukins, prostaglandins, bradykinin, serotonin, and histamine from surrounding lymphocytes and mast cells. These mediators produce itch as well as a local inflammatory reaction [45]. The presence

of a number of different potential mediators may explain why systemic drug treatment of itch is unpredictable and not always successful. Itch may occur as a paraneoplastic phenomenon, and drugs are also commonly implicated, of which opioids are probably the most relevant. There is a particular distribution of pruritus associated with the use of spinal opioids.

There are two components to this, local skin care and systemic management with drugs. Achieving optimal skin hydration is important. Dry skin is commonly found in patients with advanced cancer and pruritus. Washing with soap tends to dry out the skin, so it is advisable to substitute it with aqueous cream or add emollient to the bath water. Aqueous cream can also be applied to the skin once or twice daily. Because of the range of mediators implicated in the genesis of itch, there are a number of potential pathways that can be targeted by drug treatments. In practice, the most relevant are histamine, serotonin, and endogenous opioid. Histaminergic drugs include H1 antagonists such as chlorphenamine and promethazine, H2 antagonists such as cimetidine, and mixed antagonists (doxepin). Serotonergic drugs are probably more useful in paraneoplastic pruritus. Selective serotonin reuptake inhibitors (SSRI) such as paroxetine and the antidepressant mirtazapine are both effective. The 5-HT3 antagonist ondansetron is also used in opioid-induced pruritus. The opioid antagonists naloxone and naltrexone have been successfully used for the pruritus associated with uremia and cholestasis. Anti-inflammatory and immunomodulatory drugs such as prednisolone and thalidomide are also useful in certain circumstances.

Dosing regimens:

- Paroxetine 10–20 mg once daily
- Mirtazapine 15–30 mg at night
- Chlorphenamine 4 mg three times daily
- Ondansetron 8 mg twice daily
- Cimetidine 400 mg twice daily
- Thalidomide 100 mg at night

Hypercalcemia

Hypercalcemia is one of the commonest paraneoplastic syndromes. In health calcium metabolism is tightly regulated by the interplay of parathormone (PTH), vitamin D, and calcitonin, their effects being mediated via alterations in absorption of calcium and phosphate from the kidney, gut, and bone. This complex interplay can be disturbed in malignant disease, the commonest mechanism being production of humoral factors by the primary tumor. In the majority of cases this is a parathyroid hormone-related protein which mimics the effect of PTH, but on occasion the tumor may produce 1,25-dihydroxy vitamin D or even true PTH. A second, less common mechanism involves direct bone osteolysis by the presence of bony metastases.

Hypercalcemia in malignancy tends to present with confusion, but sometimes with more subtle psychological problems such as depression, memory loss, or

profound fatigue. This can develop into coma, made worse by dehydration which accompanies hypercalcemia. Nausea, vomiting, constipation, and abdominal pain are also frequent. The development of any of these features should prompt the measurement of a blood calcium level. The severity of symptoms correlates with the elevation of calcium level, although the relationship is fairly loose. The rate of change of the blood level is also relevant and it is worth looking over serial calcium measurements in the presence of suggestive symptoms.

Management

Symptomatic hypercalcemia is accompanied by dehydration because the increased calcium level induces a diuresis. The reduction in circulating volume can be life threatening but, even when less severe, contributes to symptoms and should be reversed, initially with intravenous fluids.

The mainstay of therapy for hypercalcemia of malignancy is to give a bisphosphonate. This can be given as a single dose by infusion. Several are available; zoledronate has been shown to be superior to pamidronate which in turn has been shown to be superior to etidronate [46, 47]. Whether bisphosphonates should be used or not depends on the severity of symptoms and the level of hypercalcemia. Most physicians would certainly use a bisphosphonate if serum calcium is above 3 mmol/L, and many feel that they are appropriate at lower levels bearing in mind that bisphosphonates not only lower calcium levels acutely but also increase the average time to recurrence of hypercalcemia.

Bisphosphonates act by preventing the osteoclast-driven resorption of calcium from bone, stimulated by the PTH-like protein. There are other agents available which can help via different mechanisms, and which can be tried if the response to bisphosphonates is disappointing. Calcitonin directly reduces osteoclast activity and also promotes calcium excretion by the kidney. It is an effective calcium-lowering agent but unlike bisphosphonates has to be administered continually to be effective. Conventional wisdom is that corticosteroids do not work in hypercalcemia of malignancy, but when the mechanism is tumor production of hydroxy-cholecalciferol steroids are often effective. Furosemide can also have a calcium-lowering effect by virtue of increasing renal calcium excretion.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH occurs as a paraneoplastic phenomenon in a number of malignancies, the commonest of which is small-cell lung cancer (SCLC), in which the incidence is about 6% [48]. The clinical features of the condition depend on how low the plasma sodium level is. At levels between 110 and 120 mmol/L, there are emotional changes such as fatigue or confusion, with anorexia, nausea, and vomiting. At lower sodium levels the patient may lose consciousness or have fits. SIADH may be suspected in patients with a low plasma sodium alone (less than 130 mmol/L), but it is necessary

to show that the patient is euvolemic (neither dehydrated nor fluid overloaded). The diagnosis is confirmed by checking the urine and plasma osmolality at the same time. A combination of plasma osmolality less than 300 mosmol/L, paired with urine osmolality more than 300 mosmol/L, is diagnostic. Urinary sodium excretion is also raised, but it is usually not necessary to check this in the palliative care context. The other endocrine condition to be excluded is hypoadrenalism. Management of SIADH consists of:

- Fluid restriction (less than 1 L/24 h).
- Demeclocycline: initially 300 mg three to four times daily, reducing to twice daily. This acts by blocking the renal tubular effect of ADH [49].
- Tolvaptan 15 mg daily is an alternative treatment which acts as a vasopressin receptor antagonist.
- Treat the underlying cause.
- Symptomatic treatment of neurological symptoms.

In patients who have had SIADH at presentation of their SCLC, the plasma sodium is a good marker of disease activity. It returns to normal as the disease responds to chemotherapy, but drops again with relapse.

Stridor

Stridor is the inspiratory wheezing sound indicating significant narrowing or near obstruction of the vocal cords, trachea, or large bronchi. The obstruction may be intrinsic (by tumor) or extrinsic, from tumor or lymph nodes. Tracheal obstruction is life threatening and extremely distressing and needs urgent management. The treatment options include external beam radiotherapy, some form endobronchial intervention such as stenting (Fig. 6.1), or both (very occasionally, and only in SCLC, chemotherapy may be the preferred option). If possible, endobronchial treatments should be offered, as they give quicker symptomatic relief, but the patient has to be fit enough to have the procedure. There is very little evidence comparing any of the interventions listed below in terms of efficacy, and the choice is largely determined by local availability [50]:

- External beam radiotherapy
- Endobronchial brachytherapy
- Cryotherapy
- Thermal laser ablation
- Photodynamic therapy
- Airway stents (current standard is the self-expanding metallic airway stent made from nitinol) [4]

Our experience suggests that a combination of laser and subsequent stent insertion gives prompt palliation.

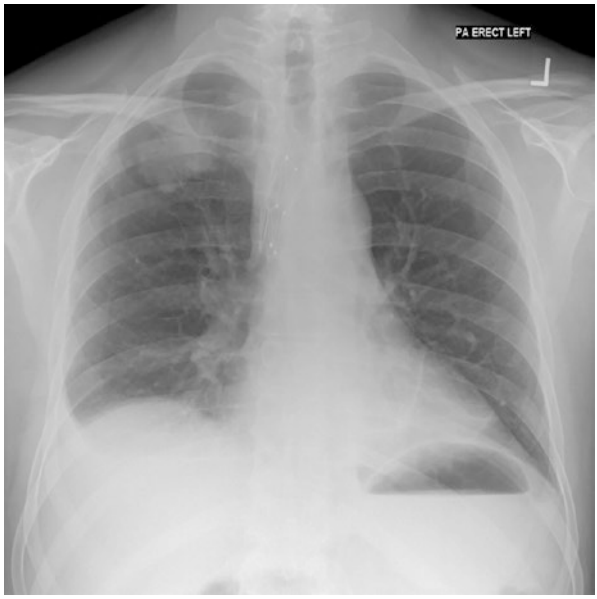

Fig. 6.1 Plain chest radiograph showing bronchial stents positioned in the right main bronchus and bronchus intermedius. The primary tumour is visible in the right upper zone and there is a small right pleural effusion

Hoarseness

Hoarseness in lung cancer is due to vocal cord paralysis. The paralyzed cord is unable to adduct against the other cord and the result is a hoarse voice and the inability to close the cords prior to coughing. The resulting "bovine" cough arises because inadequate pressure is built up before the cords are relaxed. Management is by a surgical technique to fix the affected vocal cord in the adducted position. Usually this is achieved by injection of Teflon® or Bioplastique® [50].

Superior Vena Cava Obstruction

The superior vena cava (SVC) is a large but short vessel formed from the right and left brachiocephalic veins. It carries the venous return from the head, neck, and arms to the right atrium. The intravascular pressure is low in the SVC and it is a relatively thin-walled structure, and thus vulnerable to compression. Lung cancer is the commonest cause of the syndrome in which flow through the SVC is obstructed (SVCO) although other tumors, particularly lymphoma and thymoma, can produce the same syndrome as can rare benign conditions. Patients with SVCO often complain of cough and breathlessness, although these may equally be due to the primary tumor. More specifically, patients notice swelling of the face, neck, and arms; dizziness; or headache. These symptoms may be made worse by anything which impedes venous return from the upper body, such as bending over. Symptoms are very variable, due in part to differences in the rate at

which the obstruction develops. Collateral vessels may open up over time, and if the SVCO is of gradual onset may be well established by the time complete obstruction occurs. Collateral routes include the azygos, internal mammary, and long thoracic venous systems. Dilated collateral vessels may therefore be visible on the chest wall or over the abdomen. Although SVCO is principally caused by external compression of the vena cava, sometimes clot forms in the vessel lumen. SVCO can be confirmed by a contrast CT scan of the thorax.

There is a paucity of good-quality data about the treatment of SVCO. Simple measures such as nursing the patient upright can help. It is common practice to give large doses of steroids, typically dexamethasone 8–16 mg/day, to patients with SVCO. This treatment has never been formally studied and it is difficult to judge its efficacy from retrospective studies since it is usually quickly followed by some other form of treatment. Since the benefit is uncertain it is important not to prolong steroid treatment unduly.

Radiotherapy offers a reasonable prospect of shrinking the tumor and relieving obstruction in both non-small cell and small-cell tumors, and indeed in less common diagnoses such as lymphoma. When the diagnosis is known to be non-small cell carcinoma, retrospective studies have shown that radiotherapy relieves SVCO in 63% of cases [51]. There is controversy about the use of radiotherapy to reduce tumor bulk when the diagnosis of lung cancer is strongly suspected but has not yet been proven. Radiotherapy can make interpretation of subsequent histology difficult and it is usually preferable to obtain diagnostic tissue before using radiotherapy. However, this is only an issue when SVCO is part of the presentation of a new tumor.

There are no randomized control trials comparing chemotherapy to radiotherapy for the relief of SVCO. In small-cell cancers, which cause a disproportionate amount of SVCO, the response rate in retrospective studies of chemotherapy suggests that it is relieved in 77% of cases [51]. The response to radiotherapy is roughly the same, and the choice will depend on whether the patient is fit enough to receive a course of chemotherapy as definitive treatment, in which case it may be best to use chemotherapy from the onset. There is no benefit in giving both chemotherapy and early radiotherapy in SCLC, at least in terms of relieving SVCO.

Self-expanding intravascular metal stents can be inserted into the SVC via the femoral or brachiocephalic veins, and offer a means of relieving SVCO even when tumors are nonresponsive to chemotherapy or radiotherapy. It may not be technically possible to insert a stent depending on the presence of clot and the tightness and the length of the obstruction. However, placement can usually be achieved and case series suggest that SVCO can be relieved in over 90% of cases [51]. One small comparative study suggested that stents provide relief more reliably than radiotherapy [52]. Thrombolysis before stent insertion does not increase the success rate, although many centers will give heparin.

Should stents be used in all cases, since they appear to offer the highest success rate? It should be noted that the superiority of stenting has not been tested in a controlled trial. We would suggest that stenting should be employed when symptoms are severe and rapid relief is required, or when patients are not suitable for

chemotherapy or radiotherapy, including those with no diagnosis in whom rapid symptom relief is required.

Spinal Cord Compression

The incidence of spinal cord compression is uncertain but it probably occurs in <5% of cases of lung cancer. Nonetheless, although relatively uncommon it is an extremely important condition because once established it has a devastating effect on quality of life and reduces life expectancy. Early recognition and treatment are crucial; there is a significant association between the walking ability at presentation and following treatment [53]. The commonest mechanism of cord compression is in association with collapse of one or more vertebrae. However, tumor can grow directly into the spinal cord without causing collapse, metastases can deposit directly into cord structures, and in any of these situations the position can be complicated by involvement of the blood supply to the spinal cord. The rate of onset of symptoms is therefore highly variable, but the large majority of people with cord compression have reported severe central back pain for a period of time beforehand. This may be accompanied by radicular pain, and later by weakness of the lower limbs. In over half the cases the development of central symptoms below the level of compression occurs. It is a sensible idea to warn patients known to have metastatic spinal cord deposits of the potential development of these symptoms so that they can report them promptly.

Management

An X-ray of the spine may show vertebral collapse. However, magnetic resonance imaging is the optimal modality for identifying spinal metastases and for demonstrating the site and extent of cord compression (Fig. 6.2). Patients should be given analgesia appropriate to their degree of pain, but urgent definitive treatment must be considered to prevent permanent neurological damage. Spinal cord decompression should probably be attempted as first-choice treatment, although direct comparison with the main alternative, radiotherapy, has been mainly observational [54]. It is difficult to give firm guidance, but the choice between the two must involve an assessment of the site of the tumor and the general condition of the patient, as well as the prognosis of the primary tumor. There are no randomized, controlled trials of the two forms of treatment; retrospective analysis of outcomes favors surgery, but case selection is likely to have influenced this conclusion [55]. Of course, the two modes of treatment are not in competition, and in many instances it is appropriate to give additional radiotherapy after surgery.

Surgery needs to be performed urgently. This improves neurological outcomes, and final ability to walk is better the shorter the time between symptom onset and surgery [56, 57]. It has been said that paraplegia and tetraplegia of more than 20-h duration will not recover. For most patients posterior decompression and internal fixation are the appropriate surgical procedures. If surgery is not feasible, radiotherapy may be an effective treatment, but again must be deployed swiftly. Current

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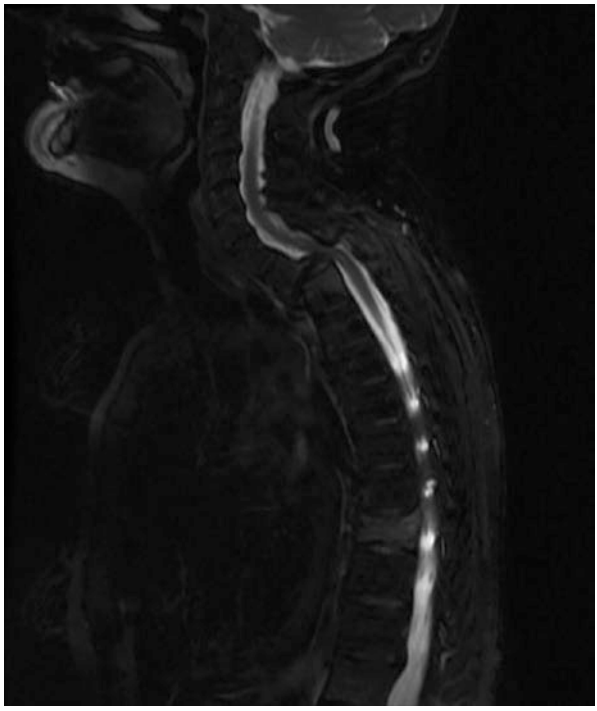

Fig. 6.2 MRI scan showing spinal cord compression of the upper thoracic spine due to metastatic lung cancer

clinical practice in the UK is to give fractionated radiotherapy over 5–10 days, but good comparative studies of different regimens are lacking and this continues to be an area of research. When it is has not been possible to give treatment soon enough to avoid paralysis, radiotherapy may still have a role as a means of controlling pain as, more rarely, might surgery in the form of spinal cord stabilization. When pain relief is the objective, several studies have shown that a single fraction of 8 Gy is as good as more complex radiotherapy regimens.

Carer Support and Progressive Disease

Patient and Family Support

Patients and their families need considerable support throughout the course of the disease. Emotional distress fluctuates, tending to peak at the time of diagnosis, when disease progression is confirmed and as the end of life approaches. Continuity of care is helpful in dealing with the different phases of the disease, and in the UK there is a particular emphasis on the role of a lung cancer nurse specialist, the primary care general practitioner, and the respiratory physician in co-coordinating care throughout the disease trajectory. In addition a number of voluntary and charitable services are available to support families in coping with the effects of lung cancer.

Many services have close links with patient/carer support groups, often run by the lung cancer nurse specialists or by bereaved carers wishing to offer experience and support. At a national level, the Roy Castle Foundation offers a variety of functions including patient and carer involvement forum, awareness volunteers, a helpline, and fact sheets.

Living with Advanced Lung Cancer

Two studies have compared the quality of life and service utilization in patients with lung cancer and advanced COPD [7, 58]. In general, quality of life, both physical and emotional, was maintained longer in the lung cancer patients. They had greater use of district nursing and specialist palliative care nursing services, but less social care and use of aids and appliances. The likelihood of impending death and therefore choices around this was discussed earlier and more consistently in the lung cancer patients, who were more likely to die at home or in a hospice than in hospital. In those wishing to be at home when dying, the community nurse and specialist palliative care teams are well placed to provide care and support in the patient's home.

End of Life

Compared with most chronic lung diseases with a fluctuating course, the end-of-life phase is more predictable in lung cancer. The recognition of this stage is considered in detail in Chap. 14. Features include profound fatigue, loss of powers of concentration, or short attention span and sometimes drowsiness, confusion, or agitation ("terminal agitation"). Both appetite and thirst decline, as does urine output. Of the common symptoms of lung cancer, breathlessness, cough, and pain often subside as death approaches and more troublesome ones may be agitation and noisy secretions ("death rattle"). Specific management strategies for these symptoms are considered in Chap. 14.

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Malignant Pleural Effusions and Mesothelioma

7

David Cooper and Tim Peel

Introduction

Pleural effusions are a common problem in the palliative phase of a number of different conditions. Malignant pleural effusions occur in up to 15% of patients with cancer, affecting more than 750,000 persons each year across Europe and the United States [1]. They usually indicate advanced or metastatic disease and survival is therefore poor. They are often recurrent and can be associated with a high symptom burden. The incidence is set to rise alongside global cancer incidence and as overall survival improves. Breathlessness is the most commonly reported symptom and management should focus on both relieving symptoms and minimizing the need for repeated procedures.

Malignant pleural mesothelioma is an aggressive primary tumor of the pleura, almost always caused by previous exposure to asbestos. Global incidence has been rising steadily and is due to peak in the coming years. Prognosis is poor and symptoms can be difficult to manage. Until recently, treatment options and clinical trials have been limited and the disease has been poorly responsive to both radiotherapy and standard chemotherapy. However, more recently, there has been an increasing number of good-quality clinical trials for mesothelioma, and newer therapeutic options such as immunotherapy seem promising. This chapter focuses on the management of symptomatic pleural effusions and then discusses the specific problem of malignant mesothelioma.

D. Cooper
Department of Respiratory Medicine, North Tyneside General Hospital, Tyne and Wear, UK

T. Peel (✉)
Policy, Ethics and Life Sciences, Newcastle University, Newcastle Upon Tyne, UK
e-mail: e.t.peel2@newcastle.ac.uk

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Investigation of a New Pleural Effusion

Several guidelines have been published detailing the assessment and management of pleural effusions and mesothelioma specifically [2–4]. Chest radiography and thoracic ultrasound are the initial investigations of choice when a pleural effusion is suspected clinically (Fig. 7.1). A diagnostic pleural aspiration should be performed under ultrasound guidance to obtain samples for biochemistry (protein, lactate dehydrogenase (LDH), pH, and glucose), microbiology, and cytology. If the patient is symptomatic, a larger volume of fluid can be aspirated at this stage to relieve breathlessness. Computed tomography (CT) is used to assess pleural thickening and pleural nodularity and for assessment of the lung, lymph nodes, and other organs. The pleura enhances late with contrast and therefore a dedicated pleural phase CT can increase sensitivity.

Malignant pleural effusions may be diagnosed by pleural fluid cytology in about 60% of cases but this figure is lower for malignant mesothelioma. A recent large prospective cohort study in the UK found that the overall sensitivity of fluid cytology to diagnose malignancy was 46% [5]. There was variation in sensitivity depending on the primary cancer with mesothelioma and hematological malignancies being significantly lower than adenocarcinomas and effusions secondary to ovarian cancer. The yield from sending more than two specimens, taken on different occasions, is very low and should be avoided. Where there is clinical and radiological suspicion of malignancy but pleural fluid cytology is negative, a pleural biopsy should be obtained (via either medical thoracoscopy, surgical video-assisted thoracoscopic (VATS) biopsy, or CT-guided biopsy) but only if the patient is well enough to undergo further investigations and the result will alter their future management. Both CT-guided biopsy and thoracoscopy have high diagnostic yields for malignant pleural disease. CT-guided biopsy should be used when pleural thickening is present, with only a small volume of pleural fluid or when thoracoscopy is not available.

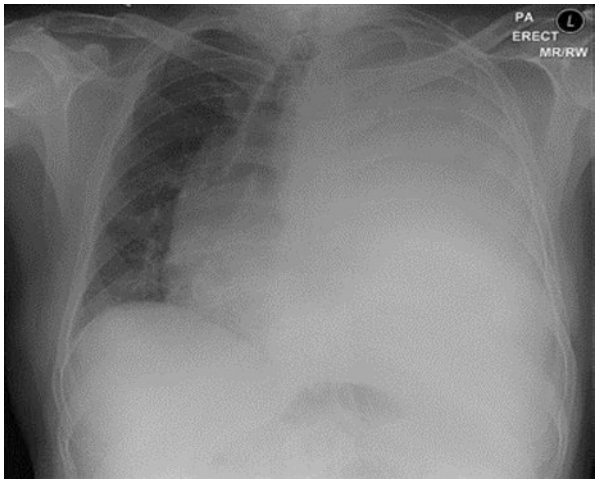

Fig. 7.1 Chest radiograph showing a large left pleural effusion causing a "whiteout" of the left hemithorax and deviation of the mediastinum to the right

When diagnostic pleural aspiration is negative or inconclusive, thoracoscopy should be considered if the patient's general physical condition allows it. Thoracoscopy can be performed either under local anesthetic with conscious sedation (medical thoracoscopy) or via a surgical VATS procedure. It allows direct visualization of the pleura and good-sized pleural biopsies and, if indicated, either talc pleurodesis or insertion of an indwelling pleural catheter (IPC) can be performed, thereby providing a combined diagnostic and therapeutic intervention in one sitting. Medical thoracoscopy is increasingly available and becoming the most common and rapid way of achieving a diagnosis and symptom control. In those patients with poor performance status or significant comorbidities, further invasive investigations may not be appropriate and the focus should therefore be on symptom control rather than trying to achieve a definitive diagnosis.

Management of Recurrent Symptomatic Pleural Effusions

There are several approaches to the problem of recurrent pleural effusions. The main focus should be on symptom control and reducing the need for repeated procedures by achieving pleurodesis, or allowing the safe and effective repeated drainage of the pleural space when pleurodesis cannot be achieved. In a small number of treatment-sensitive tumor types, such as lymphoma and gynecological malignancy, the effusion may respond to chemotherapy and this would therefore offer an effective first-line treatment. Symptoms, performance status, and patient's wishes are key factors in deciding the most appropriate management strategy.

Therapeutic Aspiration

Repeated therapeutic aspiration of large volumes of fluid via commercially available sets using local anesthetic may be appropriate for a small number of patients such as those with a very poor functional status or prognosis or in the rare situation where fluid re-accumulates slowly. However, the majority of patients with malignant effusions will experience re-accumulation of fluid following therapeutic aspiration and the relief of breathlessness is therefore often short-lived. Repeated aspirations are inconvenient for the patient and can be associated with an increased risk of infection, pneumothorax, and tumor seeding, such that it is often preferable to undertake a more definitive intervention such as pleurodesis or insertion of an indwelling pleural catheter.

Pleurodesis

Pleurodesis is the process of achieving symphysis of the visceral and parietal pleura in order to obliterate the pleural space and therefore prevent the re-accumulation of fluid. Mechanical or surgical pleurodesis is usually performed by thoracic surgeons

and involves either pleural abrasion or partial pleurectomy. This can be done by either an open or more often a VATS procedure, under general anesthetic. Chemical (or medical) pleurodesis is usually performed by respiratory physicians and involves the intrapleural injection of a chemical agent. Both processes result in pleural inflammation progressing to fibrosis. This fibrotic reaction can result in adhesion of the pleural surfaces and obliteration of the pleural space. In addition, there is some evidence that repeated negative pressure aspiration via indwelling catheters can result in auto-pleurodesis.

Two systematic reviews have demonstrated that sterile, graded particle talc is the most effective and safest agent for chemical pleurodesis in malignant pleural effusions [1, 5]. Talc can be introduced into the pleural space either via poudrage (surgical VATS or medical thoracoscopy) or at the bedside as talc slurry through an intercostal chest drain. Thoracoscopic talc poudrage seems to be more effective than talc slurry in achieving pleurodesis, but may be associated with more adverse events [1–7]. An ongoing randomized trial in the UK is aiming to answer this question [8]. Furthermore, surgical VATS and medical thoracoscopy are less widely available. Surgical pleurodesis procedures (pleurectomy and abrasion pleurodesis) are no more effective than talc, especially in mesothelioma [9]. In terms of the administration of talc slurry via a chest drain, larger bore tubes (e.g., 24F) are associated with higher pleurodesis success rates than smaller bore tubes (e.g., 12F) but are less frequently used due to the fact that most physicians are less familiar with placing a large-bore tube [10, 11].

Pleurodesis can be a painful procedure for some patients and it is therefore important to use local anesthetic and ensure adequate analgesia at the time of and after the procedure. Most physicians use a combination of oral analgesia (oral morphine solution or nonsteroidal anti-inflammatory drugs) and intrapleural 1% lidocaine before the instillation of talc slurry. The Therapeutic Interventions in the Malignant Effusions-1 trial demonstrated that nonsteroidal drugs can be used as effective analgesia and are non-inferior to opiate analgesia in terms of pleurodesis success [11].

Indwelling Pleural Catheters (IPC)

IPCs are multi-fenestrated catheters inserted into the pleural space and tunneled through the subcutaneous tissue using local anesthetic (Fig. 7.2). The soft cuff sits in the tunnel and allows fibrous growth around the drain, thereby securing it in place and acting as a barrier to infection. The external portion of the drain has a one-way access valve and is covered with a padded dressing when not being used making it inconspicuous. Therapeutic drainage can be performed by the patient, carers, or community nurses at a time and place convenient to the patient.

IPCs are increasing in popularity and offer a cost-effective long-term outpatient management strategy for regular drainage of malignant effusions. In addition, recurrent drainage can result in spontaneous pleurodesis. Findings from the Therapeutic Interventions in the Malignant Effusions-2 trial showed that IPCs conferred similar

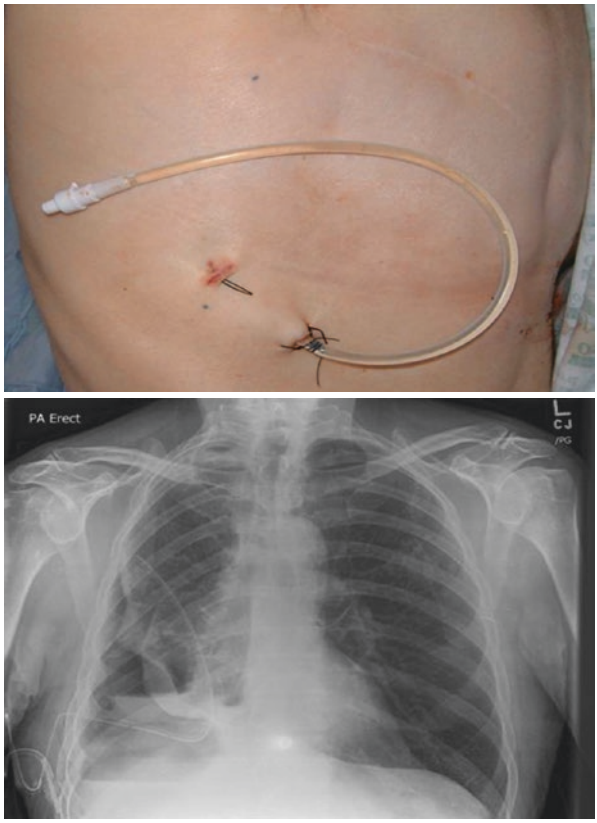

Fig. 7.2 Indwelling pleural catheter

control of breathlessness and quality of life but significantly shorter length of hospital stay than did inpatient talc pleurodesis [12]. The AMPLE study demonstrated shorter hospital stay and fewer subsequent pleural interventions in patients with IPCs compared to talc pleurodesis [13]. They can be inserted as a day case (or at the time of surgical VATS biopsy or medical thoracoscopy) and are increasingly being used worldwide as a first-line option over attempts at pleurodesis. They are also a useful option in those patients where talc pleurodesis fails.

The optimal regimen of drainage after insertion is not well established and varies worldwide. A recent study looking at aggressive versus symptom-guided drainage via IPC found no differences between the aggressive (daily) and the symptom-guided regimens in terms of controlling breathlessness [14]. This study suggested that daily drainage was more effective at promoting spontaneous pleurodesis and might improve quality of life.

IPCs can also provide a portal for the delivery of therapeutic agents directly into the pleural space. The IPC-plus study [15] found that the outpatient talc administration of talc through an IPC resulted in a significantly higher chance of pleurodesis at 35 days than an IPC alone, without adverse effects in those patients who did not

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have substantial lung entrapment. Furthermore there may be a role for IPCs in the delivery of targeted therapies such as monoclonal antibody treatment and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer. Further studies are needed.

Predicting Prognosis in Malignant Pleural Effusions

Prognosis is a key factor in deciding the most appropriate management strategy for patients with malignant effusions. Those patients with a better prognosis are likely to require a more definitive management strategy whereas the approach to those patients with shorter life expectancy should be to reduce interventions and to maximize quality of life and time at home. Prognostication in mesothelioma will be addressed later in this chapter.

Tumor type and stage are well-accepted predictors of prognosis. Malignant effusions usually represent metastatic disease and therefore higher stage and shorter survival. Certain tumor types such as breast cancer and gynecological malignancies tend to have better prognosis in part due to their sensitivity to treatment [16–18]. Pleural effusions due to lung cancer carry the worst prognosis. Low pleural fluid pH (<7.28), low LDH, and massive effusions (defined as fluid occupying the entire hemithorax) have all been shown to be associated with a worse prognosis [18–20].

Only one prognostic scoring system for malignant effusions has been externally validated. The LENT score is a simple and easy-to-apply system that combines pleural fluid LDH, Eastern Cooperative Oncology Group (ECOG) Performance status, serum neutrophil-to-lymphocyte ratio (NLR), and tumor type. Scores separate patients into low-, moderate-, or high-risk groups with median survivals of 319, 130, and 44 days, respectively [21].

Malignant Mesothelioma

Malignant mesothelioma is a rare incurable tumor primarily affecting the pleura and less frequently the peritoneal membrane. Approximately 90% of cases are linked to previous asbestos exposure and so a number of occupations, notably shipbuilding, railway engineering, insulation, plumbing, electrical installation, and asbestos product manufacturing, are associated with an increased risk of the disease. There are rare familial cases related to mutations of the breast cancer-associated protein 1 (BAP1) gene [22]. Malignant mesothelioma develops over a long period of time but once clinically apparent is often rapidly progressive. It affects an increasingly aged population who often have substantial comorbidities. Breathlessness (due to either pleural effusion or lung encasement by tumor), pain, weight loss, and sweating are predominant symptoms. Psychological and emotional problems are common and both patients and families require substantial support throughout the course of the disease. Palliative care is therefore an

important consideration for all patients from the time of diagnosis. There are often complex medicolegal issues to deal with due to the tumor's close association with previous occupational asbestos exposure.

Epidemiology

Mesotheliomas are closely associated with occupational asbestos exposure and are approximately 1000 times more common in those with typical occupational exposures. The current worldwide mesothelioma epidemic reflects exposure during the second half of the twentieth century. The risk of developing mesothelioma increases with the extent of previous asbestos exposure but this is often difficult to quantify accurately and the relationship appears relatively weak. The tumor can occur following low-level exposures such as washing the clothing of a family member. Crocidolite (blue) and amosite (brown) asbestos persist longer in the lung and are more potent causes of mesothelioma than chrysotile (white) asbestos. Industrial workers generally had mixed exposures and the epidemiology of mesothelioma is dominated by the time from first exposure. The risk increases exponentially with time and mesotheliomas are therefore rare within 20 years of first exposure and occur on average after about 40 years. Most patients are over 70 years of age at presentation and men account for the large majority of cases reflecting their greater occupational exposure.

Recorded cases of mesothelioma have been steadily increasing since the late 1960s. Because asbestos exposure came under increasingly stringent control from the early 1970s onwards, mesothelioma incidence is currently around its peak in most industrialized countries. In the UK there are currently approximately 2500 cases per annum with predictions suggesting that this figure will remain static for the rest of this decade before numbers begin to fall. The UK rate is five times that in the USA and the total numbers of cases are similar in the two countries despite their different populations. The rates in other European countries are also lower than in the UK, the latter's high rate being attributed to its greater and more prolonged use of amosite asbestos.

Presentation and Symptoms

Malignant mesothelioma can cause both local and systemic symptoms. Local symptoms tend to predominate in early-stage disease and systemic symptoms become more common with disease progression. Local symptoms include chest pain, breathlessness, and cough. The prevalence of these symptoms is not consistent in different studies. The most prominent systemic symptoms are weight loss, sweating, and fatigue. Given its doubling time, most mesotheliomas are likely to have been present subclinically for a number of years before diagnosis. Occasionally the tumor is identified on a chest radiograph or CT performed for other reasons but for most, the onset of breathlessness due to the development of a pleural effusion is the

first symptom of note. Although mesothelioma can and does metastasize via the bloodstream, symptoms of distant spread rarely predominate over local ones.

The pain caused by mesothelioma can be nociceptive, neuropathic, or sympathetically maintained. The tumor usually originates from the parietal pleura and as such localized opioid-sensitive pain is common, particularly if there is no associated pleural effusion. As it progresses, the tumor invades surrounding structures with chest wall invasion resulting in compression or destruction of the intercostal nerves resulting in neuropathic pain, as well as muscles, ribs, subcutaneous tissue, and skin. Medially, the mediastinal structures and vertebral column can be affected. At the thoracic inlet, brachial plexus involvement results in neuropathic pain, and involvement of the subclavian sympathetic chain causes sympathetically maintained pain in the arm. Advanced disease can invade and penetrate through the diaphragm resulting in ascites and intra-abdominal lymphadenopathy.

Breathlessness is usually initially due to the development of a pleural effusion and will often respond well to removal of that fluid. As the tumor progresses it can encase and therefore restrict expansion of the lung on the affected side and in this situation more general dyspnea management strategies are required. Mesothelioma can also affect the pericardium causing pericardial effusion or tamponade requiring aspiration and, more rarely, phrenic nerve damage due to mediastinal invasion, resulting in diaphragmatic paralysis.

Cough in mesothelioma is due to pleural irritation and is usually dry. Opioids are generally effective in this situation. Systemic symptoms are less common at presentation and tend to be associated with advanced disease. Fatigue, anorexia, and weight loss become more prevalent as the disease progresses. Fever and sweats tend to be more prevalent in mesothelioma patients than those with lung cancer. Fever has been reported in 3–9% of patients at diagnosis and sweats in 20%.

Approach to Patient with Suspected Mesothelioma

The diagnosis of mesothelioma may be suspected if someone with a history of asbestos exposure or asbestos pleural plaques on a chest radiograph presents with a unilateral pleural effusion, particularly if that is associated with chest pain and weight loss. The history of asbestos exposure may need to be actively sought as many patients initially deny exposure and only recall it later after detailed enquiry. Many patients will not be aware that they have had asbestos exposure and as such exposure may have been brief or may have occurred indirectly such as through domestic contact (for example the washing of overalls) possibly many decades prior to presentation. The risk of developing a malignant mesothelioma is in the region of 2% for most asbestos-exposed workers although some groups who were heavily exposed to crocidolite asbestos have much higher rates than that.

Even if the diagnosis of mesothelioma is suspected, alternatives need to be considered. The pleural cavity is a common site for metastases from other primary tumors (lung, breast, upper gastrointestinal, and gynecological cancers). Metastatic pleural adenocarcinomas are often clinically and radiologically very similar to

mesothelioma. Furthermore, nonmalignant alternatives such as cardiac failure, tuberculosis, or rheumatoid pleural disease need to be included in the differential diagnosis. Asbestos can cause benign pleural disease with effusions that resolve resulting in diffuse pleural fibrosis (or chronic fibrinous pleuritis). This can be clinically very difficult to distinguish from mesothelioma although they are less likely to be associated with chest pain or systemic features.

Diagnostic Investigations

Usually, the first investigation of a patient with suspected mesothelioma is a chest radiograph. Unilateral pleural effusion and/or nodular pleural thickening may be apparent but it is the subsequent contrast CT that provides more detailed evaluation of the pleura, lung, lymph nodes, and other organs and allows accurate staging of the disease. The portal-venous phase is optimal for demonstrating pleural enhancement rather than the arterial phase imaging used for standard thoracic CT. Features such as pleural nodularity, mediastinal extension, and chest wall invasion suggest malignancy rather than benign disease though they do not differentiate mesothelioma from metastatic pleural tumors. The differentiation between mesothelioma and metastatic pleural malignancy is very difficult. Lung involvement and mediastinal or hilar lymphadenopathy may point towards metastatic pleural disease while the presence of pleural plaques, as an indicator of previous asbestos exposure, increases the likelihood that the diagnosis is mesothelioma.

A diagnostic pleural aspiration can be obtained in the outpatient setting and should be performed using thoracic ultrasound. However, as previously discussed, the overall sensitivity of fluid cytology to diagnose mesothelioma is very low. The largest prospective study of pleural fluid cytology to date showed that in asbestos-exposed males with exudative pleural effusions, the risk of malignancy was 60%, but cytological sensitivity was only 11% [5]. Repeated samples are rarely useful. This can help inform discussion with patients about the need for further investigations and suggests that in patients presenting with a clinical suspicion of mesothelioma more definitive investigations such as thoracoscopy could be performed early in the diagnostic pathway. If there is an identifiable pleural mass, it can be biopsied under CT guidance which can identify up to 80–85% of mesotheliomas and has low complication rates.

Histology

Histologically, mesotheliomas can be difficult to diagnose and classify. They are classified into three types: epithelioid mesotheliomas account for approximately 60% of cases; sarcomatoid mesotheliomas, which have spindle cell morphology, account for approximately 20%; and biphasic mesotheliomas demonstrate both epithelioid and sarcomatoid features and are subclassified into biphasic-E (epithelioid) or biphasic-S (sarcomatoid) depending upon which morphology predominates.

Histological subtype is an important consideration as it has implications for treatment and has been shown to be associated with patient outcomes. Patients with purely epithelioid histology have a better predicted survival of between 12 and 27 months, whereas those with sarcomatoid histology have a worse prognosis of approximately 6–18 months [23, 24].

Predicting Prognosis in Mesothelioma

Tumor staging, histology, and performance status are well-established parameters used for predicting prognosis. Several prognostic scores have been developed for mesothelioma. The EORTC prognostic score and CALGB prognostic groups were based on patients recruited to chemotherapy trials and therefore are less representative of typical patients presenting with mesothelioma [24, 25]. The Brims prognostic model included all patients newly diagnosed with mesothelioma in Western Australia and has been validated in a UK cohort [26]. The validation cohort is likely to be a good representation of typical new patients with mesothelioma presenting in the UK. Weight loss was found to have the greatest influence on survival with histological subtype, performance status, hemoglobin level, and serum albumin making up the other variables.

Management Strategy

The management of malignant mesothelioma remains primarily palliative. One-year survival is approximately 40% and the typical patient at presentation is elderly and has comorbidities. Less than 50% of patients have a WHO performance status of 0 or 1 at presentation, therefore precluding active treatment such as chemotherapy, immunotherapy, or debulking surgery [27, 28]. However, recently there has been significant progress in terms of our understanding of the disease process through research resulting in improved awareness and newer treatment options. Patients are increasingly well informed and connected and can access information regarding their disease and potential treatment options or clinical trials. The development of specialist nurse roles, specialist mesothelioma multidisciplinary teams, and publications such as the British Thoracic Society (BTS) guidelines [4] and Royal College of Physicians National Mesothelioma Report 2018 [28] as well as work by various mesothelioma charities have resulted in major improvements in data collection and recording, access to specialist care, and opportunity to take part in clinical trials.

Chemotherapy in Malignant Mesothelioma

The commonest treatment decision in patients diagnosed with mesothelioma is whether or not they are candidates for chemotherapy. It is generally accepted that

only patients with a WHO performance status of 0–1 are suitable for this. The BTS mesothelioma guidelines recommend the use of first-line pemetrexed/platinum chemotherapy based on good-quality randomized control trials and currently antifolate and platinum combination chemotherapy remains the only established treatment [29, 30]. There is some evidence from a phase III randomized controlled trial that the addition of bevacizumab to pemetrexed and cisplatin chemotherapy leads to longer survival than pemetrexed and cisplatin alone [31]. However, bevacizumab is not currently licensed for use in the UK. At present, after first-line chemotherapy, there is no established second-line treatment and patients with good performance status should be offered referral to specialist centers for consideration of second-line clinical trials. In early clinical trials, immunotherapies and treatments targeting cancer-associated antigens and oncogenic alterations are emerging as potential future treatment options.

About 40% of patients diagnosed with mesothelioma are suitable for chemotherapy at presentation. When advising patients it seems reasonable to suggest that chemotherapy on average prolongs life in the region of 3–4 months and improves symptoms at the expense of the inconvenience and potential adverse effects of the chemotherapy itself. There is likely to be a range of responses to treatment with some patients doing significantly better than average and others worse. Some patients are reluctant to start chemotherapy at an early stage in their disease when they are relatively well and wish to defer treatment until they become more symptomatic. It is not known whether the response to treatment is better when given early. There is one small study that suggests a nonsignificant improvement of 3 months in the time to symptom progression, and a 4-month improvement in survival in those randomized to early treatment, but there were no differences in quality-of-life measures [32]. Patients' clinical condition can deteriorate rapidly and deferring chemotherapy therefore runs a risk of them never receiving it.

Surgery

The BTS mesothelioma guideline summarizes current views on the role of surgery in mesothelioma in the UK [4]. Attempts at radical treatment with extrapleural pneumonectomy, with or without adjuvant chemotherapy and radiotherapy, are not recommended. Similarly VAT partial pleurectomy, when compared with talc pleurodesis, gave no improvement in overall survival and resulted in more adverse effects and longer hospitalization. It is therefore recommended that talc pleurodesis should be used before any surgical procedure, as described earlier in this chapter.

Radiotherapy

There are three contexts in which radiotherapy has been used in the management of mesothelioma. These are as a radical treatment either alone or in combination with

surgery and/or chemotherapy, as a prophylactic treatment to intervention sites (to prevent tumor growth), and for the palliation of local symptoms [4]. Although an initial study suggested that there may be a role for prophylactic treatment to the sites of previous needle or other invasive intervention sites, subsequent studies have shown that here is no evidence of benefit in terms of prevention of recurrent tumor nodules by the provision of local radiotherapy to those intervention sites [4]. Similarly radical radiotherapy alone, or as an adjunct to surgery, has not been shown to have any beneficial effect on survival. Retrospective, uncontrolled studies of localized radiotherapy for palliation have shown improvement in pain, but the duration of relief is short. There is no agreed optimal dose or fractionation. In summary, the only context in which radiotherapy may be of benefit in mesothelioma is for palliation of pain due to localized disease [4].

Symptom Control

Throughout their illness, patients' symptoms will need to be addressed and they will tend to worsen as the disease progresses. There have been no mesothelioma-specific randomized controlled trials of any treatment for any symptom of mesothelioma [4]. The general management strategies for the individual symptoms are described in the following chapters:

- Breathlessness (Chap. 2)
- Pain (Chap. 5)
- Fatigue (Chap. 6)
- Anorexia and cachexia (Chap. 6)
- Sweats (Chap. 6)
- Cough (Chap. 4)

Percutaneous Cervical Cordotomy

The pain of mesothelioma can be complex and very troublesome. It is often a combination of nociceptive pain from pleural and chest wall invasion and neuropathic pain from infiltration of the intercostal nerves, brachial plexus, or even spinal cord. Sometimes good pain control is not achieved, even with a combination of opioids and drugs for neuropathic pain, because of lack of adequate effect or unacceptable adverse effects. In these circumstances, neurolytic blockade may be appropriate. One such technique is percutaneous cervical cordotomy. In this procedure, the contralateral anterolateral spinothalamic tract is interrupted at the C1/2 level by thermocoagulation. The procedure has a good success rate with 38% of patients being able to stop their opioids and is safe with no treatment-related deaths or major complications reported in one study [22]. Unfortunately this intervention is only available at a few centers in the UK. Other anesthetic procedures available include intercostal nerve block and spinal anesthesia.

Psychological and Legal Aspects

A diagnosis of malignancy is associated with a variety of emotional and psychological responses. Care of patients with mesothelioma is usually coordinated and managed by lung cancer teams and services are therefore likely to be designed in line with those provided for lung cancer. Ball and colleagues propose that patients diagnosed with mesothelioma potentially have different sources of psychological distress than those with lung cancer [33]. Through a systematic literature review they found that in addition to the shared concerns of physical symptoms and family/carer burden, patients with mesothelioma reported higher levels of distress relating to hope and hopelessness, legal/financial issues, and blame. Previous knowledge of asbestos exposure and the risk to health can heighten anxiety of a diagnosis, as mesotheliomas cluster in occupational groups and patients often have previous experience of mesothelioma in friends and colleagues and may worry about their own clinical course. Moore and colleagues quantified emotional functioning in patients with mesothelioma and their families [34]. They recorded anxiety in two-thirds of patients and depression, fear, and isolation in about half. Carers reported higher levels of psychological morbidity with 80% reporting anxiety and depression. Most patients (71%) were found to reach an acceptance of their disease in contrast to family/carers where acceptance was low (23%). Healthcare teams should be aware of the need to offer psychological support at all stages of the disease trajectory.

Support groups can form an essential part of the patient's support network and despite the rarity of the condition there are many groups throughout the UK, and patients should be given details of groups available to them. Healthcare teams should also be aware of increasing social media use in the mesothelioma community on both a national and international scale. Due to the limited treatment options, patients and families are often highly motivated to learn about new and emerging treatments and network with others on social media platforms to find information and receive support from those in a similar situation.

Legal considerations set asbestos disease apart from most other illnesses. Because most mesotheliomas are caused by work there are systems for compensating sufferers in most countries. These can form part of the state benefit system or involve civil litigation. Patients are likely to need professional legal guidance to assist them with a number of complex legal issues.

In the UK, state compensation for malignant mesothelioma is available principally through the Industrial Injury Benefits scheme. Benefit is paid at approximately 150% of the state pension level for the remainder of life. A separate scheme is in existence for those who were exposed while in the armed forces. A lump sum can be paid to those who were self-employed or who are unable to obtain compensation in the civil courts because the employer or their insurer cannot be identified or is no longer in business. Mesothelioma patients remain entitled to additional benefits available to those who require support because of disability, cancer, or other advanced illnesses. Referral to a benefits advisor is therefore helpful. Awards made by civil courts for damages can be more substantial than those of the state scheme

when, for example, they take into account loss of earnings caused by premature death. The prospect of taking civil action against a former employer can be daunting and distressing, and patients should be advised to seek advice from a solicitor specializing in industrial disease claims. Enlisting specialist legal teams can help to minimize further distress.

Management of Peritoneal Mesothelioma

Peritoneal mesothelioma usually presents with abdominal pain and ascites. As it progresses there are increasing problems with bowel transit due to the presence of peritoneal tumor. Subacute and ultimately complete bowel obstruction may occur as terminal events.

Management of Malignant Ascites

In principle, management options for malignant ascites include paracentesis, diuretics, periton ovenous shunts, and tunneled indwelling peritoneal catheters. A systematic review of these options examined 32 studies of 849 patients [35]. Paracentesis was shown to give good but temporary relief in up to 90% of patients. There was no consensus about speed of fluid withdrawal, and intravenous fluid replacement was not usually necessary if less than 5 L was being removed unless the patient was hypotensive or dehydrated. There is no clear role for intravenous albumin either. Shunt insertion is associated with potentially serious adverse effects and is only recommended when other options have failed [35].

Diuretics are often given with the aim of slowing re-accumulation of the fluid. A survey of clinical practice showed that 98% of clinicians used paracentesis and 61% diuretics [36]. The most commonly used diuretics were furosemide and spironolactone, with spironolactone being the preferred. Doses were not specified but in practice doses of spironolactone of up to 200 mg are sometimes used. The evidence supporting any of the interventions used in managing malignant ascites is weak, largely because of the poor quality of the evidence base [35].

Impending Bowel Obstruction

Because of the risk of bowel obstruction, it is important to give adequate laxatives to maintain stool consistency on the loose side. Docusate (a softener and stimulant laxative) is commonly used initially. Osmotic laxatives such as polyethylene glycol are also appropriate. The dose cannot be predicted for an individual patient and dose titration is necessary. To improve bowel transit it is often appropriate to add a prokinetic agent such as metoclopramide or domperidone orally.

As the disease progresses, symptoms of subacute obstruction such as abdominal colic, increased distension, noisy bowel sounds, vomiting, and constipation may

appear. These can be managed by converting the prokinetic drug to a continuous subcutaneous infusion (CSCI) of metoclopramide (30 mg/24 h, titrated up to a maximum of 120 mg/24 h), with high-dose subcutaneous dexamethasone (8 mg twice daily) and additional laxatives.

Ultimately the patient may well obstruct completely. Here the focus of management shifts to purely symptom control. Colic may be palliated by a CSCI of hyoscine butyl bromide starting at 60 mg/24 h, titrated up to 120 mg/24 h if necessary. Intestinal secretions can be reduced by a CSCI of octreotide 300 μg/24 h, titrated upward; the antiemetic of choice is cyclizine CSCI 150 mg/24 h. Any other drugs needed, such as analgesics, should also be given by CSCI. Feculent vomiting is a distressing symptom and cannot always be completely eradicated by the above measures. An alternative, favored by surgeons, but not so many palliative care specialists, is a nasogastric tube aspirated regularly. Some patients may opt for this if offered, and others will not.

After Death

Where death is thought to have been caused by the patient's occupation, the legal requirements of the particular country must be complied with. In England and Wales, all deaths in which an occupational cause is suspected should be reported to the coroner. Usually an autopsy is performed before an inquest is held, although sometimes the coroner will accept the evidence of a histologically confirmed diagnosis of mesothelioma. Ideally the patient's relatives or carers should have been warned about this in a sensitive manner beforehand. The inquest is usually opened and then adjourned, to allow funeral arrangements. The formal inquest then takes place some months later.

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Chronic Obstructive Pulmonary Disease

8

Graham P. Burns and Katherine E. Frew

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term for the constellation of respiratory conditions associated with cigarette smoking, principally chronic bronchitis and emphysema. It represents an enormous burden of disease on a global scale. In the UK alone an estimated three million people have the disease (though only about 900,000 are diagnosed) [1]. By 2030 the World Health Organization expects it to be the third biggest cause of death worldwide. At an individual level, there is a wide spectrum of severity though it often causes substantial disability and significant impairment of quality of life.

Chronic bronchitis is associated with mucus hypersecretion and is manifest as chronic cough and sputum production. Emphysema and the associated airway obstruction lead to gradually progressive breathlessness. Because of large respiratory reserve, patients with a sedentary lifestyle often do not notice breathlessness until a great deal of lung function has been permanently lost. Most patients are not diagnosed until they are in their 50s when the disease can be at an advanced stage.

The disease course of gradual progressive breathlessness and disability is punctuated by episodes of an acute worsening of symptoms, usually associated with infection. These exacerbations tend to occur with increasing frequency and severity. In advanced disease they are accompanied by breathlessness at rest, often necessitate hospital admission and can be life threatening.

G. P. Burns (✉)
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: Graham.Burns@nuth.nhs.uk

K. E. Frew
Department of Palliative Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK
e-mail: Katie.Frew@nhct.nhs.uk

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There is now increasing recognition of the importance of the non-respiratory manifestations of COPD. These result from the deconditioning associated with disability, the commonality of risk factors (e.g. smoking) and direct sequelae of the disease (e.g. right ventricular failure). They include fatigue, malaise, muscle wasting, reduced appetite, weight loss and osteoporosis. A very important and, until recently, unrecognised aspect of this chronic disease is its psychological impact. Approximately 60% of patients with COPD have symptoms of anxiety and 50% symptoms of depression [2]. Good-quality, holistic care of COPD should address all facets of the condition and not merely focus on inhalers aimed at improving airway obstruction.

Palliative Care in COPD

The issue of palliative care in COPD has been the focus of much discussion in recent years.

It has proved to be a difficult and controversial topic. Advocates for improved access to palliative care services for COPD patients have rightly argued that the advanced stage of the disease is characterized by a high frequency of symptoms, loss of functionality and frequent exacerbations leading to a significant deterioration in a patient's quality of life similar or even higher than the final stages of advanced cancer [3]. Yet despite the promotion of access to palliative care for COPD patients by national and international guidelines [1, 4] a large UK cohort study in 2018 identified the fact that only 16.7% of deceased COPD patients without lung cancer had received palliative care support, whereas the majority of patients who had died with lung cancer had been in receipt of that support [5]. This disparity has often been cited as evidence of a failure by clinicians to accept and deal with the difficult issue of the "inevitable mortality" of the disease. The real reasons for the "lack of progress" towards increased access to palliative are however far more complex.

COPD has a very different disease trajectory to cancer. It is much more unpredictable. Patients may live for many decades with the condition and more commonly die with COPD than of COPD. Unlike cancer, there is no natural transition point to a purely palliative phase of management when active treatment of the underlying condition would become inappropriate. Further, in COPD no treatment can offer the prospect of cure, nor is there any disease-modifying intervention (other than smoking cessation); therefore, in the broadest sense, all management of (chronic stable) COPD is palliative in its intent. There is, however, a subtle but important difference in emphasis between this "palliative" approach and the unspoken understanding of the aims of treatment when a cancer patient reaches the palliative phase of management. In COPD life expectancy is usually many years; treatment is therefore not about managing an inevitable decline to death; it is very much about enhancing the quality of life, with the emphasis on life.

Identifying the Nature and Timing of Specialist Palliative Care Is Not Straightforward

In a prospective observational cohort study [3] COPD patients with advanced disease (GOLD stage IV and poor performance status) were referred for follow-up by a "Palliative Home Care Team". It was observed that the majority (91%) were given opioids for symptom control and 93% of patients died of respiratory failure with a median survival of 8.3 months. The authors argued that the findings suggested that the characteristics of the group indicated that they were suitable for this modality of care. It is noteworthy however that these findings are in marked contrast to most longitudinal cohort studies which indicate that most people with COPD do not die from respiratory causes [6]. Further, based on the reported BODE score (see below) of this group (BODE: range 6–10, mean 8.6), the expected (median) survival might have been between 3 and 4 years. It is just possible that a premature or comprehensive transition to a model of palliative care designed in the context of advanced cancer could lead to increased mortality in the context of COPD, even "advanced" COPD.

Respiratory teams should be well placed to deliver the type of holistic care that patients with COPD need. Indeed best practice already supports this approach with the focus on the physical, psychological, and social aspects of the condition. Palliative care services however can offer a particular expertise beyond the usual skill set of the respiratory team. This could bring significant advantages to patients with what are distressing and disabling symptoms.

In the absence of a clear transition point, care should be based on need and symptoms rather than prognosis. Thus, rather than a wholesale transfer of care to a specialist palliative care team, the support COPD patients need would perhaps best be delivered in an integrated way, led by the respiratory team. The best respiratory units already deliver a holistic approach with a team of healthcare specialists offering a broad suite of effective interventions, including: smoking cessation support, pharmacological management of breathlessness, cough and exacerbations, physiotherapy for airway clearance, patient education, pulmonary rehabilitation for cardiovascular deconditioning, and cognitive behavioral therapy for anxiety and depression. The expertise of the palliative care specialist should be integral to that holistic approach and could be invaluable in complex patients, irrespective of the stage of their disease.

Specialist Palliative Care and COPD

Specialist palliative care teams should work alongside the respiratory teams to identify and manage the symptoms and holistic needs of patients with COPD. Respiratory clinicians deliver excellent symptom control for patients as part of the management of the underlying condition. However, when the underlying condition cannot be modified, in the stable phase of the disease, the remaining symptoms may be amenable to "palliation"—i.e. the experience of the symptoms or their intensity may be

reduced. The use of specific medication for frequently occurring symptoms is discussed later in this chapter, and whilst they form part of the "toolkit" of any respiratory or palliative care clinician the value of the palliative care team is often the ability to enable cross-site multidisciplinary team working. A holistic needs assessment may identify a number of areas which can be influenced, and the coordination of services across primary and secondary care settings may enable more supportive, non-acute, care to be delivered in the community. The development of multidisciplinary meetings has been considered as an approach to enable more care to be delivered in the primary care setting, supporting the work of community nurses and general practitioners [7]. Recognition of the impact of symptoms, and other concerns, on a patient's quality of life is a crucial potential barrier to being able to meet symptom needs. The identification, for example, of the needs of a carer, and the ability to provide respite care or ensure that appropriate financial benefits are obtained, may relieve financial stress and anxiety, which may significantly improve a patient's symptoms and quality of life. Collaborative and cross-site working must be considered as the optimal approach for specialist palliative care teams, working collaboratively with respiratory and primary care teams, to identify and manage patient needs in this complex and diverse group of patients.

In the end-of-life phase—when the downward trajectory to death becomes inevitable and relatively predictable, the aims and focus of treatment clearly change. In this context, the skills of the palliative care specialists may come to the fore. Because of the nature of COPD however, in most cases death only becomes firmly predictable in the last few hours of life.

Typically a formal decision to switch to end-of-life care is made when attempts at prolonging life have clearly failed. This is most often in hospital after an intense period of active treatment, perhaps including non-invasive ventilation. In such circumstances, when death finally intervenes, one is apt to reflect and question whether the outcome should have been foreseen and a less aggressive, more symptom-focused approach adopted sooner. The question is whether there are earlier signs that might indicate that death is essentially inevitable, indicators that would prompt a transition to a purely palliative mode of treatment. The question is eminently reasonable, the answer not always straightforward.

Can We Predict Survival in the Stable Phase of the Disease?

COPD is generally regarded as being associated with a poor prognosis. Many healthcare professionals managing patients' COPD however might be surprised to know that most people with COPD don't die from COPD. In the TORCH study [6] around 6,000 patients with an FEV1 <60% predicted were followed up for a 3-year period to observe the effect of various inhaler treatments on all-cause mortality. Of the deaths that occurred a minority, only 30%, were COPD related. Other common causes of death included cardiovascular disease and cancer. In fact in the group on maximal inhaled therapy the probability of death from any cause at 3 years was only 12.6% and the probability of COPD-related death was only 4.7%.

It may seem reasonable to assume that in more advanced disease (lower FEV1) survival will be worse. In a study by Celli et al. [8] however, FEV1 (% predicted) was not a strong predictor of mortality. Celli identified four variables: body mass index (B), degree of airflow obstruction (O), dyspnea (D) and exercise capacity (E) that when combined in a multidimensional 10-point scale (the BODE index) proved to be much better at predicting mortality over the 52-month follow-up. When the BODE score was divided into quartiles, the highest (worst) quartile (BODE 7–10) had a survival of around 20% after 52 months of follow-up compared with a survival of around 80% in the lowest quartile (BODE 0–2). Nevertheless, it should be noted that even the patients in the worst quartile, with the very worst prognosis, were more likely to be alive after 3 years than not.

Individual prognosis is very hard to predict in COPD and most patients will die of something other than COPD. These 'challenging' facts make discussions about end-of-life care with patients who are in a stable phase of the disease particularly problematical.

Can We Predict Survival During an Acute Exacerbation?

Some acute exacerbations are severe enough to warrant hospital admission and are, in a very real sense, life threatening. Perhaps in this acute context we can be more confident about predicting survival. Might there be an early indicator of impending mortality that could prompt a transition to a purely palliative modality of treatment?

Acidotic Respiratory Failure

In patients admitted to hospital with exacerbations of COPD the group who develop acute acidotic respiratory failure (pH <7.35) have a much greater risk of death. Treatment for this condition includes the use of non-invasive ventilation (NIV). The treatment involves the use of a tight-fitting mask over the nose and mouth and represents a significant step-up in intensity from other standard therapies such as antibiotics and oxygen. NIV is therefore sometimes identified as a Rubicon that it may be appropriate not to cross in certain circumstances. In a seminal study in this context, Plant et al. [9] found that the introduction of NIV early after admission, to patients with an acute respiratory acidosis, was effective at reducing mortality. In patients receiving "standard therapy" mortality was 20%; in those given NIV this was reduced to only 10%. When treatment with NIV offers a 50% reduction in the risk of death and a probability of survival of 90% a decision "not to pursue NIV" in that context is perhaps an audacious step. Certainly such decisions should be taken only after very careful consideration and discussion with the patient. Such shared decision-making must involve a patient who is fully aware of the likely impact on survival.

In a national UK audit of clinical care of 9716 patients admitted with COPD [10], management tended to be far more conservative than the evidence would suggest it should be; 30% of those with persisting acidosis did not receive NIV. In a real-life retrospective analysis of survival in patients receiving NIV similar deficiencies in management were identified [11]. However in follow-up post-discharge,

70% of patients were still alive 1 year later. Therefore it would seem that if the optimal care identified in studies could be offered to those patients presenting in acute respiratory failure then the vast majority would not only survive to discharge but also still be alive 1 year later. Far from "overusing NIV", currently, active treatment of severe exacerbations seems to be inhibited by a nihilistic view on prognosis fed by a poor understanding of the data.

Invasive Ventilation

Even when NIV is applied appropriately it is often set as the ceiling of treatment. This probably reflects a widely held belief that COPD patients who fail to respond to NIV are severely unwell and have such little reserve that their prospects of being successfully weaned from endotracheal ventilation would be so poor that to offer it would be futile. However, in a long-term retrospective analysis of COPD patients (mean FEV1 0.74 litres) in acute respiratory failure managed with endotracheal ventilation, 79.7% were successfully weaned and survived to discharge [12]. The median duration of ventilation was 2 days, a finding contrary to the perception that weaning problems are common. Neither FEV1, functional performance scores nor the use of long-term oxygen prior to admission were significant determinants of long-term survival. Even in this context, mortality is difficult to predict.

DECAF Score

To date the best predictor of survival at the time of hospital admission with an exacerbation of COPD is the DECAF score [13]. Based on the factors, dyspnea, eosinophil count, consolidation, acidaemia and atrial fibrillation, a score in the range of 0–5 can be calculated which has a strong correlation to 30-day mortality (range 0.5–70%). Therefore if a patient had a score associated with the worst prognosis in this, the most accurate prognostic tool we have, it would be the case that the chance of survival at 30 days (with appropriate treatment) is around 1 in 3. Whilst such a mortality risk would give cause for grave concern and should prompt open and frank discussion, in its own right it would seem wrong to argue that it would, alone, be sufficient justification to withdraw disease-specific treatment and switch to purely palliative management. A treatment for cancer offering a 1 in 3 chance of cure would surely be offered.

It would seem that survival, even in the context of a severe exacerbation with respiratory failure, is probably better than many clinicians would estimate. It would also appear to be very difficult to predict in an individual case. The model of palliative care that has traditionally evolved in the context of cancer, in which a point is reached when "active" treatment has nothing further to offer and a formal transition is made to treatment with purely palliative intent, would seem to be a very poor fit in the context of COPD. The recent development of an alternative model, however, which is concerned more with patients' symptoms than prognosis in patients with cancer, may have more to offer. "Enhanced supportive care" is a model endorsed by NHS England to improve care for patients with early-stage cancers, and recognizes a need to have a more flexible and integrated approach than the more traditional models of delivering palliative care [14]. Whilst this is a development in care for

patients with cancer, the model may offer insights into an alternative approach for patients with non-malignant diseases such as COPD.

This lack of certainty and the absence of a transition point of course should not preclude good-quality holistic medicine with an integrated approach to care. Specialist palliative input should be based on need rather than assumed prognosis. A holistic assessment of spiritual, emotional and physical needs and the balancing of benefit and burden can take place in the context of uncertainty and ongoing active management. Prognostic uncertainty should never be an excuse for denying good supportive and specialist palliative care if needed. Both active and palliative care can work in parallel to the benefit of patients.

Preferred Place of Death

In general surveys, most people say (when the time comes) they'd like to die at home. Approximately 70% of COPD deaths occur in hospital [15]. In recent years there have been a number of national end-of-life care strategies intended to reduce the chances of a death in hospital. There was at best a small (8%) reduction in the proportion of hospital deaths between 2004 and 2014 [15]. On the one hand this could be seen as a failure to implement an appropriate strategy, a failure to comply with patients' wishes. Alternatively the results may simply reflect the very different nature of the end-of-life trajectory in COPD compared with cancer, the context in which the strategy was designed. The clear separation of an active and palliative phase of treatment in cancer maps relatively easily into a recognition of the most appropriate place to deliver care. Once "active" treatment is no longer possible then admission to hospital no longer carries any specific advantage when palliative care can be delivered at home just as effectively. COPD is characterized by a trajectory of a prolonged phase of relatively stable disease punctuated by recurrent exacerbations. Such acute exacerbations can be very frightening for patients and their families, prompting patients to seek the security of hospital. Perhaps most importantly, treatment of such episodes can lead to full recovery. A decision to admit to hospital in such circumstances is therefore usually quite appropriate. In-hospital mortality following an admission with COPD is very low; however when death occurs, by the time it becomes inevitable, time is often very short indeed and the patient usually too unstable to allow transfer home.

The national end-of-life care strategy promoted dying at home as representing optimal care, as it reflects the literature regarding patients' preferences for place of death. Achieving a patient's preferred place of death has developed into being recognized as a measure of quality for end-of-life care, with an implication that dying in hospital is a less "good" death (because more of those who express preferences wish to die at home). That dying at home does reflect optimal care for all has not been formally evaluated nor has account been taken account of the potential for changes in preferences over time. For patients dying with dyspnea it is perhaps challenging to consider how acute symptoms may be managed at home, and especially in more rural populations.

Advance Care Planning and End-of-Life Discussions

In 2009 a qualitative study of healthcare professionals looking at barriers to advance care planning (ACP) in COPD revealed "inadequate information provision about the likely course of COPD at diagnosis" and a "lack of consensus in relation to initiating ACP" [16]. This is certainly a challenging area and respiratory specialists have come in for some criticism for their lack of engagement on these issues.

Frank discussions about mortality and patient wishes on eventual end-of-life care form an integral part of cancer care, particularly at the time of the transition to the palliative phase of treatment. The apparent failure of healthcare professionals to engage in similar discussions in the context of COPD may, in fact, reflect the uncertainty in the likely course of COPD rather than reluctance on behalf of the healthcare professional to communicate. To discuss with a patient the "inevitable mortality" of their condition, one should be confident that the condition in question does indeed have an inevitable mortality. Whilst this can be a confident assumption in cancer, it is not as consistently so in COPD. As discussed above, even in patients with advanced disease, most will not die of COPD. Therefore, to tell a patient, at a mild or even moderate stage of the disease, that they are effectively suffering from a "terminal condition" is both factually wrong and potentially very damaging. In addition to this, there is evidence that patients with COPD, whilst willing to talk about the future and their wishes, and wanting to be involved in decision-making, did not want to be "bound" to a more traditional "plan" of care for the future [17].

The distressing symptoms and physical limitations that come with COPD have, in themselves, a major negative psychological impact. Depression is common. Patients "give up" and avoid a number of activities that their physical condition would not absolutely preclude. One of the aims of good COPD care is to empower and enable patients; to change the mindset from one of "life is over" to a more positive outlook where activity, function and quality of life are maximized; to talk about death in this context risks setting the wrong tone. In a study which set out to examine the barriers to end-of-life care communication for patients with oxygen-dependant COPD, 115 patients were interviewed by trained research interviewers [18]. Rather than a lack of opportunity or apparent unwillingness on the part of their physician, the barrier to such discussions most commonly cited by the patients was "I'd rather concentrate on staying alive".

In a systematic literature review of end-of-life care discussion in COPD, Momen et al. [19] identified the fact that patients' preferences for such discussions varied greatly. About 50% of patients felt strongly enough to inform researchers, when asked, that they specifically did not want end-of-life discussions with healthcare professionals. Healthcare professionals therefore have to respect the wishes of those not wanting to discuss end-of-life care. Of course this needs to be balanced by the need for clinicians to provide adequate opportunity for such discussion for those that do.

It has been suggested that the answer to the question "Would you be surprised if this patient died in the next six months?" should be a prompt to initiating an end-of-life discussion. This may not be a useful reference point in the context of

COPD. Given the unpredictability of death, the question is more likely to initiate a discussion on the semantics of "surprise" than offer any real insight into the likelihood of death.

We need to acknowledge that the decision on when (and even whether) to have an end-of-life care discussion is not a trivial one. It is a difficult issue, and there are risks associated with getting the timing wrong. We should also think carefully about what we are trying to achieve by having such discussions. Even if we felt there would be no negative psychological impact, a discussion about dying, with a patient who hasn't yet themselves come to terms with the stark reality of their own mortality, will tend to be very much in the abstract. When reality bites, what had seemed reasonable in discussion a year earlier is often entirely at odds with the immediate choices a patient might make in a crisis. At some point in some indeterminate future, most people say that they would like to die at home, surrounded by their family, not in pain. In a crisis, even in the context of a known terminal illness, those same individuals often call an ambulance and seek the comfort and security of hospital. This is not an abject failure of medical services to deliver what patients really want but a reflection of the distinction between an abstract wish about the future and a choice made in the stark reality of the present. The same concern must be acknowledged when considering a patient's preferred place of death: when experiencing a distressing symptom, the decision made at an earlier point in time might become irrelevant in preference (or need) for symptom control in an inpatient environment. In the context of terminal cancer this choice may be motivated by a sense of security and the desire for effective palliation of symptoms. In the context of an exacerbation of COPD there is the additional expectation that treatment will make them well again. They believe that what the hospital can offer is their best chance of survival. Particularly in cases when NIV is required, this belief is, in fact, correct.

Perhaps the most appropriate and indeed productive time to initiate a discussion about end-of-life issues is an outpatient visit following an admission with life-threatening respiratory failure in which NIV was used. In this context about 30% of patients will die over the coming year (though to put it another way, 70% will still be alive a year later). A discussion about preferences for treatment in the event of a similar episode in future, at the very least, has clear meaning to the patient. The conversation could then focus for example, on whether, given similar circumstances, they would wish to have NIV treatment again. It would not be ethical however if the discussion did not include an explanation on the improved chance of survival with NIV and not just its potential discomfort and inconvenience. Following such an unhurried, fully informed discussion, away from the fog of the acute crisis, the decision reached by the patient would seem to be the best possible representation of their true wishes.

If, some 6 months later, the patient were readmitted in need of NIV, of course the decision would be reviewed. The patient should not feel bound by any earlier decision. This is supported by patient preferences expressed in the literature: an openness to discussion but avoidance, because of the fluctuating nature of the condition, of being bound to decisions [17]. The problem with discussions away from the acute situation is that in the next acute crisis patients may have changed their mind. We

have a duty to revisit the decision. This is the inherent challenge of advance care planning and decisions about preferred place of care in many conditions, not just COPD. However, just because it is difficult we should not deny the patient the opportunity to explore choices. Not having NIV or not coming to hospital in a crisis is still a choice for the patient, even if as clinicians it might be considered unwise. The duty of the clinician is to explore options and help patients make a fully informed decision.

The acute symptoms of dyspnea and anxiety experienced during an acute exacerbation must be acknowledged as symptoms which can be difficult to control at home, without extensive discussion and planning involving the patient and their family, and the primary and secondary care teams. In many situations it can be possible to manage these symptoms when they arise in a more gradual way, but acute and severe symptoms experienced out of hours, even with planning in advance, can be difficult for the most determined of patients and carers to experience. Future care planning must take this into account, and wherever possible consider a "plan B" which includes admission to a healthcare environment where a patient can feel safe and have their symptoms managed, even without the use of NIV. As compared with other life-saving interventions, NIV is relatively new. Doctors, as well as patients, are perhaps still formulating their own ethical frameworks around it. More work has been done in relation to cardiopulmonary resuscitation and the decision of a patient to forgo it.

Patient Preferences

In a study exploring the factors that might influence patient preferences on life-sustaining treatment options in COPD [20] researchers found a strong association between depression and a preference against life-sustaining treatment options (50% of patients with depression refused resuscitation whereas only 23% of non-depressed patients did so). Health-related quality of life was not associated with preferences contrary to common assumption. Therefore, before conversations on end-of-life care take place, healthcare professionals need to ensure that "active" care treatment options have been optimized which not only means optimum symptomatic control of breathlessness but also screening for and treatment of depression. Additionally, there is a need to ensure that patients have as much information about their condition as is possible—acknowledging the uncertainty regarding prognosis [17]. Patients may well wish to be involved in decisions about life-sustaining treatments, and engaging in the, albeit uncertain, discussion about the future is considered an important part of care for patients.

Doctors' Views

When doctors make decisions on the appropriateness of withholding treatment they are influenced by what they believe to be fairly objective assessments of the patient's global quality of life, physical comfort, mobility and mood [21]. Critically however, the doctor's estimate tends to be worse than patient's own estimate of his/her quality of life.

Perhaps doctors are influenced by how they imagine they would view things if suddenly confronted by the predicament the patient finds himself/herself in. However well intentioned, this seems to be wrong. Trying to second-guess a patient's wishes makes little sense. It is no substitute for open communication. We also need to remain acutely aware of how much we influence the decisions of our patients. We must strive to be as balanced as possible.

When doctors and patient do open up the communication channels it is often the doctor who learns more. Natural assumptions about what the patient may think or be concerned about are often wrong. It may well be that mortality per se is not the issue. A common overriding fear is of dying of breathlessness or "suffocation". Once the concern is understood some relevant reassurance can often be offered. Perhaps the best way forward is to establish a rapport between physician and patient that allows open regular discussion of the individual patient's hopes and expectations as well as fears in relation to symptom control and evolving end-of-life care. This would form the basis of an effective integrated palliative care approach focusing on quality of life at all stages. For many this broader approach may be more appropriate and more productive than focusing primarily on death [22].

Futility

When it is clear that a patient will not survive, even with NIV, it is important to communicate this to the patient where possible, and to the family. In this situation the patient must be recognized as dying, and the focus of care should be to support the patient and family at this stage of life. A patient could request NIV, but when the clinician is clear (using the best prognostic tools available and taking into account comorbidities) that it would be ineffective NIV should not be delivered. This is a medical decision; to offer a "futile" treatment in this situation may be considered unethical, as it reduces the potential for a patient and their family to communicate about dying, express their wishes and address any spiritual needs they may have. In such a situation the onus is very much on doctors to satisfy themselves that the treatment is overwhelmingly unlikely to produce benefit. In the context of COPD, doctors need to familiarize themselves with the statistics on outcomes from both NIV and invasive ventilation.

Symptomatic Control

Dyspnea

Much of the management of COPD, from the time of diagnosis until death, is about the palliation of dyspnoea. Dyspnoea in COPD is driven largely by the mechanisms that relate to airway obstruction and the resulting hyperinflation. These are discussed in detail in Chap. 2. Anxiety is a very common accompaniment, triggered by breathlessness but also providing a positive feedback loop augmenting both the sensation and its unpleasantness.

Pharmacological Management of Dyspnea

Bronchodilatation

To palliate a symptom, first deal with the root cause. This is true throughout the life of a patient with COPD; there is no reason why it wouldn't remain so towards end of life. Contrary to popular belief, bronchodilators do bronchodilate in COPD. More importantly this effect is associated with objective measurable relief from dyspnea. Bronchodilators fall into two categories: those that stimulate the sympathetic pathways, beta-2 agonists, and those that block the parasympathetic pathways, the anticholinergics. In each of these groups there are short-acting and long-acting drugs.

Salbutamol is the most commonly used bronchodilator; it is a short-acting beta-2 agonist. It can be delivered via an inhaler which is convenient for portable everyday use. Its quick onset of action, though with short duration of effect, makes it ideal as an "as-required" reliever. Some degree of maintenance bronchodilatation can be achieved by long-acting beta-agonists (LABAs) such as formoterol whose duration of action is around 12 h or indacaterol lasting approximately 24 h. Any one of these long-acting agents can be used in conjunction with salbutamol to achieve and maintain maximum beta-agonist stimulation. When patients are severely unwell and hospital admission is required, they may need higher doses than can be easily delivered by an inhaler. Under these circumstances it would be reasonable to deliver the drug via nebulization. For longer term (chronic) management however maximum bronchodilatation can be achieved by correct use of an inhaler. There is generally no place for home nebulizer use in long-term management.

Ipratropium bromide is a short-acting anticholinergic bronchodilator. As it acts via a different mechanism to salbutamol the two drugs can be used together with an effect above and beyond what either agent would deliver alone. Nebulized ipratropium is still commonly used in situations when nebulizer therapy is necessary. In its inhaler form ipratropium has been superseded by a number of long-acting muscarinic antagonists (LAMAs) such as tiotropium, glycopyrronium and aclidinium. As with the short-acting equivalents, LABAs and LAMAs can be combined to achieve maximum bronchodilatation. There are several dual-bronchodilator inhalers on the market that combine a LABA and a LAMA in a single device.

Oxygen

Many patients (as well as their families and some doctors) believe that the best treatment for breathlessness is oxygen. It is crucial for healthcare professionals to understand that a patient "short of breath" is not necessarily "short of oxygen". Giving supplemental oxygen to a patient who is not hypoxic will achieve nothing.

In the UK there are three modalities of home oxygen delivery: (1) long-term oxygen therapy, which is proven to reduce mortality in carefully selected patients; (2) ambulatory oxygen which can improve exercise tolerance and quality of life, in carefully selected patients; (3) short burst oxygen therapy which is the only modality in which the indication remains ill defined and which has no formal assessment criteria.

When healthcare professionals are asked why they might prescribe short burst oxygen therapy in patients with advanced disease they give any one of a number of reasons. These include (perhaps in increasing order of honesty) to address hypoxia, to reduce breathlessness, to provide comfort, for reassurance of the patient and family, to provide psychological relief, to feel like you're doing something and because it's very difficult to say "no".

In a prospective double-blind, randomized controlled trial on the effect of palliative oxygen versus room air in relief of breathlessness [23, 24] oxygen showed no benefit in alleviating dyspnea in patients without hypoxemia. Only hypoxic patients may derive a symptomatic benefit. In considering the appropriateness of oxygen prescription it is also important to remain mindful of its significant potential drawbacks: restriction of activities, possible impairment of quality of life and psychological dependence. If the patient is not hypoxic prescribing oxygen will achieve nothing and is potentially damaging. Reliance upon it may suggest that some alternative (useful) treatment has been neglected.

Opioids

Used systemically in the acute setting these have an important role to play. Their use is discussed in more detail in Chap. 2.

Studies that have examined the effect of nebulized opioids on breathlessness in respiratory disease have consistently demonstrated that they are no more effective than nebulized saline. This is probably because the afferent signals which inform the sensation of breathlessness in the advanced stages of COPD do not originate within the airways.

Non-pharmacological Management of Dyspnea

Anxiety Management

Anxiety as an issue in its own right is discussed below. Its link with breathlessness however is an intimate one with a two-way causal relationship and powerful positive feedback loop. When dealing with breathlessness at any stage of COPD, including very advanced disease, "think anxiety". It can, otherwise, easily be overlooked.

Pulmonary Rehabilitation

Pulmonary rehabilitation is a multidisciplinary programme of care for patients with chronic respiratory impairment. It comprises individualized exercise programmes and educational talks which aim to prevent deconditioning and allow patients to cope with their disease. It is an effective treatment for patients from moderate-to-severe COPD and is proven to lead to statistically significant and clinically meaningful improvements in dyspnea, exercise capacity and health-related quality of life. Though clearly not appropriate for true "end-of-life" care, it should not be overlooked as an effective addition to management even in advanced disease.

Other Non-pharmacological Management

A Cochrane review [25] examined a number of other non-pharmacological strategies and techniques tried for the alleviation of breathlessness. These are discussed in detail in Chap. 2.

Symptoms Other Than Breathlessness

Anxiety

There is little in the realm of human experience more frightening than not being able to breathe. In severe attacks of breathlessness patients often report that they feel as if they are going to die. Clearly when such attacks become a frequent, though unpredictable, part of life even in the most psychologically robust individuals a general sense of anxiety is almost inevitable. In the midst of an episode of severe breathlessness, anxiety is an entirely understandable and, in fact, normal human response. Though normal, it is never helpful. Breathlessness leads to anxiety, anxiety leads to an abnormal breathing pattern (more rapid, more shallow and at a higher lung volume) and this abnormal pattern only heightens the sense of breathlessness, which fuels further anxiety, thereby fuelling further breathlessness in a vicious circle. On occasions this spirals out of control into a full-blown "panic attack". Panic disorder is up to ten times more prevalent in patients with COPD than in the general population.

Depression

COPD brings physical limitation to life's activities. Patients note a gradual contraction of their world. At some point their ability to walk around town is lost, not long after that they find they are unable to get to the corner shop, soon the garden gate is the limit of their world and finally they are unable to get beyond their own front door. They become isolated. They cease to take part in life. "Life" is then what the people walking past the window are doing; they are no longer part of it. Depression is common in COPD. Perhaps the only surprising feature is that it seems to be just as common in mild as in severe disease.

In our unit we recently investigated a stable outpatient COPD population. A stable outpatient population was screened using the Hospital Anxiety and Depression (HAD) questionnaire over a 6-month period [2]. Approximately 60% of patients had anxiety and 50% of patients had depression (respective scores ≥ 8). There was no significant correlation with either severity of airflow obstruction or gender.

Anxiety and depression are critically important issues in their own right and worthy targets of treatment in COPD. But their impact on the individual extends beyond the purely psychological. Whilst breathlessness itself can reduce physical activity, the fear and frustration so common in COPD are potent demotivating forces leading to a whole series of maladaptive avoidance behaviors. Exercise and exertion in general are shunned, which in turn leads to deconditioning and increased

breathlessness. Offers to attend pulmonary rehabilitation programmes are politely declined. There is also an increase in safety-seeking behavior such as (physiologically) inappropriate presentations to emergency departments, or calling an emergency ambulance as patients feel they are about to "breathe their last". It is no surprise therefore that anxiety is a significant predictor of the frequency of hospital admissions and readmissions for acute exacerbations of COPD [26].

In COPD depression has an effect on smoking status, symptom burden and physical functioning and even rates of admission to hospital [27].

Identifying anxiety and depression is a necessary step in providing support for patients. As many of the symptoms of anxiety (such as breathlessness) and depression (such as fatigue) overlap with the symptoms of COPD, recognition of the problem can be difficult. Formal screening using tools such as the HAD questionnaire should be a routine part of practice. Once identified, anxiety and depression should be addressed just as conscientiously as airway obstruction. This rarely occurs. The reasons for this are complex. It is often thought that patients might misunderstand the focus on anxiety and panic as a suggestion that their symptoms are not "real" or that they may be resistant to acknowledging the problem because of the stigma associated with mental illness. Experience suggests that this is rarely the case. Once given the opportunity to discuss anxiety, panic and depression patients often feel a great sense of release and are not only keen to open up and discuss these issues but are very amenable to accepting treatment. It remains true, however, that many healthcare professionals feel ill equipped to deal with psychological issues and the dominant medical model culture results in very little attention being paid to the patient's psychological well-being.

In the management of anxiety and depression patients should have access to psychological treatment, pharmacological treatment or both in combination [1]. Cognitive behavioral therapy (CBT) is a psychological "talking" treatment, which explores the links between situations, thoughts, feelings, physical symptoms and behavior. Unhelpful thoughts and behavior can be challenged and changed. In coming to understand these links patients develop new skills and can, in the longer term, effectively act as their own therapists. Patients are empowered. Learning to address psychological problems can be empowering for the healthcare professional too.

Access to trained therapists remains a stumbling block; one possible solution, which has been pioneered in Newcastle, involves the respiratory healthcare professionals looking after patients with COPD acquiring formal training in CBT skills [2]. This has been shown to reduce not only nxiety but also emergency department attendance and hospital admissions. It is a very cost-effective treatment.

Fatigue

Fatigue is a complex issue and a common symptom in many end-of-life conditions. In the context of advanced COPD the factors contributing to the sensation are most likely to be breathlessness, depression and deconditioning, each of which may be identifiable and amenable to treatment as discussed above. There is also increasing

evidence that COPD is a systemic condition. "Spillover" of inflammatory mediators into the circulation can result in systemic manifestations of the disease, such as muscle wasting and cachexia which can also contribute to the sense of "fatigue". Research to better understand this systemic component of COPD, and hopefully manage it, is ongoing. Until specific remedies are developed, it is at least useful to recognize its existence. Nutritional supplements may offer some support.

Xerostomia

Xerostomia is commonly reported in the advanced stages of COPD. Potential factors contributing to the condition include adverse effects of treatment (e.g. anticholinergic and opioids), mouth breathing, non-humidified oxygen, dehydration, candidiasis, anxiety and depression. Any one, or any combination of these factors, may be present in advanced COPD. Identification of the contributory factors should assist with management as most can be modulated. Other non-specific symptomatic measures would include frequent sips of (ice cold) water, and stimulation of the production of saliva using, for example, chewing gum, acid drop sweets, lemon drinks and sucking ice cubes.

Cough

Cough is a very common symptom in COPD in general. Chronic bronchitis (persistent productive cough) is the facet of COPD that can improve or even resolve on smoking cessation. Resolution however tends to take a month or two as the awakened airway cilia set about clearing the accumulated excess airway mucus. After smoking cessation, unless the patient has co-existing bronchiectasis, productive cough more commonly tends to be restricted to periods of "exacerbation" (which are usually, though not always, associated with infection). These usually respond to courses of antibiotic and steroids. When exacerbations are frequent, regular inhaled therapy with the triple agents, corticosteroids, long-acting beta-2 agonists and long-acting muscarinic antagonists, significantly reduces frequency. If additional treatment is required, thrice-weekly azithromycin 250 mg can be effective at reducing exacerbation frequency. In the context of severe disease (FEV1 <50% predicted) chronic productive cough can be improved by roflumilast which in the UK has now been approved by the National Institute for Health and Care Excellence (NICE). Cough characterized by thick, tenacious mucus can be helped with the use of carbocisteine as a mucolytic. This makes mucus easier to clear and the net effect is a general improvement in cough.

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Interstitial Lung Disease

9

Ian Forrest and Anne-Marie Bourke

Background

Interstitial lung disease (ILD) refers to a diverse range of over 200 different disease entities that affect the alveoli, distal airways, and interstitium of the lung. The pathology of ILD is characterized by inflammation and fibrosis, often coexisting and commonly resulting in chronic progressive fibrotic lung disease with substantial morbidity and significant mortality. The diagnosis of ILD relies on careful integration of clinical features, radiology, and, in a subgroup of patients, histopathological findings in a multidisciplinary approach to these challenging diseases [1]. International guidelines have attempted to classify the ILDs and a useful working classification, which helps inform prognosis and treatment decisions, is outlined in Fig. 9.1 [2].

Many forms of ILD are idiopathic, where no etiological factor can be identified, whereas others are clearly linked to connective tissue diseases, prescribed drugs, cigarette smoking, and environmental exposures to antigens or dusts. The most common ILDs are idiopathic pulmonary fibrosis (IPF) and other idiopathic interstitial pneumonia, sarcoidosis, connective tissue disease-associated ILD, and hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis). Whilst the clinical presentations and course of ILDs are variable, all ILDs can demonstrate progressive fibrosis.

Interstitial lung diseases commonly present with dry cough and breathlessness. Examination findings may confirm finger clubbing and crackles on auscultation whilst chest radiography may show diffuse abnormalities including infiltrates, fibrosis, and reduced lung volumes. The loss of lung volume typical of ILD is

I. Forrest (✉)
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: Ian.Forrest@nuth.nhs.uk

A.-M. Bourke
Department of Palliative Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust and Marie Curie Hospice, Newcastle Upon Tyne, UK

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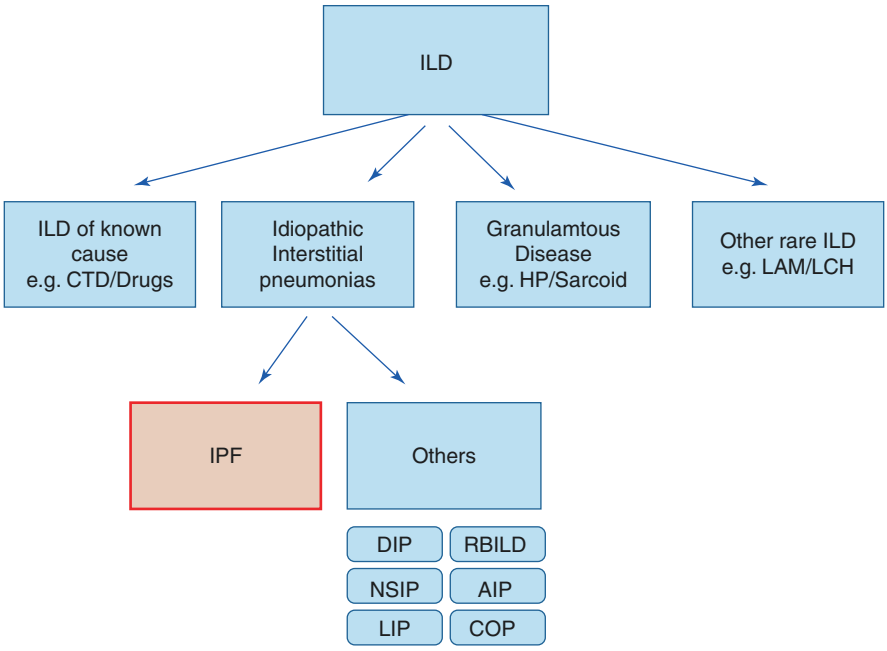

Fig. 9.1 Classification of interstitial lung disease (*ILD*). Idiopathic pulmonary fibrosis (*IPF*) is the most common idiopathic interstitial pneumonia (*IIP*) and is the archetypal fibrotic lung disease. All ILDs however can result in progressive fibrotic lung disease (*PF-ILD*), worsening symptoms, impaired gas exchange, and ultimately death. The figure describes a classification of ILD adapted from the 2002 international consensus (2). *CTD* Connective tissue disease, *HP* Hypersensitivity pneumonitis, *LAM* lymphangioleiomyomatosis, *LCH* Langerhans cell histiocytosis, *DIP* Desquamative interstitial pneumonia, *NSIP* Nonspecific interstitial pneumonia, *LIP* Lymphoid interstitial pneumonia, *RBILD* Respiratory bronchiolitis ILD, *AIP* Acute Interstitial pneumonia, *COP* Cryptogenic organizing pneumonia

usually confirmed with restrictive lung function tests and reduced gas transfer measurements. Often there is a delay in diagnosis whilst patients are treated for lower respiratory tract infections or for pulmonary edema, conditions more prevalent than ILD that commonly form a differential diagnosis until a full clinical assessment including definitive imaging with high-resolution computed tomography (HRCT) is performed (Fig. 9.2).

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common ILD and is the archetypal progressive fibrotic lung disease. IPF is a specific form of chronic fibrosing interstitial lung disease of unknown cause. IPF is characterized by a usual interstitial pneumonia pattern and has an estimated incidence globally of 5–10 per 100,000

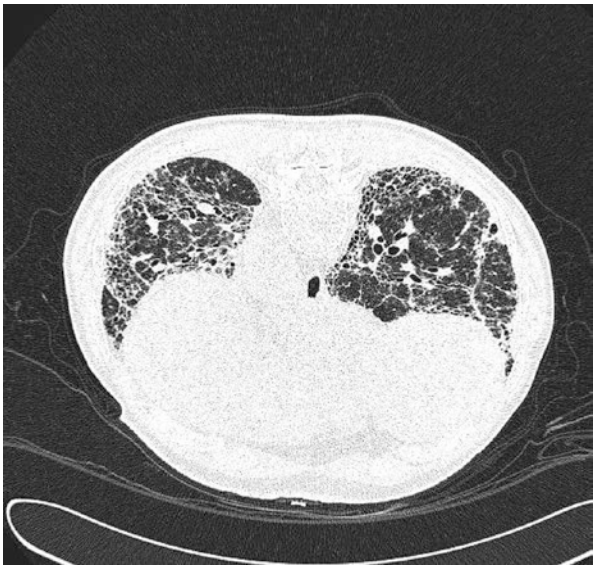

Fig. 9.2 Imaging of IPF. High-resolution CT scan (*HRCT*) of an 82-year-old male patient with advanced IPF. The image, acquired prone, shows evidence of severe basal fibrosis in a typical subpleural distribution, minimal "ground-glass" change, "honeycomb" lung, and secondary bronchial dilatation. The patient had presented with progressive breathlessness and dry cough. Lung function tests confirmed severe intrapulmonary restriction with low lung volumes and impaired gas transfer. The patient developed worsening respiratory failure and died 18 months from presentation

population/year [3], with the prevalence generally accepted to be rising by 5% per year [4]. It is believed that over 500,000 patients are affected by IPF in the USA and Europe. IPF is typically a disease of the elderly, with a mean age at diagnosis of around 70 years, and is more common in men. IPF is characterized by relentless progression of lung fibrosis, impaired lung function, worsening gas exchange, and prominent symptoms of breathlessness and dry cough. Survival of patients with IPF is worse than for many cancers with a median survival of only 3–5 years from diagnosis [5]. In the UK, 1 in 100 of the general population will die of IPF [6].

Whilst population survival in IPF is predictably poor it is recognized that there is heterogeneity in the clinical course of the disease as well as unpredictable acute worsening or exacerbations of IPF [5]. There appear to be several possible natural histories for patients with IPF which makes accurate prognostication difficult. The possible natural histories for IPF are summarized in Fig. 9.3.

Methods to predict the course of the disease and the survival in individual patients have been proposed by both duBois et al. and Ley et al. [7, 8]. The GAP model reported by Ley suggests a quick and simple screening method for estimating the individual risk for patients, based on gender (G), age (A), and two lung physiology variables (P) as forced vital capacity (FVC) and transfer factor for carbon monoxide

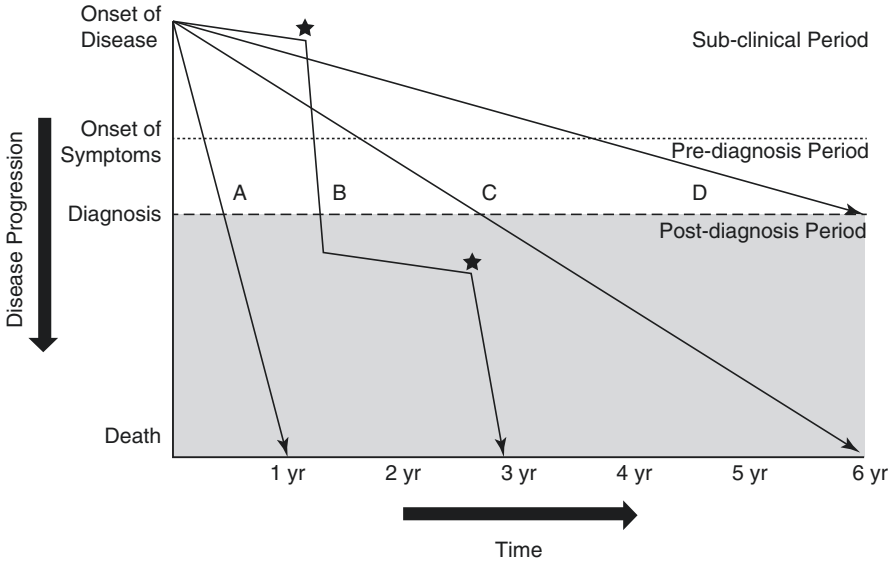

Fig. 9.3 The natural history of IPF (reproduced with permission from Ley et al. [5]). The variable and unpredictable clinical course of IPF is represented schematically. Following the onset of disease which may be only detectable on high-resolution CT scan or chest radiograph there is a subclinical period. There follows a symptomatic period which is typically present for some time before the diagnosis is secured. The rate of decline may be rapid (A), more slowly progressive (C) and (D), or mixed where a relatively indolent deterioration is punctuated with periods of acute decline (∗) due to recognized complications such as pneumonia or unexplained AE-IPF. These deteriorations may be fatal or leave the patient with significantly worsened disease

(DL_{CO}). More recently, a reduced 4 m gait speed has been suggested to be a predictor of poor outcomes including mortality in IPF [9]. These approaches may facilitate decision-making by patients, carers, and clinical teams although they clearly need careful prospective evaluation and validation in other IPF populations before firm recommendations regarding clinical management and prognostication can be made.

A number of patients are recognized to have acute worsening of their disease due to identifiable conditions such as pneumonia, pneumothorax, pulmonary embolism, acute coronary syndromes, or cardiac failure. However, it has been estimated that up to 15% of patients will experience an acute exacerbation of IPF (AE-IPF) each year [10]. These exacerbations are characterized by an acute deterioration (<30 days), with new or worsening breathlessness often accompanied by cough, fever, and flu-like symptoms. Imaging confirms new bilateral ground-glass shadowing whilst no other explanation for the exacerbation, including infection, can be identified. Whilst the mechanism of AE-IPF remains unclear and may simply represent an acute acceleration of the fibrotic process underpinning IPF, some authors have speculated that occult infection or gastroesophageal reflux may play a role [11]. Whilst corticosteroids, antibiotics, and supplemental oxygen are commonly deployed, there

remains no proven effective therapy for AE-IPF [11]. These exacerbations can have a serious impact on both the quality of life and survival of patients with IPF, with up to 50% of patients dying during an exacerbation [10].

IPF is associated with other diseases that can contribute to worsening symptoms, deterioration, and death. It has been recognized that patients with IPF are at significantly increased risk of lung cancer, acute coronary syndromes, and pulmonary embolism. In addition, comorbidities such as pulmonary hypertension and chronic obstructive pulmonary disease (COPD) may contribute to the disease course whilst treatments such as radiotherapy, surgery, and potentially chemotherapy for coexistent lung cancer can precipitate a deterioration or AE-IPF [11].

Intensive Care for Patients with IPF?

Patients with IPF in whom the disease progresses to a stage of respiratory failure may trigger a referral to the intensive care unit (ICU) for consideration of ventilatory support. Available data however show that the outcome for these patients is very poor, mechanical ventilation is mostly futile, and ICU support for these patients is usually not appropriate. The international practice guidelines make a (weak) recommendation against the use of mechanical ventilation to treat respiratory failure in IPF [12].

It is important for the clinical team to be aware of the clinical course of the patient's disease. If a patient has demonstrated the typical inexorable decline in lung function, gas exchange, and symptoms that characterizes IPF, it is not appropriate to offer ICU-based organ support. More challenging is the previously stable patient with IPF who appears to have an acute deterioration or AE-IPF. In this situation ICU may be an appropriate setting to perform the necessary extended investigations required to exclude reversible causes of deterioration [13]. IPF treatment guidelines recommend that the majority of IPF patients with respiratory failure should not receive mechanical ventilation, and when used this should occur after assessing patient-specific goals of care or lung transplant candidacy. It is rare that transplant centers support the use of mechanical ventilation as a bridge to lung transplantation [14]. There are reports of success in using non-ventilated extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation in highly selected patients with advanced ILD [15].

For many patients presenting with AE-IPF, achieving adequate oxygenation is difficult and usually requires very high inspired oxygen concentrations which have typically been delivered through a non-rebreather face mask. The use of face masks is often uncomfortable, limits oral intake, and impairs communication. More recently, the use of high-flow nasal cannula (HFNC) therapy has allowed delivery of up to 100% humidified and heated oxygen to patients who are felt not to be suitable for mechanical ventilation. This approach appears to be effective and tolerable and may improve patient-reported outcomes [16]. The use of HFNC as a palliative measure in respiratory failure, including its use in a home setting, may offer patients a choice of preferred place of care at the end of life. This opportunity requires further study.

Patients and their families should be informed about the prognosis, outcome, and overall outlook before making decisions about ventilation and organ support. It is important that all clinicians involved in the management of ILD are aware of the issues relating to the ICU care of these patients and ideally have agreed institutional guidelines which the medical, ICU, and palliative care teams can share [17].

Treatment of IPF

Lee et al. [18] propose a "3 pillars of care" model for patients with IPF which focuses on (1) disease-centered management, (2) symptom-centered management, and (3) education and self-management.

Disease-Centered Management

It is clear that many pharmacological treatments aimed at reversing the progressive fibrosis that characterizes IPF have been unsuccessful and often harmful because of significant adverse effects. International guidelines recently confirmed that the use of corticosteroids and other immunosuppressive strategies were harmful and not to be recommended [12].

The introduction of anti-fibrotic therapies, pirfenidone and nintedanib, has seen a dramatic advance in the management of IPF over the last 5 years [12]. These treatments have been shown to slow the rate of decline in FVC by 50% over 1 year [19, 20]. Moreover, there is a suggestion from analysis of pooled studies that anti-fibrotic drugs may improve survival and reduce exacerbation frequency and hospitalization rates.

In the UK, the use of anti-fibrotic therapy is limited to patients, confirmed by a specialist ILD multidisciplinary team to have IPF, with a FVC of 50–80% [21, 22]. The National Institute for Health and Care Excellence (NICE) recommendations also suggest stopping these treatments if the FVC declines by over 10% in 12 months. Patients in other healthcare settings globally have fewer constraints on treatment and may have access to these therapies at an earlier stage of disease. However, these treatments are expensive, and costs may exceed $100,000 per patient annually [23].

Increasing use of anti-fibrotic drugs has highlighted that both therapies can lead to adverse effects, often gastrointestinal, that can compound the symptom burden of the disease itself. Careful anti-fibrotic choice with management of adverse effects has become a critical role of the ILD clinical nurse specialist [24]. Support from specialist ILD nurses can increase concordance with anti-fibrotic therapies, and reduce dose interruption and cessation of treatment. The nurse specialist can also support discussions around oxygen therapy, pulmonary rehabilitation, ILD support groups, and palliative care, a holistic approach welcomed by patients [25].

The use of long-term oxygen therapy has been recommended for patients with IPF who have resting hypoxemia using the same criteria as recommended for patients with COPD [12]. It remains unclear however in the absence of clinical trial

data whether the survival benefits of oxygen seen in patients with COPD can be extrapolated to patients with IPF.

Lung transplantation is an effective treatment for a minority of patients with IPF. In selected patients transplantation can dramatically improve the disease trajectory, although the timing of referral for assessment remains critical to prevent patients becoming too unwell for consideration of lung transplant or dying on the waiting list [26]. Unfortunately, many patients with IPF are elderly and have comorbidities which make them unsuitable for transplantation.

Despite the use of anti-fibrotic drugs, most patients continue to deteriorate and further research into combination therapy approaches is critical. A number of new therapeutic targets are being investigated [23] .The inclusion of suitable patient-reported outcome measures in studies of both novel anti-fibrotic therapies and clinical trials of palliative care in progressive fibrotic ILD is critical to progress the concept of "living well with ILD" [27] and personalize ILD treatment [28].

Symptom-Centered Management

Symptom management ought to be a therapeutic focus for two reasons. Firstly, as IPF is a progressive disease with a poor prognosis "best supportive care" (a range of interventions from disease-specific information to symptom control and end-of-life care) is advocated by NICE from the point of diagnosis [29]. Secondly, patients with IPF have a high burden of distressing symptoms [27, 30].

Supportive care and symptom control are routinely delivered by respiratory services in conjunction with primary care practitioners. Referral to specialist palliative care can be considered for those with the most severe symptoms, worsening symptoms, and/or progressive disease [27, 29]. Palliative care does not equate to the cessation of active treatment, neither should it be reserved for the last days of life [27, 29, 31]. Instead care should be patient centered [29]. In practice, this often means that patients are reviewed by palliative care teams for short periods of time over their disease trajectory (for instance to relieve side effects caused by anti-fibrotic medication or to manage dyspnea).

Measurement of Disease and Symptom Severity

Meeting the holistic needs of patients and their carers necessitates the proactive measurement of disease severity, symptoms, and quality of life [27]. The standard measures of disease severity and progression are lung function as measured by FVC and DLco, oxygen saturation, and 6-min walk distance. It is widely accepted that a fall in FVC $\geq$10% or DLco $\geq$15% over a 3–6-month period is indicative of disease progression and a poor outcome [5].

Measuring symptom severity and health-related quality of life (HRQOL) has been the subject of recent research. Olson et al. [32] concluded that the factors most detrimental to HRQOL are shortness of breath and reduced physical ability.

Breathlessness is almost universal in patients with IPF and whilst assessment tools for this symptom exist there is a paucity of data on their clinical utility [33]. The severity of dyspnea cannot be inferred from measures of respiratory function [33, 34]. This is because the unpleasant sensation of breathlessness results from a complex interplay between physical disease and psychological factors [33]. When chronic, dyspnea is so strongly associated with depression that Ryerson et al. suggest that patients be routinely screened for mood disorders [34]. Most tools which capture the presence and severity of breathlessness were developed for COPD; however Dyspnea-12 (a 12-item patient-reported measure of breathlessness) has been validated in patients with ILD and can be completed quickly in a clinic setting [33, 35].

Many patients with IPF are troubled by cough which is usually dry, distressingly frequent, and more likely to be experienced during the day than at night [36]. Cough is more common in advanced disease and may be a predictor of mortality [36, 37]. Cough in IPF negatively impacts well-being because it affects many aspects of life including talking and the ability to exercise [36, 38]. The mechanism of cough in IPF is poorly understood although it may be due to heightened cough reflex sensitivity [39]. It has been postulated that this increased sensitivity is caused by physical stretching and destruction of nerve fibers as a direct result of fibrosis [36]. Neurotrophins influence the expression of sensory receptors within the lungs which may also play a role in increased cough sensitivity [36]. Neurotrophins are known to be associated with inflammation and when compared to controls are more concentrated in the sputum of IPF patients [36, 40]. Other coexistent causes of cough, such as gastroesophageal reflux, upper airway cough syndrome, asthma, and COPD, should be considered. The Cough Quality of Life Questionnaire and the Leicester Cough Questionnaire (LCQ) have been validated in IPF patients; both are patient-reported measures which cover multiple domains [36, 41, 42]. Additionally, Key et al. found that the LCQ correlated well to objective measurement of cough frequency [41].

Despite the dominance of dyspnea and cough, patients with IPF experience multiple other symptoms including insomnia, fatigue, anxiety, and depression [34, 38, 43]. Individuals and their carers also have information needs with regard to future planning and end-of-life care but find initiating conversations difficult [43]. In clinical practice, single holistic questionnaires may be more useful than accurate measures of individual symptoms because they can identify hidden, unaddressed concerns [44]. The St George's Respiratory Questionnaire (SGRQ) is one such tool which has been shown to accurately reflect HRQOL in IPF patients [32, 45]. The King's Brief Interstitial Lung Disease Questionnaire (K-BILD) is another patient-reported tool which assesses HRQL in three domains: psychological impact, breathlessness/activities, and chest symptoms [46]. Sinha et al. found that in a sample of 57 patients with ILD K-BILD had a minimal important difference of a 5 unit change when used to assess the same patients over time [47]. Tools developed for use in palliative care such as the Palliative care Outcome Scale (POS) can also be used for the longitudinal assessment of holistic needs and have the advantage of presenting information in a format familiar to palliative care teams [48]. Whilst not

validated for use in ILD, POS is being used as a measure of HRQOL in clinical practice [31, 49].

Specific Symptom-Centered Treatment

The foundations of "best supportive care" for patients with IPF include smoking cessation, addressing nutrition, treating right heart failure, and offering influenza and pneumococcal vaccination. These are likely to improve symptoms and prevent the development of complications. This chapter considers the management of four of the most common symptoms experienced by this group: breathlessness, cough, fatigue, and anxiety and depression.

Breathlessness

A systematic review focusing on the management of breathlessness in IPF concluded that data relating to this group were scant and there was little robust evidence to support the use of specific treatments [50]. The review suggested that supplemental oxygen, pulmonary rehabilitation, and opioids may be beneficial. Extrapolating NICE recommendations for the management of dyspnea (irrespective of cause) it is important to first optimize non-pharmacological strategies [51]. These include adequate explanation of the underlying condition, breathing exercises, pacing of activity, and management of psychological distress. Such interventions have the advantage of being free from side effects.

Supplemental Oxygen

The British Thoracic Society oxygen guidelines 2017 recommend that ILD patients with persisting hypoxemia should be considered for oxygen therapy delivered by a concentrator, aiming for saturations of 94–98% [52]. These individuals may also benefit from ambulatory oxygen for use outside the home. In an important study, patients who were not hypoxic at rest but who desaturated and became dyspneic on exertion benefitted from ambulatory oxygen [53]. Visca et al. recruited 84 patients with fibrotic lung disease—all of whom desaturated on exertion to 88% or less—to a prospective, crossover trial comparing 2 weeks with ambulatory oxygen to 2 weeks without oxygen [53]. Oxygen was titrated aiming for saturations of 90% or greater for more than half of a 6-min walk test, to a maximum of 6 L/min. In this patient group, oxygen resulted in a statistically significant improvement in total K-BILD scores and K-BILD domains relating to breathlessness and activities; however, there was no significant change in psychological symptoms. The evidence is less clear for the use of oxygen as a purely symptomatic treatment for dyspnea in ILD [54]. Although some patients who are breathless but not hypoxic derive benefit from oxygen therapy, non-pharmacological strategies and opioids are often more effective [52]. It is recommended that oxygen be prescribed for this group only if other measures have failed [52].

Supplemental oxygen has inherent problems (including the fact that cylinders are bulky) which should be included in conversations about the risks and benefits of this treatment [53].

Pulmonary Rehabilitation

Several studies have shown that pulmonary rehabilitation has a positive impact on breathlessness in patients with ILD [55]. For example, a recent study of 41 patients with ILD who participated in pulmonary rehabilitation across two centers showed a statistically significant improvement in dyspnea and total SGRQ score following the intervention [56]. Rehabilitation has other benefits including improving physical function and quality of life and has therefore been recommended for patients with IPF [29]. Specifically tailored rehabilitation for patients with IPF is beneficial because the condition (and its associated education and health needs) differs from other lung pathologies such as COPD [49].

Opioids

Studies of the use of opioids for the relief of breathlessness in IPF are limited. A literature review analyzed the available data and concluded that there is some evidence that systemic morphine relieves the sensation of breathlessness in this patient group [57]. Importantly, there was no evidence of severe adverse effects. This finding is similar to that of a Cochrane review which concluded that there was low-quality evidence to suggest a beneficial effect of oral or parenteral opioids in adults with dyspnea resulting from advanced disease or terminal illness [58]. Doses of morphine required to relieve breathlessness are often low. An uncontrolled study of 11 elderly patients with advanced IPF concluded that 2.5 mg of subcutaneous diamorphine and subsequent modified-release oral morphine (20–60 mg/day) reduced symptoms of breathlessness with no significant respiratory depression [59]. A more recent phase 1 study concluded that a single 1 mg or 2 mg subcutaneous injection of morphine was safe (meaning that it did not cause respiratory depression or hypotension) in six patients with ILD and refractory dyspnea [60]. Currow et al. studied optimal doses for once-daily modified-release morphine in a heterogeneous population of 83 opioid-naïve patients with dyspnea (12% of whom had a diagnosis of ILD) [61]. The average dose of morphine was 14 mg/day among the 52 participants who reported an improvement in breathlessness of 10% or more over their baseline. There is evidence that the beneficial effect is sustained over time in those who respond [61]. Despite the fact that some people do not derive benefit from morphine, it should be trialled when dyspnea persists despite optimization of other therapies [62].

Cough

Although cough can occur as a direct result of progressive ILD it is important to consider other, potentially treatable, causes of cough. Examples include obstructive sleep apnea and sinusitis [36]. In addition, there is a high prevalence of gastro-esophageal reflux in IPF patients which may not present with typical symptoms [36]. Micro-aspiration of acidic gastric contents is thought to contribute to the

symptom of cough as well as causing epithelial damage which accelerates disease progression [36].

A recent study supports the potential for antacid therapy (twice-daily proton pump inhibitors) to improve cough in patients with IPF [63]. Clinicians should consider reflux in patients with ILD who present with cough and should have a low threshold for initiating antacid treatment [12, 29].

Studies using cough as an endpoint of pharmacological intervention in ILD are lacking. There is some evidence that corticosteroids may improve cough but their routine use in these patients is not advocated because of the potential adverse effects [12, 29, 64]. Reduction of cough severity and sensitivity may be a direct effect of anti-fibrotic therapy; there is more evidence at present for the antitussive effect of pirfenidone than nintedanib [64, 65]. A recent international, multicenter trial of 31 IPF patients concluded that pirfenidone produced a statistically significant reduction in cough count and an improvement in HRQOL scores [66]. However this trial was limited by the lack of a placebo arm and a relatively short, 12-week, follow-up period. There is better quality evidence to support the use of thalidomide as an antitussive in IPF [65]. However, as thalidomide is associated with significant adverse effects including constipation and anorexia, NICE recommends that it be reserved for those with intractable cough [29, 65]. A phase 2 trial of inhaled cromolyn sodium (PA101) concluded that cough frequency in 24 patients with IPF reduced over the 2-week treatment period as compared to placebo [67]. Interestingly, no such improvement was observed when the same treatment was given to patients with "chronic idiopathic cough" leading the authors to conclude that the nature of cough in IPF is different. Unlike other available therapies, PA101 was not associated with any significant adverse effects.

Oral codeine and stronger opioids are often used for their antitussive effects although specific evidence to support their use in ILD is lacking [29]. There is emerging evidence for the use of pregabalin, gabapentin, specialist speech therapy, and physiotherapy in patients with refractory cough [36]. P2X3 receptors may also play a role in downregulating heightened cough sensitivity [68]. P2X3 antagonists are a novel class of antitussives and include AF-219 which has shown benefit over placebo in a phase 2 study of patients with chronic cough [68]. More research is needed but if the etiology of cough in ILD is indeed disease specific the results of studies into treatment of chronic cough should be extrapolated to the IPF population with caution [67].

Fatigue and Deconditioning

Fatigue is reported by many IPF patients as a dominant symptom which may not receive the same degree of attention as the symptoms of breathlessness and cough [38]. As is seen in COPD, fatigue is exacerbated by cardiac and peripheral muscle deconditioning which leads to a vicious cycle of fatigue, immobility, and further deconditioning. Pulmonary rehabilitation has been demonstrated in several small studies to improve HRQOL and exercise capacity [69]. At present it is unclear if this improvement is sustained over time in patients with ILD [70]. Even in those whose 6-min walk distance does not improve, rehabilitation has a role in preserving

function and independence [69]. Crucially, rehabilitation is acceptable to patients and should be offered as part of standard care to those with ILD [69]. In addition to individualized exercise training, the multidisciplinary approach to patient assessment, nutritional modulation, education, and psychosocial counselling that forms part of rehabilitation courses also produces benefit [49]. The use of supplemental oxygen in hypoxemic patients is likely to improve participation in pulmonary rehabilitation. Furthermore, hypoxemia can itself contribute to reduced energy levels and impaired social and physical functioning [71].

IPF is known to affect quality of sleep and has been associated with reduced rapid eye movement phases and greater sleep fragmentation when compared with people without the condition [72]. This results in less refreshing sleep, greater daytime somnolence, and reduced quality of life. These changes are most pronounced in those with proven nocturnal hypoxemia. Patients with daytime oxygen saturations of 90% or less are at greatest risk of nocturnal hypoxemia [71, 72]. However, it is possible for patients to have normal oxygen saturations when awake and desaturation when asleep [73]. Whilst there is a lack of evidence to confirm that supplemental oxygen improves the symptom of fatigue in this scenario, it should be considered to prevent pulmonary hypertension which is a poor prognostic factor [73]. In addition, IPF is associated with sleep-disordered breathing. Studies have suggested that significant obstructive sleep apnea is present in over two-thirds of IPF patients and should be considered, investigated, and treated [72, 74].

Finally, it is important to consider other reversible contributors to fatigue such as anxiety, depression, and adverse effects of medication (fatigue is associated with pirfenidone [75]).

Anxiety and Depression

Anxiety and depression frequently complicate ILD. Studies suggest that approximately a quarter of patients suffer depression [34, 76]. One study found the prevalence of anxiety among 256 patients with IPF to be 21.4% [76]. Ryerson et al. found a correlation between the reported severity of dyspnea and severity of depression [34]. This is not surprising because breathlessness can negatively affect mood and depression and anxiety can worsen the experience of breathlessness [35]. Patients diagnosed with IPF and their carers report frustration and anger at the way in which the illness influences all aspects of their lives [30]. That is, ILD negatively impacts the psychological well-being of patients, even if they do not meet the diagnostic criteria for clinical depression. It has been suggested that depression is a modifiable factor in the control of breathlessness [34]. Cognitive behavioral therapy has proved effective in the management of anxiety and depression in other respiratory conditions but its effect in ILD has not been studied [77].

When considering antidepressant therapy, there is evidence that sertraline (a serotonin-specific reuptake inhibitor [SSRI]) directly relieves the sensation of breathlessness in COPD [78]. A recent case series of six patients, two of whom had ILD, found that mirtazapine (a noradrenergic and specific serotonergic

antidepressant) also reduces breathlessness [78]. It is postulated that mirtazapine is advantageous over SSRIs in ILD because it has a role in the management of anxiety as well as depression, promotes sleep, enhances appetite, and has a faster onset of action [78].

Low-dose benzodiazepines (e.g., lorazepam 500 micrograms as required) are often used in the management of anxiety which has failed to respond to other therapies. Although there is an association between benzodiazepine prescription and admission to hospital, it is likely that such medications are only used for the most symptomatic patients who are near the end of life [79]. A recent study concluded that low-dose benzodiazepines (defined as ≤15 mg/day oral oxazepam equivalent) are not associated with harm even when prescribed for patients with severely compromised respiratory function [79].

Education and Self-Management

From the time of diagnosis patients should be offered individualized, clear, and accurate information regarding the diagnosis, treatment options, and prognosis. This includes appropriate written information as well as sign-posting to quality Web-based information and materials relating to their disease and its treatment (Table 9.1).

In order that patients, families, and the clinical team can continue to engage in ongoing education and review, regular assessment has been recommended. There will be variability in the frequency of follow-up appointments based on patient and disease factors, though 3–6-monthly follow-up is recommended as a minimum for adequate monitoring for disease progression [29]. This frequent contact between the patient and clinical team allows reassessment of both the patient's and clinician's goals of care.

The structure of clinical services shows variability within countries as well as internationally. There is recognition that, in view of the diagnostic challenges involved, specialist regional ILD multidisciplinary teams are needed to support

Table 9.1 Useful resources for education and self-management

Website	Details
http://www.lunguk.org	British Lung Foundation patient charity with website and telephone support. Funding lung fibrosis research and supporting healthcare professionals.
http://pulmonaryfibrosis.org	US-based nonprofit organization supporting patients and research into IPF with personalized patient platform.
https://www.actionpulmonaryfibrosis.org	UK charity focusing on improving the quality of life for patients with pulmonary fibrosis and funding research.
http://www.ipfcharter.org	Supports equal access to IPF treatment and care standards in Europe. Annual IPF World Week raising awareness.

clinicians and patients in securing an accurate diagnosis and thus prognosis, often in a "shared care" approach with the local clinicians [29].

Guidelines and standards of care for ILD recognize the role of a multidisciplinary team in supporting ILD patients. In addition to accessing a specialist palliative care team, people with IPF should have a specialist nurse available to them [29]. NICE guidelines recognize that a specialist nurse can ensure that people with IPF, and their families and carers, receive all the information and support they need throughout the care pathway.

Specialist nurses and interdisciplinary healthcare professionals are fundamental to the care of patients diagnosed with progressive fibrotic ILD [80]. In 2011 many patients were denied access to ILD specialist nurses with only one-quarter of UK centers having a specialist nurse [81]. Whilst there has been improvement in recent years, often led by the need to support anti-fibrotic drug prescribing, there remains disparity in healthcare provision. In the UK, 90% of patients reported that an ILD specialist nurse was their main clinical contact for IPF healthcare [82]. However, a UK national patient survey of 122 patient and carer respondents reported that only 39% of patients have frequent contact with a specialist nurse [83]. The ILD specialist nurse provides expert knowledge and advice to patients, their families, and carers, throughout all stages of their care [25, 81].

Advance Care Planning

Issues relating to advance care planning (ACP) should ideally be anticipated and discussed early before a crisis has developed and before the last days of life. As with other diseases, some patients with ILD choose not to discuss future deterioration [31]. However, evidence suggests that ACP is beneficial for these patients [31, 84]. For example, bereaved carers of decedents with IPF report that early discussions about end-of-life care allowed time for families to be together and to arrange financial and legal affairs [84]. Pooler et al. suggest that a better understanding of the condition enables out-of-hospital deaths because deterioration is recognized and care better coordinated [84]. In a study by Bajwah et al. only 28% of patients who received the intervention—a palliative care community case conference—died in hospital [31]. This figure contrasts with a retrospective population-based study which found that 70% of patients with ILD died in hospital over the 14-year period 2001–2014 [85]. However, due to its retrospective nature, the authors could not make any conclusion about whether the location of end-of-life care was appropriate [85]. Rather than being a default option, admission to hospital in the event of sudden deterioration can be clinically beneficial given that treatments are available [85]. Clinical services could provide better support to patients by offering urgent reviews for those who are deteriorating to distinguish patients who are likely to benefit from admission from those whose disease is entering the end-of-life phase [86]. ACP conversations should focus on personal goals and values in addition to preferred location and priorities of care. Wishes may evolve over time; therefore ACP should be viewed as a process to be revisited as the disease progresses [84].

Integrating Specialist Palliative Care into an ILD Service

Despite the high burden of physical and psychological symptoms associated with ILD, patients have historically not accessed specialist palliative care services [27, 31, 84]. Barriers to referral include insufficient clinic time and unpredictable disease trajectories [27]. Poor symptom control, poor interdisciplinary communication, and poor ACP impact patients negatively and their carers [84]. Swigris et al. found through interviews with IPF patients that they want "assurance that their symptoms would be controlled, that their passing would be peaceful, and that the dying process would occur on their own terms" [38]. Government guidance advocates individualized, patient-centered care plans for all those living with terminal illness [87].

To date, there have been only a small number of studies looking at the impact of palliative care on HRQOL when compared to standard care alone. Available data suggest that early access to specialist palliative care services is beneficial but the effect size is small [88]. Bajwah et al. [31] found that early palliative care intervention had a positive impact on symptom burden and quality of life as compared with standard care in a group of 53 patients with ILD.

Since there is no cure for IPF at present, palliative care should be incorporated into the management of these patients from the time of diagnosis [29]. The specific way in which services integrate will depend on factors such as local geography and available resources. Examples of existing integrated service models include (1) a holistic, multi-professional case conference delivered by a palliative care nurse specialist in patients' homes [31]; (2) the embedding of a palliative care consultant in a respiratory ILD clinic [89]; and (3) a collaborative multidisciplinary team discussion platform [90].

In recognizing the often scant evidence supporting palliative care approaches in the management of ILD there is a clear need for further high-quality clinical trials. These should focus on symptom control, quality of life, carer support, and service organization in addition to novel disease-modifying treatments. Important outcomes in a progressive and ultimately fatal disease should include both "living well" and achievement of a "safe death" [27, 91].

A "top ten points" approach to the integrated palliative care of ILD is suggested:

1. Use a multidisciplinary approach to secure the correct diagnosis.
2. Ensure that patients and their families have access to high-quality information about their disease and access to appropriate support both in the clinic and at home. This should include access to an ILD nurse specialist.
3. Patients should be assessed for, prescribed when appropriate, and supported in taking anti-fibrotic drugs such as pirfenidone and nintedanib.
4. Patients should be offered access to clinical trials looking at both disease-centered and symptom-centered outcomes.
5. Patients should be monitored closely for evidence of deterioration and, if eligible, referred early for consideration of lung transplantation.

6. Ensure that all patients have timely access to smoking cessation support, pulmonary rehabilitation, oxygen services, and palliative care.
7. Actively enquire about and monitor symptoms of breathlessness, cough, fatigue, anxiety, and depression.
8. Consider the use of opioids for the relief of breathlessness and benzodiazepines for the relief of anxiety in patients who have not derived benefit from non-pharmacological interventions.
9. Ensure that therapies which have had no benefit or have caused harm are withdrawn.
10. Share decision-making with patients and their families and actively offer discussions about advance care planning and end-of-life issues.

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Cystic Fibrosis

10

Stephen J. Bourke and Rachel Quibell

There are about 10,500 people in the UK and 30,000 people in the USA who are living their lives with cystic fibrosis (CF) [1, 2]. They are treated in specialist centers by multidisciplinary teams who strive to provide comprehensive holistic care and support. As the disease progresses patients experience an increasing level of symptoms and an increase in the burden of treatment. Although the prognosis of patients with CF continues to improve many still die in early adulthood. National registries show that in 2017 there were 132 deaths from CF in the UK and 380 in the USA, at a median age of 31 years [1, 2]. Nowadays very few deaths occur in childhood, the majority occur in early adulthood, and an increasing number occur in middle to older age (Fig. 10.1). The median predicted survival for a child born with CF in 2017 is about 47 years [1–3]. Palliative care of patients with CF is often undertaken by CF teams rather than palliative care teams because of the specialist nature of the disease and the potential role of lung transplantation, which is paradoxically intertwined with palliative care. Palliative care is a crucial component of a comprehensive adult CF service [4].

Overview of Cystic Fibrosis

CF is an autosomal recessive disease caused by mutations of a gene on chromosome 7 that encodes for a protein named cystic fibrosis transmembrane conductance regulator (CFTR), which functions as a chloride channel in the apical membrane of epithelial cells [5]. Reduced chloride conductance results in viscid secretions and

S. J. Bourke (✉)
Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: stephen.bourke@nuth.nhs.uk

R. Quibell
Department of Palliative Medicine, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

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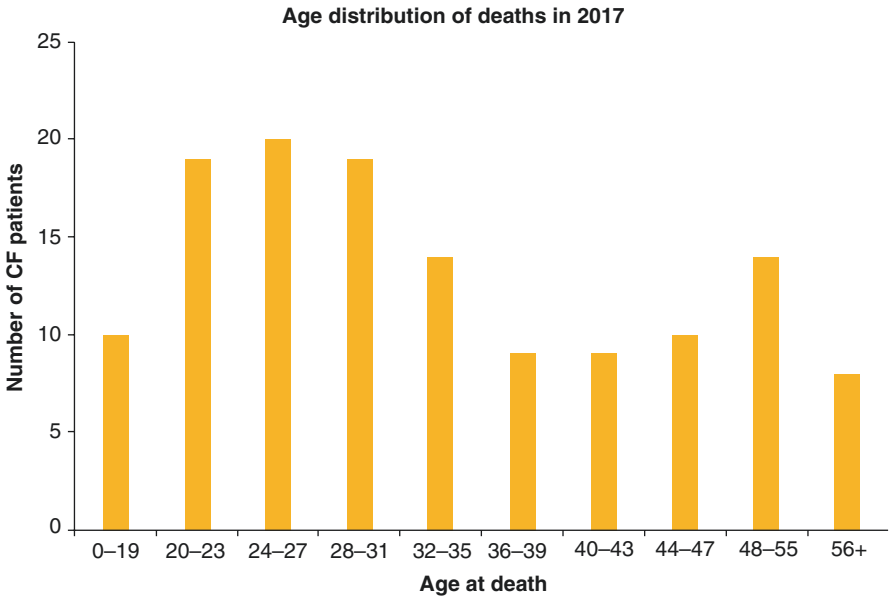

Fig. 10.1 Age distribution of deaths from cystic fibrosis in the UK, 2017. Nowadays very few deaths occur in childhood, the majority occur in early adulthood, and an increasing number occur in middle to older age (reproduced with permission from the Cystic Fibrosis Registry 2017 [1])

organ damage in the respiratory, gastrointestinal, hepatobiliary, and reproductive tracts. It affects about 1 in 2500 births in Caucasians, and about 1 in 25 of the population is a carrier of the disease.

More than 2000 mutations of the CF gene have been identified and this partly explains the wide spectrum of severity of the disease although other factors such as environmental influences and modifier genes affecting the inflammatory response are also important. Mutations are categorized into five main classes according to their effect on CFTR processing and function (Fig. 10.2). This is increasingly important as new CFTR modulator treatments are targeted against specific mutations [2, 5]. The most common mutation, traditionally known as ΔF508 (F508del), results in the loss of phenylalanine at position 508 of the protein. This causes misfolding of the mutant CFTR which is then degraded such that no CFTR reaches the cell membrane. In certain mutations the mutant CFTR retains some function and this may be associated with less severe disease. Some rare patients have non-classic CF in which they have two mutations of the gene, abnormal sweat chloride, some manifestations of the disease (such as male infertility, pancreatitis, or nasal polyps) but little or no lung disease. There is a spectrum of severity and the treatment regimen is adjusted according to the type, severity, stage, and complications of the disease.

The traditional treatments of CF have focused on managing the consequences of the disease such as lung infection, inflammation, and thick secretions. However in

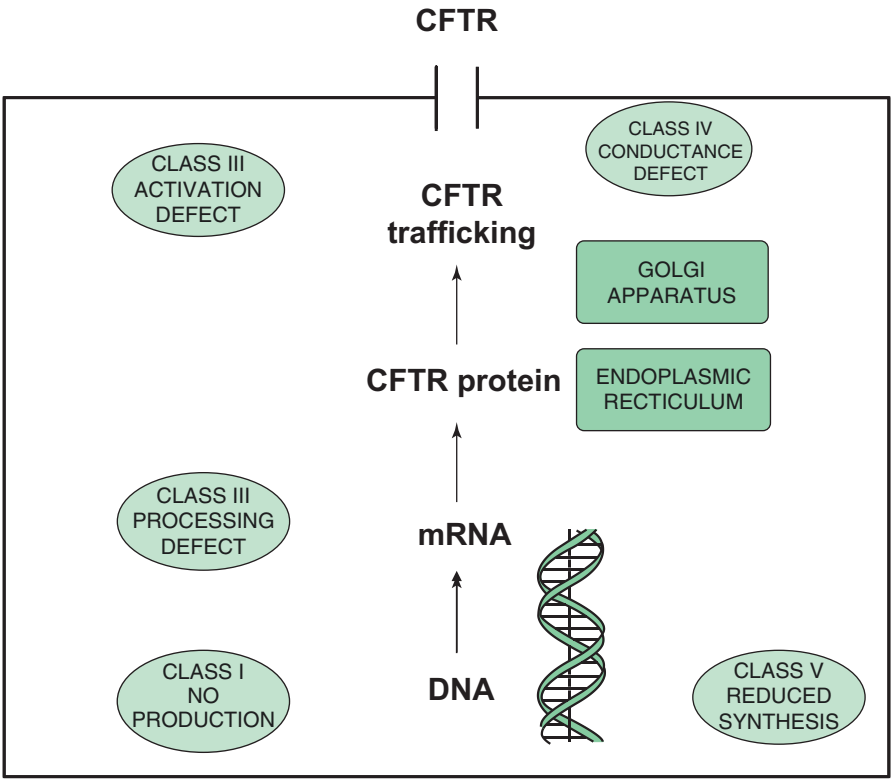

Fig. 10.2 CFTR processing. The CF gene is transcribed via messenger RNA which forms a template for translation into the CFTR protein which consists of 1480 amino acids. This is then trafficked through the cell via the endoplasmic reticulum and Golgi apparatus to be inserted into the apical membrane where it functions as a chloride channel. Class I mutations (e.g., G542X) disrupt synthesis of CFTR. These include nonsense and frameshift mutations which lead to premature termination codons and lack of protein production. Class II mutations (e.g., F508del) result in misfolded CFTR, which is then degraded in the endoplasmic reticulum such that there is no CFTR function at the cell membrane. In Class III mutations (e.g., G551D) CFTR reaches the epithelial membrane but has reduced function. Class IV mutations (e.g., R117H) are associated with reduced chloride conductance. In Class V mutations (e.g., A455E) there is reduced synthesis of normal CFTR. CFTR modulator drugs improve the processing and function of CFTR. "Correctors," such as Lumacaftor® and Tezacaftor®, bind to mutant CFTR, enabling it to move through the cell and avoid degradation. "Potentiators," such as Ivacaftor®, improve the function of the CFTR chloride channel at the cell surface

recent years major progress has been made in developing CFTR modulator drugs which improve the processing, trafficking, and function of the CFTR protein [5]. Treatments are targeted at specific mutations. Thus Ivacaftor® was introduced into clinical practice in 2013 as a tablet treatment which improves the function of the CFTR chloride channel in the epithelial membrane in patients with Class III mutations (e.g., G551D). It dramatically improves clinical status in these patients, typically reducing sweat chloride levels by about 50 mmol/L, with a 10% improvement

in forced expiratory volume in 1 s (FEV_1). Follow-up data confirms a sustained effect resulting in slowing of progression of the disease. A combination of Ivacaftor® and Lumacaftor® as a corrector and potentiator has been developed for patients with F508del mutations [5]. The corrector (Lumacaftor®) binds the mutant CFTR protein allowing it to traffic to the cell surface where Ivacaftor® acts as a potentiator of the gating channel function, typically resulting in a small improvement of 2.4% in FEV_1 with reduced exacerbation rates. The next generation of CFTR modulators consist of triple combinations of potentiators and correctors and these are showing substantial benefits in clinical trials, typically of up to 13% improvement in FEV_1 [6]. These new treatments are likely to improve the outcome for patients with CF.

In the bronchial mucosa reduced chloride secretion and increased sodium reabsorption result in secretions of abnormal viscosity with reduced water content of the airway surface liquid and disrupted mucociliary clearance. This predisposes to chronic infection with associated inflammation progressing to bronchiectasis, respiratory failure, and death. Initially infection is often with *Staphylococcus aureus*. Subsequently *Pseudomonas aeruginosa* becomes the dominant pathogen. Different strains of pseudomonas can be identified and they vary in their virulence and transmissibility. *Burkholderia cepacia* complex is a group of Gram-negative bacteria which have a high level of antibiotic resistance. Patients with CF are vulnerable to these bacteria and infection can spread from patient to patient. The most virulent strains are *B. cenocepacia* and *B. multivorans*. Nontuberculous mycobacteria (such as *Mycobacterium abscessus* or *Mycobacterium avium* complex) can also infect the lungs in CF and are difficult to treat. Adverse microbiology can be a contraindication to lung transplantation. Patients are segregated according to their infections when attending hospital and contact between patients is discouraged.

In the pancreas plugging and obstruction of ductules cause progressive destruction of the gland. Pancreatic enzymes (such as lipase) fail to reach the small intestine and this results in malabsorption of fats with steatorrhea and weight loss. Approximately 40% of adults develop diabetes from destruction of the endocrine pancreas. Lack of pancreatic enzymes with viscid intestinal secretions and reduced motility can result in distal intestinal obstruction which is usually treated by intestinal lavage and osmotic agents (such as Gastrografin®). Men with CF are nearly always infertile because of obstruction of the vas deferens but can achieve biological parenthood by sperm aspiration from the testes with in vitro fertilization. Women with CF have essentially normal fertility and many undertake pregnancy and motherhood, but may not survive to see the child reach adulthood.

The key elements of treatment are clearance of bronchial secretions by physiotherapy, treatment of pulmonary infection by antibiotics, and correction of nutritional defects by pancreatic enzyme supplements and dietary support [7]. Children are typically given flucloxacillin continuously to prevent or suppress *Staphylococcus aureus* infection. When *Pseudomonas aeruginosa* is first isolated attempts are made to eradicate it by prolonged courses of oral ciprofloxacin and nebulized colistin or tobramycin. When pseudomonas infection becomes established long-term nebulized antibiotics are used to suppress infection. Exacerbations are treated by

combinations of intravenous antibiotics (such as ceftazidime or meropenem with tobramycin or colistin). Treatment is facilitated by use of indwelling central venous access devices and many patients self-administer antibiotics intravenously at home (Fig. 10.3). As the disease progresses the frequency of antibiotics increases. Even in late-stage disease intravenous antibiotics are effective in improving the level of symptoms. Malabsorption is controlled by use of pancreatic enzymes with food. As the chest disease progresses patients have difficulty in maintaining their energy requirements because of decreased appetite and the increased energy expenditure associated with chronic lung infection. Dietary supplements are used when anorexia limits intake and supplemental feeding is often given overnight via a gastrostomy tube. Mucoactive agents, such as nebulized 7% sodium chloride or deoxyribonuclease (rhDNase), aid in clearance of airway secretions. Lung transplantation is the main treatment option for patients with end-stage lung disease but lack of donor organs limits this treatment. Approximately 80% of patients with CF die of progressive lung disease. The second most common cause of death is complications of lung transplantation accounting for about 16% of all deaths [2]. Palliative care is paradoxically intertwined with high-intensity treatments including lung transplantation and many patients who die will be on a transplant waiting list at the time of death.

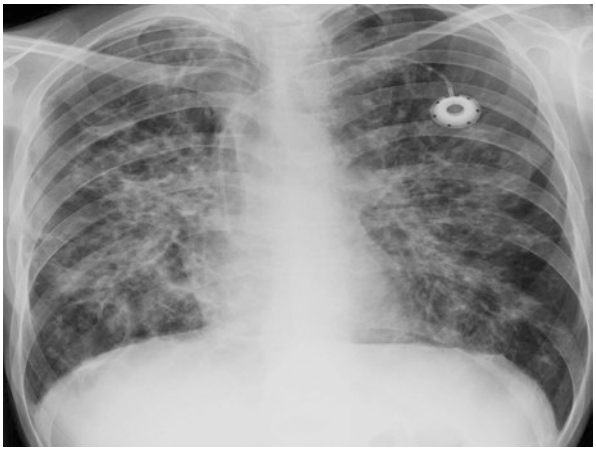

Fig. 10.3 This man died at 21 years of age of respiratory failure from progressive cystic fibrosis lung disease. Two years previously he had been deemed unsuitable for lung transplantation because of *B. cenocepacia* infection. He had a prolonged phase of palliative care of advanced disease during which he had supplemental gastrostomy feeding, intensive physiotherapy, and frequent courses of intravenous antibiotics. He also attended a specialist palliative care symptom control clinic, but he did not find a hospice day care facility helpful. His chest radiograph shows severe diffuse bronchiectasis and a central venous access system in the left subclavian vein. After several exacerbations he deteriorated into terminal stage disease and died at home with end-of-life care from the community palliative care team

Lung Transplantation for CF

Lung transplantation is generally considered at a stage where the FEV_1 has fallen to below 30% of the predicted value, but only a minority of carefully selected patients actually go on to receive donor lungs [8]. In most patients there is a gradual, generally predictable progression of lung disease that allows a planned approach to both lung transplantation and palliative care, but patients can suffer an acute crisis from complications such as massive hemoptysis, pneumothorax, or a severe exacerbation. Some patients are unsuitable for transplantation because of resistant infections (such as *B. cenocepacia*, *Mycobacterium abscessus*), poor nutritional status, psychosocial problems, or additional systemic disease [8]. The success of lung transplantation has been based on careful selection of individuals most likely to benefit. There is a "window of opportunity" during which the patient is sick enough to need transplantation but well enough to undergo such major surgery. Identifying patients in this window of opportunity is challenging and requires careful discussion and decision-making by both the patient and the clinical team. A fall in FEV_1 to below 30% of predicted is often a trigger point for such discussions as some studies suggest that this indicates an approximately 50% risk of dying within 2 years [9]. Additional factors such as the rate of decline, frequency of exacerbations, development of hypoxia and hypercapnia, and occurrence of complications are also important in predicting a poor prognosis [10].

Paradoxically the consideration of potential lung transplantation is intrinsically intertwined with consideration of palliative care, and discussion of risk of dying from the disease or from complications of transplantation. Physicians experience significant difficulties in discussing intensive treatment preferences with CF patients and their families, and encounter issues such as denial of disease severity, optimistic expectations of treatment outcomes, inability of ill patients to participate in discussions, and family disagreements about treatments. Physicians have concerns about taking away hope and are uncertain about when to address treatment preferences [11, 12].

Even when accepted onto an active lung transplant waiting list about 40% of patients die before donor lungs become available [8]. Several options have been considered as a "bridge to transplant" including noninvasive ventilation, ICU invasive ventilation, extracorporeal membrane oxygenation, and extracorporeal carbon dioxide removal [13]. Deterioration to the point of needing ICU mechanical ventilation or extracorporeal life support is associated with a worse outcome from subsequent transplantation with a 58% increased risk of dying within 1 year after lung transplantation [13]. This poses substantial clinical and ethical dilemmas in making decisions as to whether transplant remains the best option for an individual patient and whether transplantation with poorer outcomes makes best use of the scarce resource of donor lungs. Overall survival rates posttransplantation are approximately 80% at 1 year, 60% at 5 years, and 50% at 10 years [14].

Traditionally lung transplantation has acted as a barrier to palliative care as the psychological approach of the patient, family, and medical team is one of "fighting on" in the hope of transplantation rather than acceptance and preparation for death

from a life-limiting illness. Patients who die whilst awaiting transplantation may have an abrupt late change from intensive treatment to palliative care, with less time for the patient and family to address end-of-life and bereavement issues [15]. They are more likely to die on the ICU, to be on endotracheal ventilation, and to be less able to participate in end-of-life decisions [16]. Physicians providing care to lung transplant candidates report considerable barriers to the delivery and acceptance of palliative care and both clinicians and families can struggle with the seemingly contradictory goals of transplant versus palliative care [11]. These patients are at high risk of dying and have a very high level of symptoms and distress. Modern palliative care, however, delivers symptom-relieving measures, support, and palliation in parallel with active disease-modifying treatments including the potential for rescue lung transplantation. Nowadays many CF services and transplant teams would regard transplant assessment as a key point at which to also introduce specialist palliative care [17, 18].

Symptom Control in Advanced Disease

In advanced CF patients often have a range of complex physical and psychological problems. The dominant physical symptoms are cough, sputum, wheeze, chest tightness, breathlessness, pain, fever, and fatigue [15, 18–24]. The emotional impact of these symptoms is high, and when combined with a realization that the prognosis is poor results in frustration, anger, sadness, irritability, worry, and difficulty sleeping [25–27]. Psychological symptoms are rated by patients as causing more distress than physical symptoms [19]. Pain is a common symptom at all stages of CF but becomes more prominent as the disease progresses. Surveys show that 84% of patients with advanced CF have pain: 65% have chest pain, 55% headaches, 19% back pain, and 19% abdominal pain [22]. The majority of chest and back pain is of musculoskeletal origin related to use of accessory muscles of respiration, coughing, postural abnormalities, or osteoporosis. Several studies suggest that the problems of chronic pain in CF are not adequately addressed with a lack of use of analgesic medication or other treatment strategies [20–22]. When assessing patients with CF in addition to focusing on key elements of the disease such as lung function, oxygenation, nutritional status, and control of infection, it may also be helpful to use symptom checklists to identify the symptom burden, the emotional impact of these symptoms, and the effect these symptoms are having on activities and quality of life [19, 26]. Recently the CF-CARES project ("Coping, goal Assessment, and Relief from Evolving Symptoms of CF") developed a structured assessment of symptoms, distress, and coping to inform individualized symptom management [19]. This is designed as a primary palliative care framework which allows CF teams to apply generalist palliative care as a routine part of standard CF care. Symptom control requires detailed assessment and a multifaceted approach. Specific treatments directed against the disease, such as a course of intravenous antibiotics, result in improvements in symptoms and in quality of life. Some symptoms, such as hemoptysis, may require a specific intervention such as bronchial artery embolization.

Other interventions targeting specific symptoms include analgesia for pain, sputum clearance physiotherapy for cough and secretions, mucolytics for sputum retention, antiemetics for nausea and vomiting, and musculoskeletal physiotherapy and massage for pain [28]. Management of psychological symptoms should be part of a holistic approach [25–27].

It is also advisable to continually assess the burden of treatment. With disease progression there is often a need to intensify treatments but this may impair the quality of life further. An ever-increasing treatment regimen may not be effective as patients may have difficulty coping with it. A survey of 204 patients found a mean reported time spent on treatment of 108 min each day, even though less than half of these patients had performed their recommended physiotherapy airway clearance techniques [29]. Some patients are overwhelmed by the burden of the disease and find it difficult to maintain treatments such as respiratory physiotherapy, and they may discontinue most of their treatments. There is very little written about this aspect of the disease, but this pattern of behavior is associated with resignation, reactive depression, and lack of social and family support [30]. This is a challenging situation for the patient, the family, and the clinical team, but may be a signal to escalate palliative care as well as providing compassionate psychological support.

As in other chronic lung diseases lung function measurements are poor predictors of the degree of disability and the impact of the disease on the patient. The CF quality-of-life questionnaire is a health-related measure consisting of 52 items across nine domains (physical functioning, social functioning, treatment issues, chest symptoms, emotional functioning, concerns for the future, interpersonal relationships, body image, and career concerns). It is now increasingly being used in the clinical assessment of patients with CF and as an outcome measure in clinical trials [26]. Cognitive and behavioral factors are important in the patient's perception of their health and in the way they cope with and adapt to the disease. Cognitive behavioral therapy is a treatment for emotional and adjustment problems. It addresses unhelpful thinking and worrying and promotes understanding of how thoughts, mood, behavior, and physical symptoms interact. It is effective in reducing anxiety and depression scores in patients with CF [27].

Palliative and End-of-Life Care in Cystic Fibrosis

Most CF multidisciplinary teams are well placed to deliver comprehensive care throughout the course of the disease. Typically CF teams consist of specialist doctors, nurses, physiotherapists, dieticians, clinical psychologists, and social workers. When considering the palliative care needs of these patients and their families a key issue is how such holistic supportive care can be developed to include the ethos and skills of generalist palliative care and when additional specialist palliative care is needed [19]. CF teams may feel unprepared for their role in providing some aspects of palliative and end-of-life care [31, 32]. This has led to the development of a palliative care curriculum and training for CF teams [33]. In addition to symptom control and general supportive care, CF teams can enhance their knowledge and

communication skills in areas such as advance care planning, escalation planning, emergency healthcare planning, and patient preferences concerning end-of-life care [34–36]. Patients and their families look to CF teams to initiate discussions about end-of-life issues and generally indicate that such discussions currently occur too late [37].

However patients, families, and clinical teams still struggle with the concept of palliative care in CF. It is still difficult to overcome confusion of palliative care with end-of-life care and with concepts of "giving up." It is recognized that holistic standard multidisciplinary care of CF overlaps with palliative care. In the USA the CF Foundation sponsored a working group of clinicians, researchers, people with CF, and their caregivers to discuss current practices in palliative care for people with CF in the USA, to plan for guideline development, and to establish best standards of care [38]. They first explored a definition of palliative care as it applies to CF. Using Delphi methodology they reached a consensus that "*palliative care focuses on reducing physical and emotional symptoms and improving quality of life for people with CF throughout their lives. Palliative care occurs alongside usual treatments and is individualized according to the unique goals, hopes, and values of each person with CF*." Perhaps controversially the Delphi exercise resulted in a recommendation to omit language about end of life in order to emphasize that palliative care applies throughout the lives of people with CF whilst acknowledging that this may reflect concerns about addressing end of life as a routine part of CF care.

This definition may help overcome barriers to the early introduction of specialist palliative care but may continue the taboo about discussing end of life in CF. Concepts of palliative care very much depend on societal and cultural influences which include some hesitancy in acknowledging and discussing death and dying. Although palliative care applies throughout the course of a disease, advance care planning, emergency healthcare planning, and end-of-life priorities become particularly relevant in later stage disease at the time of disease progression. The perception of people with CF and their carers is very much influenced by the timing of discussions. Patients and their families emphasize the importance of hope and a positive psychological approach in coping but acknowledge that this can then be a hindrance in preparing for declining health [37]. In the UK the CF Trust has been promoting and encouraging open and honest discussions of end of life, providing a document for people with CF and their families "*End of life planning: things to think about*" along with a template for "*Advance care planning for people with CF*" [35, 39]. The American Thoracic Society has also developed a useful patient information and education document which emphasizes that palliative care can be provided at the same time that the person is receiving medical treatments, and that palliative care can help at the end of life [40].

The point at which the role and limitations of lung transplantation are being considered may also be a useful time to focus specifically on palliative care. At this stage the CF team is focused on the decline in lung function, the options for intensifying treatment, and the potential role of lung transplantation. These discussions provide an opportunity for considering the poor prognosis, the risk of dying, the burden and impact of symptoms, the role of palliative care, and the patient's

preferences and wishes. The patient may benefit from a specialist palliative care consultation at this stage. This introduces patients to the palliative care team and in some cases they may benefit from a specific symptom control approach.

There are two main phases to palliative care of CF: a phase of management of advanced disease which is often prolonged and a phase of end-of-life care of the dying patient which is often short. Traditionally specialist palliative care involvement has tended to occur only in the late stage of the disease when the person is dying. Guidelines now recommend early palliative care discussions in order to allow time to psychologically adjust and carefully consider options [4].

Most patients with CF die in hospital [15, 18, 41–43]. In the UK this is most commonly on a specialist CF ward, whereas in the USA many die on the ICU [41]. Even patients who have indicated in advance that they might wish to be at home when dying often chose to be in hospital when the final phase occurs [15]. This may be because of the high level of complex symptoms and because of the typical pattern of the final illness presenting initially with a potentially reversible crisis. The circumstances of death differ from patient to patient. Most have a gradual progressive deterioration that allows a planned approach to palliative care. Some suffer a sudden crisis due to a major hemoptysis, pneumothorax, or a severe exacerbation such that there is an abrupt change from being reasonably well to being terminally ill. Some die on a transplant waiting list when there is an attitude of "fighting on" followed by "unfulfilled hope." Some patients die after transplantation from transplant complications or from rejection of the donor lungs.

Typically the dying phase starts with a patient presenting with a further exacerbation with an increase in cough, sputum, and breathlessness [15, 42, 43]. Often the patient has recovered from many such exacerbations previously. The patient, family, and CF team initially expect a response to treatment and it may be only after several days that it becomes apparent that the patient is deteriorating. There is then a transition from the phase of management of chronic advanced disease to the dying phase and end-of-life care. This trajectory may be inherent to the clinical course of CF and other progressive lung diseases, and it needs to be acknowledged and managed accordingly.

Patients dying of CF usually have a high level of complex symptoms requiring palliation [15, 42, 43]. The dominant symptom is breathlessness and this is frequently linked to anxiety and fear in a vicious cycle. It is often accompanied by difficulty in expectorating sputum with retained secretions, chest tightness, and pain. Breathlessness is usually alleviated by a combination of drug treatments, such as opioids and benzodiazepines (e.g., midazolam), and general measures such as oxygen, nursing in an upright position, use of a cool air fan, breathing control methods, reassurance, and distraction techniques to encourage the patient to focus on issues other than the sensation of breathing. Cognitive behavioral therapy is sometimes useful in helping to break the vicious cycle of breathlessness, anxiety, and fear [15, 27]. This involves recognition that it is not just the impact of a physical symptom but the patient's perception and response to the symptom that may be important. There is often a particular role for the physiotherapist in using breathing control techniques to relieve breathlessness and airway clearance techniques to relieve

sputum retention. Hyoscine may be helpful in reducing secretions in the final hours of life. Other common symptoms are cough, hemoptysis, headache, and abdominal pain but these are often masked by the dominance of breathlessness as the main symptom. A particularly difficult symptom to alleviate is a sensation of general malaise, often described as "feeling awful" [18]. This is probably due to a combination of lung sepsis, hypoxia, and debility of the dying phase.

End-of-life care is particularly complex when the patient is on a transplant waiting list [11–13, 15–17]. Some patients with advanced respiratory failure remain suitable for transplantation and some who die have had a transplant "callout" within a week of their death but not received a transplant as the donor organs proved unsuitable [15]. Full palliative symptom-relieving treatments are given but it can be difficult to address some end-of-life issues, although parallel planning is possible for some individuals. Endotracheal ventilation on an ICU is usually avoided although it may be appropriate in the initial management of an acute crisis related to a potentially reversible cause such as pneumothorax or massive hemoptysis [13]. Stopping some treatments during the final stages of the disease requires careful consideration. Antibiotics and mucolytic drugs are often continued for symptom relief. Many patients still find physiotherapy helpful with the techniques adapted for relief of breathlessness, cough, and retained secretions.

Flexibility is needed in having a range of options available to meet the needs of individual patients for end-of-life care. Patients follow their own particular disease pathway and have their own needs and wishes. They are usually admitted to the specialist CF ward to a team whom they and their families have known for many years. They may be reluctant to have care transferred to a different team or to a hospice setting, but usually welcome the input of specialists in palliative care as part of multidisciplinary care. CF teams who have not had training or experience of palliative care may have difficulty in coping with some issues relating to end of life. They may experience a sense of failure in the face of the disease. Unwittingly they may distance themselves from the dying patient with a concept that "nothing more can be done." However an increasingly favored model of care in CF and other progressive lung diseases is for palliative care specialists to be fully integrated into specialist respiratory teams, such that they become full members of the overall CF service, delivering specialist palliative care in parallel with standard CF treatments [18]. Palliative physicians and nurses may then form part of the wider CF team and attend team meetings to support staff in the care of these patients and to identify patients who would benefit from additional specialist palliative care input. This allows all members of the CF team to develop the skills, knowledge, and ethos of palliation and it also allows the palliative care team to understand the problems and complexity of CF care. They get to know the patients and their families earlier in the course of the disease. Often a specialist palliative care consultation will start by focusing on symptoms and then move on to explore the patient's fears, expectations, and wishes, at a time and pace which suit the individual patient.

The death of young adults from CF is inherently sad and distressing, and has a significant impact on the family, friends, other patients with CF, and the CF team. There are some particular issues in this patient group. There is often a very high

level of symptoms requiring palliation at the end of life. There may be the tension between palliative end-of-life care and potential lung transplantation. Patients are already known to the multidisciplinary CF team and have gained confidence and trust in them over the years. It is increasingly common for patients dying from CF to have their own children, or siblings who may also have CF, visiting during the terminal illness and their needs must also be met [15]. Sometimes people find it helpful to develop a memory box, containing photos, drawings, letters, and personal belongings, which acts as a focus in remembering the person who has died.

The quality of death is very important, and an inadequate level of palliative care in the final stages of the disease may have an adverse effect on the family and friends in their bereavement, on other patients with CF and on the CF team [42]. It is common for members of the CF team to attend funerals in order to provide support to the family and friends. It is often helpful for the team to review the death and any issues arising. This can also help the team deal with the emotional impact of caring for a young adult who dies of CF [43, 44].

Achieving the active total care of CF patients and their families at a time when the patient's disease is no longer responsive to treatment is challenging and requires the specialist skills of both the CF and palliative care teams. Palliative care is a key component of a comprehensive CF service, and both CF and palliative care specialists can derive benefit in the exchange of knowledge and skills in providing care to these patients.

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Neuromuscular Disease

11

Ben Messer and Alexa Clark

Introduction

The term neuromuscular disease relates to a wide range of conditions with different prevalence, causes, natural history, and progression. The likelihood and pattern of respiratory muscle involvement may also vary significantly between conditions.

There are many ways of categorizing neuromuscular diseases but classification according to the likelihood of developing respiratory muscle weakness and the rapidity of progression helps the clinician assess the chance of developing symptoms of respiratory muscle weakness and the speed with which those symptoms are likely to progress (Table 11.1).

Reasons for Respiratory Failure/Compromise

Respiratory Failure

Different neuromuscular diseases cause a different pattern of respiratory muscle involvement and weakness. For example, Duchenne muscular dystrophy (DMD) causes predominant diaphragmatic weakness and spinal muscular atrophy has a more significant effect on the intercostal muscles. Muscle weakness causes a reduction in vital capacity (VC) and respiratory failure due to reduced alveolar minute

B. Messer (✉)
Department of Critical Care Medicine and North East Assisted Ventilation Service, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
e-mail: Ben.Messer@nuth.nhs.uk

A. Clark
Department of Palliative Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

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Table 11.1 Respiratory failure in neuromuscular diseases

Disease	Likelihood of respiratory failure	Speed of progression
Duchenne MD	Inevitable	Rapid
Motor neurone disease	High	Rapid
Cervical spine injury	Variable depending on level	Usually not progressive
Myotonic dystrophy	Common	Intermediate
Becker MD	Common	Slow
Post-polio syndrome	Variable	Slow
SMA type 1	Inevitable	Rapid
SMA type 2	Common	Slow
Facioscapulohumeral MD	Rare	Slow

MD muscular dystrophy, *SMA* spinal muscular atrophy

volume. The symptoms of respiratory failure are often caused by sleep-disordered breathing in conditions where diaphragmatic failure is present because, during sleep and particularly during rapid eye movement (REM) sleep, other respiratory muscle activity is inhibited and humans essentially become obligate diaphragmatic breathers. This leads to nocturnal episodic, REM-related, hypercapnia and desaturation which result in multiple arousals and sleep fragmentation. Sleep physiology in normal subjects and in neuromuscular disease is well described in the literature [1].

Obstruction

Obstructive sleep apnea syndrome (OSAS) is commonly seen in most neuromuscular disorders due to relaxation of weak upper airway muscles during sleep [1]. Patients with conditions such as DMD are further predisposed to OSAS due to weight gain from use of corticosteroid therapy. Patients with cervical spine injuries have a particularly high incidence of OSAS [2]. Furthermore, redistribution of dependent edema from the lower limbs to the upper airway when lying down overnight may increase obstructive events [3].

De-recruitment

Intercostal muscle and diaphragmatic weakness predispose to a low functional residual capacity which increases the work of breathing. Patients with respiratory muscle weakness are also unable to recruit to their lung volume by deep breathing and yawning, predisposing to atelectasis and chest infections.

Cough and Secretions

Expiratory muscle (intercostal and abdominal) weakness reduces cough strength and bulbar weakness reduces coordination of coughing and reduces the clearance of

secretions even when the cough is augmented. Secretions then accumulate in the airways increasing the work of breathing and predisposing to chest infections. Weakness of bulbar muscles reduces the ability to swallow which is commonly seen in motor neuron disease (MND: also known as amyotrophic lateral sclerosis). Apart from unsightly drooling which can have a profound effect on quality of life, this also causes aspiration of saliva and increases the frequency of chest infections.

Symptoms and Signs

Patients often have significant physical disability and nonambulatory patients may therefore not experience exertional dyspnea. Dyspnea at rest is a late sign of respiratory muscle involvement and the presence of orthopnea in MND can be an ominous feature with death sometimes ensuing a few weeks later [4]. Diaphragmatic failure classically leads to orthopnea. Preserved diaphragm function with intercostal paralysis, such as occurs following a cervical spine injury, leads to symptoms of breathlessness which are worse sitting up and improved by lying down. Sleep-disordered breathing and sleep fragmentation lead to symptoms of feeling unrefreshed after sleep, daytime somnolence, vivid dreams, and poor concentration. Hypercapnia causes morning headache, poor appetite, and weight loss.

Signs of diaphragmatic failure are abdominal paradox where the negative pressure generated during inspiration causes the abdomen to be sucked in and the diaphragms to rise into the chest during inspiration unlike normal breathing where the diaphragm descends and causes the abdomen to move outwards. Lateral expansion of the chest wall is preserved as this is controlled by intercostal muscles. Later signs when the sternocleidomastoid muscles have a more prominent role in inspiration due to worsening respiratory failure include shrugging of the shoulders during inspiration.

In conditions causing preserved diaphragmatic function and intercostal paralysis, such as cervical spine injury, the opposite pattern of breathing is seen with preservation of outward abdominal excursion due to downward movement of the diaphragm, but an absence of lateral chest wall movement.

Support Required

Multidisciplinary Team (MDT) Support

As most neuromuscular diseases are progressive, a MDT approach and a focus on symptom management are critical. The medical MDT will include a specialist in home ventilation. In our region, the home ventilation service has grown out of anesthesia and intensive care but in most other regions the services have been developed from respiratory medicine. Our team contains respiratory physicians, intensive care physicians, and anesthetists (for anesthesia and procedural sedation as well as pain management). Genetic muscle conditions causing neuromuscular disease require

the additional expertise of neurologists and geneticists. Conditions under the care of neurologists such as MND will expand the MDT further. Links with palliative care teams are critical for symptom management throughout life and also for advice and support during end-of-life care. Additional members of the MDT include specialist nurses and physiotherapists from the home ventilation service, specialist nurses from other specialties (MND, neurology, and muscle genetics), specialist nurses in palliative care, speech and language therapists, dieticians, and clinicians from the gastrostomy and nutrition service. Communication between teams is crucial and where patients have care provided by specialty-based teams and the home ventilation service, a joint MDT meeting is advisable to discuss challenging symptoms in often highly disabled patients. For example, we host a monthly MDT meeting with the regional MND team.

Respiratory Support

Respiratory support refers to all interventions used to treat pathology of the respiratory system resulting from neuromuscular disease. The following section explores the assessment of respiratory function, the indications for intervention, and the evidence for such interventions. With a few exceptions, evidence for interventions is not derived from randomized controlled trials and is often based on clinical experience with effectiveness extrapolated from one neuromuscular disease to another.

Noninvasive Ventilation

Assessment

Saturations (SpO_2)

SpO_2 should not be used to decide on the adequacy of alveolar ventilation particularly in patients on supplemental oxygen therapy. However the alveolar gas equation which relates alveolar oxygen tension (P_AO_2) to inspired fraction of oxygen (FiO_2) and arterial carbon dioxide tension ($PaCO_2$) would suggest that high SpO_2 (in practice >95%) makes significant hypoventilation unlikely [5]:

$$PAO_2 = FiO_2 - PaCO_2 / R$$

where PAO_2 is alveolar PO_2, FiO_2 is the inspired oxygen in %, $PaCO_2$ is the arterial PCO_2, and R is the respiratory quotient (ratio of carbon dioxide produced to oxygen consumed).

Arterial Blood Gases (ABGs)

ABGs provide information about oxygenation and ventilation and also the chronicity of hypoventilation. Hypercapnia is defined as $PaCO_2 > 6.5$ kPa (50 mmHg). Daytime hypercapnia is associated with advanced respiratory weakness and requires

urgent assessment and treatment. Standard bicarbonate levels are bicarbonate levels corrected for hypercapnia and are a good sign of renal compensation for hypercapnia. Our experience is that raised standard bicarbonate can precede daytime respiratory failure.

Pulmonary Function Tests (PFTs)

PFTs are noninvasive assessments of respiratory flows, pressures, and volumes. The vital capacity (VC) is the volume of air expelled during a full expiration from a position of full inspiration. The patient is usually encouraged to exhale with maximum effort, referred to as the forced vital capacity (FVC). A FVC of <1 L has been associated with poor long-term survival in DMD [6]. FVC is a useful measurement and in general a FVC >70% predicted makes significant respiratory failure highly unlikely in neuromuscular disease. An FVC <30% is strongly associated with respiratory failure. Regular assessment and correlation with symptoms are advised with FVC between these values. A fall in FVC from the upright to supine position may be a better predictor of diaphragmatic weakness than upright FVC but normal values are not well established [7].

Sniff nasal inspiratory pressure has been shown to predict survival in MND [8]. We commonly use maximal inspiratory and expiratory mouth pressures (MIP/MEP) to assess inspiratory and expiratory muscle weakness in neuromuscular disease.

Sleep Studies

Since symptoms commonly arise from nocturnal respiratory failure, sleep studies are a useful adjunct to respiratory assessment. Sleep oximetry can detect nocturnal desaturation in patients not on supplemental oxygen but cannot reliably distinguish between nocturnal hypoventilation, obstructive sleep apnea, and central sleep apnea. Transcutaneous oxygen saturation with carbon dioxide assessment (TOSCA) is used when diaphragmatic weakness is suspected. Figure 11.1 shows a tracing demonstrating episodic hypercapnia and hypoxia with associated tachycardia. These are likely to be occurring during REM sleep when the intercostal and other accessory muscles are paralyzed, exposing diaphragmatic weakness and hypoventilation which might not be present during the day. Since OSAS is common in neuromuscular disease, polysomnography is also a useful investigation.

Indications and Timing

The indications and timing of initiation of NIV are controversial and there is no universal agreement. National guidelines suggest the following criteria for initiation of NIV in the setting of DMD [9]:

- Symptoms of nocturnal hypoventilation
- FVC ≤50% predicted
- Maximal inspiratory pressure ≤60 cm H_2O

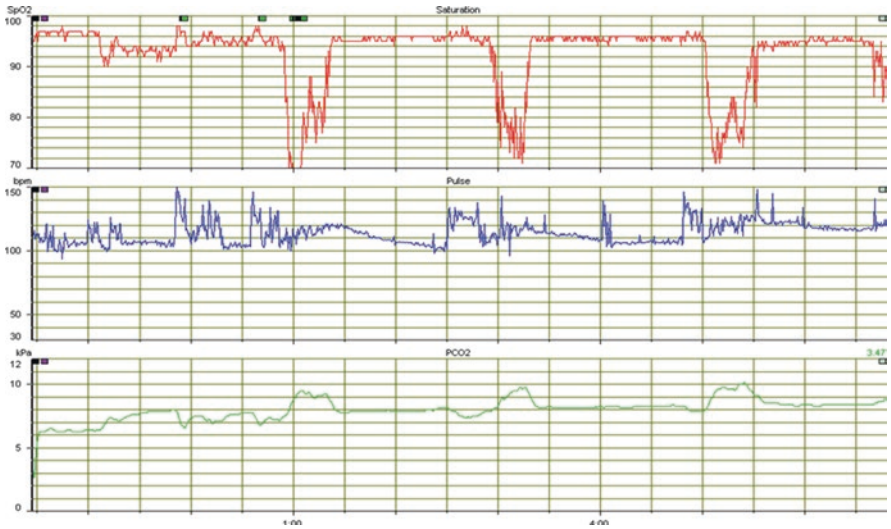

Fig. 11.1 Tracing showing episodic falls in $Sp0_2$ (red), rise in pulse rate (blue), and rise in carbon dioxide levels (green) during sleep in a patient with neuromuscular disease

- Daytime hypercapnia $PaCO_2 \geq 6$ kPa (45 mmHg)
- $SpO_2 \leq 95\%$ on room air
- Abnormal sleep studies

In general, the prophylactic use of NIV in patients without symptoms is not indicated. A randomized trial of early NIV prior to the development of daytime hypercapnia in DMD patients with a FVC between 20 and 50% of predicted values did not show a benefit of NIV, and indeed more patients died in the NIV group than the control group [10]. Asymptomatic patients often do not tolerate NIV well. Our approach is to assess patients with genetic muscle conditions in a joint clinic between home ventilation specialists and muscle geneticists. Patients are referred when they develop symptoms of nocturnal hypoventilation in the setting of a low or falling FVC (<60% predicted). Depending on the diagnosis, the FVC, and the symptoms, patients are assessed by overnight TOSCA monitoring or a sleep study.

Evidence for NIV

Duchenne Muscular Dystrophy

A non-randomized study in 1994 investigated the effect of NIV in patients with DMD and daytime hypercapnia: five patients elected to be treated with NIV and five refused the treatment. At 2-year follow-up, four out of five patients who were not treated with NIV had died with a mean survival of 9.7 months. All the patients in the

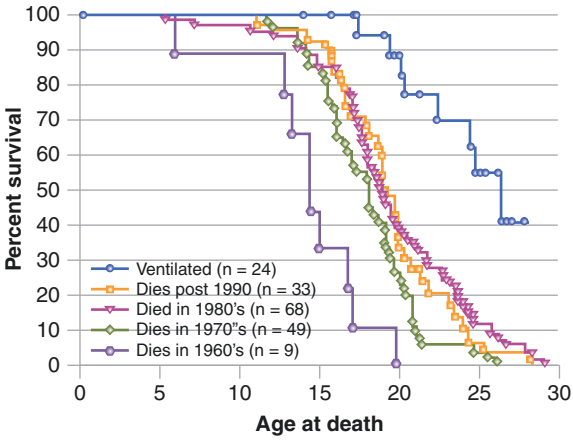

Fig. 11.2 Kaplan-Meier survival curves showing the percentage survival of patients with DMD ventilated versus non-ventilated patients, 1967–2002 [13]

NIV-treated group were alive. There was a moderate improvement in $PaCO_2$ in the NIV-treated group [11]. In 1998 23 patients with DMD and daytime respiratory failure were treated with NIV. One-year survival was 85% and 2-year survival (which was maintained at 5 years) was 73% [12]. The survival from DMD has been significantly affected by the use of NIV as part of an MDT assessment and treatment [13] (Fig. 11.2).

Neuromuscular and Chest Wall Disease

A randomized trial of 26 patients with diverse diagnoses leading to nocturnal respiratory failure showed an improvement in time spent in nocturnal respiratory failure in the NIV-treated group compared with the control group. Patients not treated with long-term NIV were more likely to require NIV in an emergency and control patients developed daytime respiratory failure after a mean of 8 months [14].

Motor Neurone Disease/Amyotrophic Lateral Sclerosis

In MND, a trial from 1995 suggested a benefit of NIV over control treatment [15]. NIV improves survival in patients who tolerate NIV compared to those who are unable to tolerate NIV. The presence of moderate-to-severe bulbar dysfunction is a predictor of poor tolerance of NIV [16]. A randomized trial of NIV in MND was published in 2006 [17]. Patients were randomly assigned to NIV or standard care when they developed symptomatic hypercapnia or orthopnea with a maximum inspiratory pressure <60% predicted. NIV improved survival in all patients and specifically in patients in whom bulbar dysfunction was not severe (Fig. 11.3).

The median survival in the NIV-treated group was 7 months. Patients who had severe bulbar dysfunction used NIV for less time than those without severe bulbar

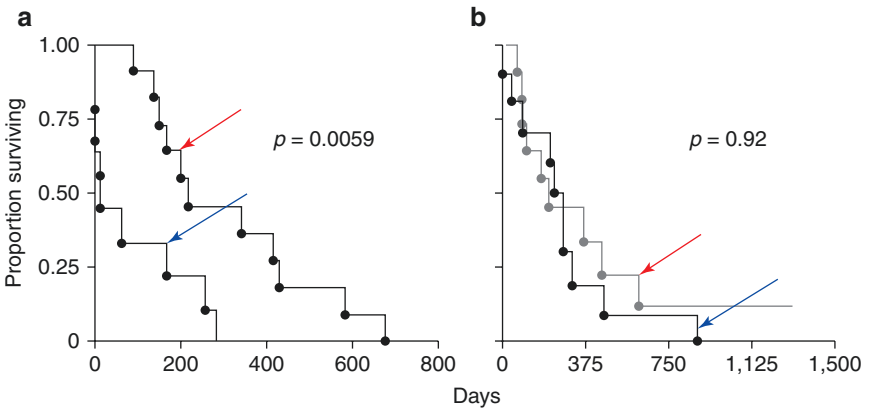

Fig. 11.3 Survival from randomization in a randomized controlled trial of noninvasive ventilation (*red*) compared to standard care (*blue*) in patients with motor neurone disease/amyotrophic lateral sclerosis and (**a**) normal or only mildly impaired bulbar function and (**b**) severe bulbar impairment [4]

dysfunction. Treatment with NIV was associated with an improvement in quality-of-life indices. There are more recent data to suggest a survival benefit in patients with MND and severe bulbar dysfunction with a median survival of 13 months in NIV-treated patients versus 3 months in patients who refused NIV [18].

Scoliosis

A 2006 prospective observational study of patients with kyphoscoliosis found an improved survival in the NIV-treated group compared to oxygen therapy [19]. Patients commenced on NIV or oxygen between 1996 and 2004 were followed up until 2006. The mortality was significantly better in the NIV group than the oxygen therapy group (32% vs. 76%) with a hazard ratio in the NIV group of 0.30 compared to the oxygen group.

Assisted Cough/Lung Volume Recruitment

Assessment of cough is undertaken by measurement of peak cough flow (PCF). Normal values are greater than 400 L/min [20]. There are no clear values which predict an ineffective cough in neuromuscular diseases, but a PCF <160 L/min predicts an inability to clear the airways following extubation [21]. A PCF >270 L/min, when well, predicts an effective cough and minimal risk of developing respiratory failure during respiratory tract infections [22]. We assess patients with inherited muscle disease with problems clearing respiratory secretions when the PCF is <270 L/min.

Available treatments for airway clearance include manual assisted cough, lung volume recruitment (LVR) bag, mechanical insufflation-exsufflation (MI-E, often termed a cough-assist machine), and percussive techniques. The details and evidence base for these therapies are well reviewed elsewhere [23]. The main improvements seen with MI-E have been a survival advantage and a reduction in hospitalization when used as part of protocolized care along with ventilatory techniques [22]. Significant improvement in clinical outcomes with the use of secretion management techniques alone has not been consistently demonstrated.

In patients with bulbar MND, there is an additional concern that the use of high insufflation pressures can predispose patients to upper airway collapse [24]. We use MI-E or LVR bag when patients with optimal secretion management and a PCF <270 L/min become symptomatic with respiratory infections.

Secretions

Management of secretions presents a challenge in neuromuscular disease with hypersalivation associated with bulbar dysfunction and consequent swallowing weakness commonly encountered in MND. Symptoms may be poorly controlled in half of such patients [25]. First-line therapy with an antimuscarinic drug such as hyoscine or glycopyrronium is effective in 61% of patients [26]. Second-line medications include amitriptyline (which also has an antimuscarinic effect) and clonidine. In general, a second antimuscarinic is unlikely to improve symptoms when a first has failed [26]. Our first line is glycopyrronium as it is shorter acting with a quicker onset than hyoscine patches. It is less likely to cause sedation and confusion as it does not cross the blood–brain barrier. Glycopyrronium has been shown to reduce salivation and drooling in young adults and in patients with Parkinson's disease [27]. Injection of botulinum toxin into the salivary glands is used to reduce hypersalivation in 14 out of 21 MND centers in the UK [25]. It reduces salivary volume with a duration of effect of 1.5–6 months [28]. The therapeutic effect may be better when injected under ultrasound guidance [29].

At least a third of patients with MND have problems with both thick and thin secretions and require medication for both [26]. Overly thick respiratory secretions are managed with carbocisteine or nebulized sodium chloride.

Bronchorrhea is a particular problem in patients undergoing tracheostomy ventilation. Azithromycin has been investigated in chronic obstructive pulmonary disease and has been shown to reduce admissions with acute exacerbation [30]. We commonly use it in bronchorrhea for its anti-inflammatory actions. Due to the presence of secretin receptors in the lung, octreotide is a second-line drug for bronchorrhea.

Although not investigated in patients with neuromuscular disease specifically, nebulized colistin has been shown to be effective in improving clinical outcomes in cystic fibrosis and in non-CF bronchiectasis [31, 32]. We use nebulized colistin in tracheostomy patients who have recurrent infections with *Pseudomonas aeruginosa*.

Tracheostomy

There are three scenarios where tracheostomy is considered in neuromuscular disease. The first is as an urgent procedure due to an emergency admission with acute respiratory failure. The second is as an elective procedure. Finally, especially in the setting of MND, a tracheostomy may be undertaken during an admission with acute respiratory failure prior to the diagnosis of neuromuscular disease having been made. The majority of data pertaining to tracheostomy use in neuromuscular disease are in the setting of MND.

There are data to suggest a prolongation of survival in patients with tracheostomy ventilation over NIV in patients with MND although there are no randomized controlled trials [33]. Factors to consider when deciding on tracheostomy ventilation include the length of time spent in hospital whilst waiting for home care to be organized. The effect on the family and care team is recognized. A German postal survey asked relatives whether they would recommend NIV or tracheostomy ventilation, and more relatives would recommend NIV than tracheostomy ventilation, and would be more likely to opt for NIV if they had MND and respiratory failure [34]. The quality of life in MND patients with tracheostomy ventilation appears acceptable and comparable to controls [35]. There are concerns about becoming "locked in" with tracheostomy ventilation due to the survival advantage and the progression of disability.

It is important for healthcare professionals to be able to adequately advise patients whether they are likely to benefit in terms of quality of life following a tracheostomy. Currently available data suggest that autonomy in terms of decision-making to undergo tracheostomy, family support, and living at home are predictive of good quality of life following tracheostomy in the setting of MND [36, 37].

The UK-based tracheostomy ventilation in MND project has recently begun with multi-professional and patient representation. One of the long-term aims is to investigate factors which predict a good quality of life following a tracheostomy in a UK setting.

Recognizing the End-of-Life Phase in Neuromuscular Disease

In most neuromuscular conditions, currently available therapies have either no or only limited effect on the underlying disease process. Supportive treatments such as NIV and gastrostomy feeding improve survival in appropriately selected patients, but do not prevent progressive disability. The primary aim of most treatments is palliative: to optimize symptom control and improve quality of life.

In patients with progressive NMD, respiratory failure is the most common cause of death. Identifying when someone with a neuromuscular condition may be approaching the end of life can be very challenging. Whilst there is often a gradual deterioration and a worsening of symptoms over the final few months and weeks of life, some patients deteriorate more rapidly and die within a few days [38]. However, there are several indicators that may suggest that the disease is progressing and trigger end-of-life discussions and planning (Box 11.1).

Box 11.1: Clinical Indicators of Deterioration in Neuromuscular Disease

- Marked rapid decline in physical status, increasing dependence, and need for support.
- Repeated unplanned hospital admissions.
- Decreasing response to treatments.
- Swallowing problems.
- First episode of aspiration pneumonia.
- Increased cognitive difficulties.
- Weight loss.
- Significant complex symptoms and medical complications.
- Low vital capacity (below 70% predicted) or initiation of NIV.
- Mobility problems and falls.
- Communication difficulties.

Adapted from the Prognostic Indicator Guidance [39]

Regular assessment, tailored to the individual patient, is essential to ensure early recognition of the onset of the end-of-life phase of the condition. Clearly, there may be occasions when there is a reversible component to an observed deterioration in a person's condition, which may respond to appropriate treatment if recognized. This may include intercurrent infections, an underlying psychological condition such as depression, or an adverse response to medication changes or increases. Furthermore, despite disease progression, survival may be extended by noninvasive and tracheostomy ventilation and gastrostomy feeding. However, not all patients desire treatment measures that may extend their life in the face of progressive disability.

Role of Palliative Care in Neuromuscular Disease

The aim of palliative care is to relieve symptoms and to provide psychosocial and spiritual support, thereby optimizing the quality of life of both patients and their families whilst minimizing obstacles to a peaceful death and supporting the family through the bereavement process [40]. The development of respiratory muscle weakness in patients with neuromuscular disease is a poor prognostic sign. It is strongly encouraged that patients are offered referral to specialist palliative care services at this stage, if this has not already occurred [41].

It has been widely recommended that optimal management should incorporate a multidisciplinary approach, with evidence supporting an improvement in both quality of life and survival in patients with MND managed in a multidisciplinary care setting [42]. Patients may benefit from non-pharmacological approaches as well as drug treatments in managing their respiratory symptoms (Table 11.2).

Table 11.2 Non-pharmacological strategies for management of respiratory symptoms and distress—adapted from MND Association [43]

Aim	Intervention	MDT input
Positioning	Breathing is often easier in upright or slightly reclined position (rather than lying flat) with arms supported. This can be enabled by use of riser-recliner chair, appropriate wheelchair support, profiling bed, and/or bed rest/pillows.	Physiotherapist, occupational therapist, district nurse
Breathing technique/ exercises	Exercises can help to maximize lung capacity and muscle elasticity, and try to prevent infection and partial lung collapse.	Physiotherapist
Cough management	Difficulty in coughing can be due to weakness in inspiratory, expiratory, and bulbar muscles. Consider referral to a respiratory physiotherapist to advise most appropriate cough management regime, and teach techniques to help cough most effectively.	Physiotherapist
Management of respiratory secretions	Humidification, nebulizers, and/or drinking pineapple juice (contains proteolytic enzymes) can all help to clear thick respiratory secretions.	District nurse
Relaxation and anxiety management	Relaxation, massage, hypnotherapy, and cognitive behavioral therapy may help reduce anxiety and breathlessness.	Complementary therapist, occupational therapist, psychologist
Cool air	Movement of air from an open window and/or fan can reduce symptoms of breathlessness.	
Aids and appliances	Use of a walking frame can help stabilize posture and balance, and hence promote better use of respiratory muscles.	Occupational therapist, district nurse
Fatigue management	Adjust activities to conserve energy for those the patient feels are most important. This may include using some aids and/or appliances and accepting some care input.	Occupational therapist, district nurse
Optimizing swallowing technique	Optimize swallowing technique in order to minimize risk of aspiration pneumonia; consider referral to speech and language therapist.	Speech and language therapist
Improving communication	Consider referral to speech and language therapist for optimizing communication and use of communication aids.	Speech and language therapist

Advance Care Planning in Neuromuscular Disease

Sensitive timing for advance care planning discussions with patients with neuromuscular conditions is important and should take into account the person's ability to communicate, cognitive status, and mental capacity. Discussions should be introduced early if these are likely to deteriorate rapidly [44] (Box 11.2).

In patients with neuromuscular conditions, advance care planning may play an important role in directing symptom management, especially in the last months of life, and prevent life-prolonging treatments being instigated or continued contrary to their actual preferences. Of importance, at the time an Advance Statement and/or an Advance Decision to Refuse Treatment is prepared and/or a Lasting Power of

Box 11.2: Advance Care Planning in Neuromuscular Disease

Triggers for advance care planning discussions

- Diagnosis.
- If there is a significant change in respiratory function.
- If interventions such as gastrostomy or noninvasive ventilation are being considered/needed.
- Recent hospital admission.
- Whenever people wish to do so.

Topics to discuss may include:

- What they want to happen (for example, their preferred place of death).
- What they do not want to happen (for example, being admitted to hospital, insertion of gastrostomy).
- Who will represent their decisions if they are unable to communicate and/or lose mental capacity.
- What should happen if they develop an intercurrent illness.
- Documenting an Advance Statement, an Advance Decision to Refuse Treatment (ADRT), an Emergency Health Care Plan, and a Do Not Attempt CardioPulmonary Resuscitation (DNACPR) order.
- Appointing Lasting Power of Attorney (LPA) for Health and Welfare and/or Property and Finance.

Adapted from NICE guidance on Motor Neurone Disease 2016 [44]

Attorney is appointed, the patient must be competent, able to process relevant information, and display an appropriate appreciation of the potential consequences of any decisions made [45].

Discontinuation of Noninvasive Ventilation in Neuromuscular Disease

Early discussions with patients and relatives around end-of-life issues, such as the discontinuation of NIV, are essential for patient-centered decision-making [41]. The ability to maintain control over decisions regarding ventilation and in particular its discontinuation is fundamental to patients deliberating over whether to commence ventilation [46].

As neuromuscular disease progresses, patients established on NIV may find that they become increasingly dependent on the ventilator to relieve symptoms of breathlessness, sometimes requiring it up to 24 h/day. During the terminal phase, ventilated patients may find that ongoing treatment brings little hope of recovery, but instead prolongs the dying process. It may be appropriate to consider or offer alternative measures to relieve breathlessness (both non-pharmacological and pharmacological) in order to allow patients periods of freedom from the ventilator.

However, the patient may ask for ventilation to be discontinued altogether, with adequate symptom control to minimize any associated distress [47]. In the event that a competent patient who is deemed to have mental capacity and is not suffering from a depressive disorder or a patient with a valid and applicable ADRT requests discontinuation of NIV, then such wishes should and must be respected. Continuation of ventilation, against a patient's will, would be both ethically and legally indefensible. Refusal of ongoing treatment is a fundamental right. However, although no different to refusal of any other medical intervention, withdrawal of ventilation challenges healthcare professionals in part because of the close temporal relationship between withdrawal of ventilation and the moment of death unlike refusal of surgery for cancer for example. Elective withdrawal of ventilator support can cause distress and anxiety to all involved and requires sensitive and thoughtful discussion, with the patient, relatives, and healthcare professionals [47]. There is a clear legal precedent to withdrawal of ventilation at a patient's request in the setting of retained capacity.

In the event that NIV is to be withdrawn, a multidisciplinary team approach is important. The patient, primary carer, and family should be central to all discussions and preparation. Palliative care services are often already involved. This is important in terms of facilitating relationships and rapport prior to the end-of-life phase during which palliative care input is very valuable.

A staged withdrawal of ventilation is usually advocated. The level of ventilatory support is typically reduced over several minutes or hours. Patients with neuromuscular disease often benefit symptomatically from adequate tidal volumes when well so our practise is to initially reduce the respiratory frequency delivered by the ventilator before reducing the airway pressures which determine the tidal volume. The ventilator settings should be adjusted to maintain symptomatic relief whilst simultaneously allowing gradual hypercapnia to develop [40]. Premedication with sedatives and opioids should be administered prior to commencement of weaning from the ventilator, particularly in conscious individuals. The effect of these medications should be assessed within 30 min and repeated if necessary, prior to reduction of the ventilator settings. Further medications should be administered and titrated as appropriate, according to the patient's symptoms and responses. This staged withdrawal of ventilation allows for rapid identification and treatment of any distress or worsening symptoms that may occur after each adjustment of the ventilator [40]. It may be appropriate to commence a continuous subcutaneous infusion of opioids, benzodiazepines, and antisecretory medications, if frequent as-required doses are needed. This management strategy should not pose any ethical dilemmas; the primary aim of care is to relieve symptoms and distress, rather than to prolong life. If managed appropriately, most patients become progressively more drowsy, then unconscious due to increasing hypercapnia, and die peacefully [48]. The use of preemptive medications for dyspnea also has a legal precedent and is no different from a moral or ethical point of view to the use of general anesthesia which is typically administered before the start of surgical procedures which would otherwise be painful and distressing.

The Association of Palliative Medicine of Great Britain and Ireland (APM) has written comprehensive guidance for professionals who are involved in withdrawal of assisted ventilation at the request of a patient with MND [49] (Boxes 11.3 and 11.4).

Box 11.3: Summary of Association of Palliative Medicine Guidance for Withdrawal of Assisted Ventilation [49]

Timing	Standard	Process to address standard(s)
When commencing assisted ventilation and throughout care	**Standard 1** A patient should be made aware that assisted ventilation is a form of treatment and that they can choose to stop it at any time. They should be in no doubt that this is legal and that healthcare teams will support them.	Inform patients that they can choose to stop the treatment at any time, that it is entirely their right and legal, and that their healthcare team will manage their symptoms in a different way. Offer patients and, with due regard for confidentiality, families the opportunity to discuss future scenarios when assisted ventilation is being considered. Promote the concept of advance care planning, and discussion of wishes and values with patients who use assisted ventilation, especially those who may have lost one modality of communication. Assess and discuss capacity for the decision about treatment and its continuation.
Withdrawal of assisted ventilation	**Standard 2** Senior clinicians should validate the patient's decision and lead the withdrawal.	Affirm the decision by assessing the patient's capacity or validity and applicability of an advance decision to refuse treatment (ADRT) and that this is a settled view; allowing a period of time for discussion and reflection between the initial conversation and the patient's final decision. Planning, coordination, and communication are vital tasks.
	Standard 3 Withdrawal should be undertaken within a reasonable timeframe after a validated request.	Discuss with the patient and family when, where, and how withdrawal will happen, including the potential for living for some hours without the ventilator and occasionally longer. Discuss with the professionals when, where, and how withdrawal will happen; identify key people and their roles. Ensure that members of the team understand the ethical principles and legal position.
	Standard 4 Symptoms of breathlessness and distress should be anticipated and effectively managed.	Make a plan for symptom management. Key decisions are as follows: – Does the patient require **sedation** *before* assisted ventilation withdrawal: ventilator-dependent patients, using >16 h/day; very short periods off ventilator before distress Or – Does the patient require **augmented symptom control**: patient can manage some hours off assisted ventilation – What drugs, doses, and route? – Who will prescribe and administer? – Who will manage the ventilator and how will the settings be adjusted and mask/tubing removed? Administer anticipatory medication, titrating opioids, and benzodiazepines to manage symptoms. For those who are ventilator dependent, assess the effectiveness of symptom management by reducing or stopping assisted ventilation for a few minutes *before* full removal. Continue to titrate opioids and benzodiazepines to manage symptoms.

(continued)

Box 11.3: (continued)

Timing	Standard	Process to address standard(s)
After death	**Standard 5** After the patient's death, family members should have appropriate support and opportunities to discuss the events with the professionals involved.	Consider the needs of family and professionals after death: – Plan who will provide support to family members – Debrief for professionals/significant event analysis

Box 11.4: Case Study of Planned Withdrawal of Assisted Ventilation

65-Year-old man with end-stage MND requested withdrawal of assisted ventilation. He was reviewed by the home ventilation (HV) team and the palliative care (PC) team, and it was established that his view was constant and consistent to family and healthcare professionals, and reflected his wishes that he had previously documented on an ADRT.

It was agreed with him and his family that withdrawal of ventilation would take place at his home on an agreed date without undue delay. It was agreed that the HV team would adjust the ventilator settings and that the PC team (physician and nurse specialist) would be present throughout the withdrawal to prescribe and administer the medication to prevent and control symptoms. The patient's general practitioner (GP), community nurses, and carers were informed and any concerns addressed. They were reassured that the procedure was ethical and legal. The GP agreed to prescribe a plentiful supply of drugs to use during the withdrawal.

On the day of withdrawal, the patient was made comfortable in bed. The patient was opioid naïve and had used low-dose lorazepam occasionally. A continuous subcutaneous (SC) infusion containing midazolam 30 mg/24 h was prescribed. The community nurses commenced this infusion 4 h before the withdrawal commenced; they also inserted three short SC lines in preparation for administration of bolus SC doses of medication to control symptoms.

The HV and PC teams visited. The family had identified a spare room for the healthcare professionals to be based in, to avoid intruding in the family space. The PC consultant gave the patient a stat dose of midazolam 5 mg SC. The dose was repeated at 30-min intervals until the patient was sedated but still rousable. She then gave morphine 5 mg SC prior to ventilator settings being reduced.

At 30-min intervals maximum, the patient was assessed and given morphine 5 mg and/or midazolam 5 mg SC prior to each ventilator reduction.

After the ventilation was discontinued and the equipment was withdrawn and removed by the HV team, the PC team continued to assess the patient regularly and administer midazolam if the patient appeared distressed and/or morphine if the patient appeared to have increased respiratory effort. They continued to support the family throughout.

The PC team had planned to leave when the patient was settled, when the CSCI had been refilled with morphine and hyoscine hydrobromide and a higher dose of midazolam to maintain control of the patient's symptoms, and when the family felt supported. A registered nurse had been organized to stay with the patient for the next 8 h in order to treat any symptoms without delay and to continue to support the family.

However, the patient deteriorated and developed airway secretions which were treated with 400 micrograms hyoscine hydrobromide SC. He continued to deteriorate and died very peacefully 75 min after the ventilator was withdrawn.

The patient's death was verified. All healthcare professionals who knew the patient were contacted and informed of his death, and the planned overnight nursing care was cancelled. The GP subsequently issued the death certificate confirming that the patient died from respiratory failure secondary to MND. The GP and PC team offered bereavement support to the family.

During our center's experience of withdrawal of mechanical ventilation, we have learnt important lessons which have facilitated good practice and are divided according to the following domains.

Preparation

All healthcare professionals should read the APM guidance for withdrawal of mechanical ventilation to reassure themselves that the course of action requested by the patient is both ethical and legal. The guidance gives a detailed review of the relevant law including the existence of ADRTs and Lasting Powers of Attorney and the appropriate way of approaching questions of best interests.

All healthcare professionals should meet with the family and with each other in advance of the date of planned withdrawal of mechanical ventilation. The roles of all members of the team should be ascertained well in advance. We felt it critical that one member of the healthcare team was identified to coordinate the planning of withdrawal of mechanical ventilation from that point.

The patient's wishes on the timing of mechanical ventilation withdrawal should be respected as far as is practicable. In some instances, planning to commence in an evening may allow withdrawal to take place sooner, but timing needs to be agreed

by all healthcare staff involved as evening withdrawal may represent a challenge for community services and access to drugs during this period.

Drugs

In our experience, it is not practical for the home ventilation team to have any role in the delivery of palliative medication, other than providing expertise and guidance in the recognition of signs of respiratory distress during the mechanical ventilation withdrawal period. Palliative medications can be administered by nurses, but we have found the input of specialist palliative care teams invaluable. This has the added advantage of involving other senior decision makers to the team and sharing the responsibility of the medication dosing and the assessment of any response to the medications.

It has been useful to have a room in the patient's home identified where drugs can be prepared away from the patient and family both for safety purposes and for privacy away from the patient and the family. It is important to ensure that there is a generous supply of drugs, especially opioids and midazolam, prescribed and available prior to commencing the withdrawal, both for giving as-required doses and for potentially commencing a continuous subcutaneous infusion to control symptoms after the ventilation is withdrawn if needed.

If patients are on long-term opioid then substituting oral medications with a subcutaneous infusion has the advantage of a more guaranteed route of drug delivery and greater flexibility in dosing. Doing this well in advance of the withdrawal of mechanical ventilation has the further advantage of reaching a steady state of drug concentration before any dose titration.

The doses of opioids and benzodiazepines are variable, but in general the higher the level of consciousness of patients at the start of the process, the higher the dose of drugs required to preemptively manage and control symptoms.

The pre-insertion of two or more subcutaneous lines is helpful. Repeated subcutaneous injection of large volumes of drugs (e.g., midazolam 10 mg/2mL) can cause the buildup of drugs and may cause local discomfort and/or unpredictably influence the speed of absorption of the drug. Rotating administration sites addressed this issue.

Ventilatory Management

Our practice is to reduce the respiratory rate and only begin to reduce the tidal volumes when the respiratory rate has been reduced by approximately 50% of the pre-withdrawal rate and the level of consciousness has noticeably reduced. Our experience of MND patients on NIV is that they are often very dependent symptomatically on adequate lung expansion.

Ventilation is stopped prior to removal of the face mask used to deliver ventilation. This is to ensure that no distress becomes apparent which may result in

the rapid reinstatement of mechanical ventilation whilst further up-titration of sedation is instituted. The mask is removed a few moments after ventilation is discontinued.

During our first experience of planned domiciliary withdrawal of mechanical ventilation, we recognized the importance of ensuring that all ventilator alarms were disabled where equipment allows. This prevents or reduces any unnecessary distress to either the patient, family, or healthcare professionals caused by ventilator alarms as ventilator parameters are reduced. This same principle is applied to switching off any heated respiratory humidification systems, so that again no alarms are activated following withdrawal of ventilation.

One patient continued to breathe for 32 h following the withdrawal of NIV. With subsequent patients, this experience enabled us to counsel relatives and patients and explain that the role of the home ventilation team is to ensure that ventilation is safely withdrawn without causing any distress to the patient.

Physiological Considerations

Following the withdrawal of mechanical ventilation, patients often have an increased respiratory rate. There has been concern that this represented distress. However, lack of consciousness and eyelash reflex reassured all present that any tachypnea was a physiological response to hypercapnia rather than patient distress. The titration of palliative medications to patient physiology rather than consciousness is not appropriate and could result in the significant overprescription of palliative medication.

Two patients opened their eyes at the moment of death despite being deeply unconscious prior to withdrawal of mechanical ventilation. Given the level of consciousness immediately prior to withdrawal of mechanical ventilation, we feel that this represents a physiological reflex to hypoxemia rather than patient distress but it is important to counsel relatives about this possibility.

Managing Symptoms at the End of Life in Neuromuscular Diseases

A multidisciplinary approach to the management of patients with end-stage neuromuscular diseases is essential. All patients should have access to specialist palliative care in a setting of their choice, including hospital, community, or hospice.

Patient may experience a range of both physical and psychological symptoms as well as social and spiritual problems. Common symptoms at the end of life include dyspnea, pain, and distress. Both patients and their carers are often concerned that the end of life may be a very distressing process. Some patients express fears about dying from choking or with uncontrolled pain. However, although choking sensations may occur, death from choking and death with severe, uncontrolled pain are extremely rare. Evidence shows that with access to palliative care, distress at the

end of life is rare and that the provision of good symptom control measures facilitates a peaceful death in the majority of patients [48].

An essential aspect of optimal end-of-life care for patients with advanced neuromuscular disease should include anticipatory preparation, both in terms of communication and provision and availability of medications, in the event of a rapid decline. Key drugs should be made available, in all care settings. The MND Just in Case (JIC) Kit is designed to store medication to relieve breathlessness, choking, and/or associated anxiety or panic, so that these are readily available if the patient becomes symptomatic [50]. The principle is the same as other JIC kits that are widely used for palliative patients [51], but it is focused on the care of patients with MND. The JIC Kit is a box containing information leaflets for the patient, carers, and healthcare professionals; it is supplied on a named patient basis, free of charge from the MND association, to the patient's GP, who then fills it with prescribed medication that is appropriate for the individual patient. It has separate compartments to hold medication for administration by carers and for medication for administration by healthcare professionals. The main classes of drugs suggested include opioid, sedative, and anticholinergic agents [50].

Breathlessness

The majority of patients with progressive neuromuscular disease die from respiratory failure due to respiratory muscle weakness. Symptoms of ventilatory failure, including progressive breathlessness, develop insidiously in the later stages of the disease. Breathlessness is common, affecting up to 85% of patients in the terminal phase [52].

Opioids

Strong opioids, such as morphine sulfate, reduce the ventilatory response to hypercapnia and hypoxia, thereby reducing respiratory effort and breathlessness. High-dose opioids in an opioid-naïve patient, or a rapid escalation in dose, may potentially cause respiratory decompensation, particularly if combined with benzodiazepines or uncontrolled oxygen. In the cancer and COPD setting, evidence supports an improvement in breathlessness at doses that do not cause respiratory depression [53, 54]. When used competently and appropriately, with gradual and individual dose titration, there is no evidence that strong opioids shorten life. Whilst there is evidence to support the safe use of strong opioids for chronic pain in patients with MND [55], concerns still remain regarding the potential risks of using strong opioids for the acute relief of breathlessness at the end of life in these patients, such that the risk versus benefit balance has to be carefully assessed. The priority at this stage in the disease trajectory remains the optimization of symptoms and minimization of suffering which may be achieved through the cautious and gradual titration of strong opioids.

Strong opioids are often used to control symptoms of pain and breathlessness, well in advance of the end-of-life phase of the illness. In patients who are already using morphine for pain, a dose of 25–100% of the 4-hourly (instant release)

analgesic dose may be needed, depending on the degree of breathlessness. However, in opioid-naïve patients, small doses of immediate-release morphine should be used initially, such as 2.5 mg orally as required. If more than two doses are required within a 24-h period, morphine should be prescribed regularly (either short- or long-acting morphine) and titrated according to response, duration of effect, and adverse effects. If the oral or per gastrostomy route is not possible, patients may benefit from having a continuous subcutaneous infusion of morphine, which is sometimes better tolerated and may provide greater relief by avoiding the peaks and troughs of oral medication. The same principles should be applied to the use of alternative strong opioids.

Benzodiazepines

At the end of life, in patients with symptomatic breathlessness, the combined use of an opioid and benzodiazepine may be more effective than either alone [57]. A Cochrane review in patients with advanced cancer and COPD concluded that currently there is no evidence that benzodiazepines by themselves relieve breathlessness but do have a role when anxiety exacerbates breathlessness [58]. Reducing anxiety may help to lessen the sensation of breathlessness and help patients to cope with the latter more effectively.

Benzodiazepines may result in impaired respiratory effort; in those patients who retain capacity, it may be appropriate to advise them of the potential risks associated with such treatment. For those patients who lack capacity, a decision to use such medications should be made by the multidisciplinary team caring for the patient, in the best interests of the patient and involving family members and carers sensitively, in the decision-making process. At this stage in the disease trajectory and in the presence of such distressing symptoms, the aim of treatment must be to optimize comfort and to minimize distress, even if this *potentially* risks shortening an already very short prognosis [40].

Oxygen Therapy

Prior to the terminal phase, uncontrolled oxygen should be avoided as it can lead to potentially fatal carbon dioxide retention, with associated symptoms such as headache and increased drowsiness. At the end of life, the risks associated with oxygen therapy may be outweighed by the need for effective symptom control. Hypoxia causes greater distress than hypercapnia and oxygen may be used to provide symptomatic relief. However, where appropriate, the patient should be made aware of this potential risk. In the cancer setting, oxygen is generally better than air in severely hypoxic patients (SpO_2 <90%) [58]. However, with lesser degrees of hypoxia or with normal oxygen saturation levels, there is no difference in the benefit achieved with oxygen or piped air delivered by nasal prongs [56]. This suggests that it may be the sensation of airflow plus the cooling effect, rather than the oxygen itself, that provides symptomatic relief in many patients [59]. It may therefore be useful to encourage patients to try the benefit of an open window or fan, before trying oxygen.

Secretions

Retention of upper airway secretions in patients with bulbar impairment commonly occurs in advance of the terminal phase in conditions such as MND. However, as any severely unwell patient approaches the end of life, they become less conscious and less able to cough and clear respiratory secretions, which can accumulate in the upper airways and result in noisy breathing. Whilst this may be very distressing for family members and healthcare professionals to witness, the patient is sometimes not aware or distressed because of their diminished level of consciousness. It is good practice to anticipate and treat early as upper airway secretions are more difficult to manage once they become established. Measures include both non-pharmacological, including reassurance to family members, and positional changes to aid postural drainage, assisted cough techniques (including MI-E), and oropharyngeal or tracheal suction. Drugs such as hyoscine hydrobromide, hyoscine butylbromide, and glycopyrronium have similar efficacy in reducing secretions.

Pain

Pain occurs commonly throughout the disease trajectory of many neuromuscular conditions, affecting up to 73% of patients during the disease progression in MND [52]. Pain from neuromuscular disease is usually multifactorial in nature and includes musculoskeletal, skin pressure, muscle spasm, and spasticity-related pain. The principles of pain management in neuromuscular disease are based on the WHO analgesic ladder which facilitates gradual, step-by-step progression from simple analgesia to weak, followed by strong opioids, together with adjuncts [60]. In the advanced phase of the disease and in the presence of a gastrostomy, the administration of analgesia can continue as normal, although dose escalation may be required. In the absence of a gastrostomy, patients may require an alternative route of administration to ensure optimal ongoing pain control and the avoidance of opioid withdrawal. The subcutaneous route is used extensively in palliative care, in patients for whom the oral route has become increasingly difficult or impossible. In patients already established on regular oral strong opioids, this can be converted to (the equivalent dose of) a continuous subcutaneous infusion.

Adjunct analgesia includes low-dose benzodiazepines (e.g., midazolam) for muscle spasm, and hyoscine for bowel colic if patient is constipated and too weak to promote defecation.

Anxiety/Agitation

Anxiety can become marked when respiratory insufficiency occurs. It can manifest in several ways, both physical and psychological. During the terminal phase of neuromuscular conditions, such as MND, a generalized restlessness is not uncommon. Management will depend upon the underlying course, as well as the stage in the disease trajectory. It is good practice to try and identify and treat any potentially reversible causes, such as uncontrolled pain, constipation, or urinary retention. Benzodiazepines are commonly used during the terminal phase, for their anxiolytic and muscle relaxant properties and their indirect effect on symptoms of breathlessness. They also have a sedating effect, which is desired by some patients during this

phase. Lorazepam (oral or sublingual) as required or regularly can be used in those patients who are able to take medications via the oral route. For those patients who are unable to swallow, subcutaneous midazolam (starting at 2.5 mg) is the drug of choice. This can be started on an as-required basis initially, to assess effectiveness. If this provides good symptomatic relief, it may be appropriate to commence a continuous subcutaneous infusion, titrated gradually according to symptoms.

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Palliative Care in the Critical Care Unit

12

Katherine E. Frew and David Snell

Introduction

Admission to the critical care unit (intensive care unit) enables patients to undergo invasive monitoring and single- or multiple-organ support while high-intensity treatments are instigated in an attempt to reverse the underlying disease process and sustain life. Although this may seem to be at the opposite end of the spectrum of medical care to palliative care, there are many similarities. Patients in critical care are at high risk of dying: 13.8% (of 22,407 patients) of general adult critical care admissions in England, Wales, and Northern Ireland in 2017–2018 died [1]. As a consequence, critical care clinicians are frequently involved in managing dying patients and their families. The ethos, knowledge, and skills of the palliative care approach are therefore paramount [2–4]. Given the complexity of the problems and the multitude of symptoms experienced by these patients, palliative care teams are working increasingly closely within critical care units [5, 6].

It is also important to remember that palliative care on the critical care unit is not confined to dying patients. Patients who respond well to intensive therapies and who recover fully also experience a high level of symptoms and distress during their critical illness and need skilled palliation and relief of symptoms and suffering throughout their care [7–9]. Palliative care is therefore a crucial component of comprehensive critical care management and must run in parallel with high-intensity interventions at all stages of a patient's admission.

K. E. Frew (✉)
Department of Palliative Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK
e-mail: Katie.Frew@nhct.nhs.uk

D. Snell
Department of Critical Care Medicine, Northumbria Healthcare NHS Foundation Trust, Northumberland, UK
e-mail: David.Snell@nhct.nhs.uk

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Respiratory Disease in the Critical Care Unit

Respiratory patients who are considered for admission to the critical care unit are either acutely unwell, rapidly deteriorating, or expected to deteriorate as a consequence of their presenting illness. Some patients present with an unpredictable and acute severe illness, having previously been healthy. Such conditions include pneumonia, pulmonary embolism, thoracic trauma, or spontaneous pneumothorax. Under these circumstances, given the potential for recovery with intensive therapies, most patients will want admission to critical care. However, in many cases respiratory admissions to critical care are secondary to an acute crisis in patients with chronic progressive lung disease. This may be an acute deterioration of their underlying condition or an additional acute severe illness. A patient with irresectable lung cancer may become acutely ill with a pulmonary embolism, major hemoptysis, or pneumonia [10]. The immediate problem is treatable, although life expectancy from the underlying cancer may be limited. Similarly, a patient with cystic fibrosis or advanced bronchiectasis may suffer a major hemoptysis or pneumothorax causing an acute crisis [11]. Aspiration pneumonia may occur in a patient compromised by neuromuscular disease and chronic respiratory failure. Acute exacerbations occur in the course of many chronic lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, or fibrotic lung disease [11–15].

The prognosis for patients with chronic progressive lung disease who experience unrelated acute severe respiratory illnesses or acute deteriorations of their existing lung disease is inevitably worse than for those with no underlying pathology. There are several scoring systems used in critical care medicine such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores which aim to predict mortality [16]. Although some do take into consideration preexisting "severe organ failure or immunosuppression" as one entity, they do not segregate conditions further or take into account the patient's preexisting performance status. For example it is widely accepted that a patient with idiopathic pulmonary fibrosis will have a very poor outcome if intubated and ventilated. Yet they will be included in the same group as patients with COPD or cystic fibrosis. As a consequence, the decision to admit a patient to critical care requires careful consideration and communication with the specialist respiratory physician regarding the likely disease trajectory. However, it is important that clinicians recognize a degree of uncertainty of that prediction in many cases.

Decision to Admit

Decisions to admit patients to critical care are complex and challenging, not least because patients are, by the nature of requiring critical care, extremely unwell: the etiology of the acute deterioration may not yet be known; background information about the patient's condition(s) may not be immediately available to the treating clinician and patients may not be able to communicate effectively or express their

wishes. A thorough patient and collateral history (if possible) and assessment of the patient are essential to try and ascertain the likelihood of full or partial reversibility of the acute deterioration alongside the patient's likelihood to survive and benefit from admission given their comorbidities and physiological reserve. Shared decision-making between the home team, critical care team, and patient and relatives is important.

Whether the decision is that admission to the critical care unit would be appropriate or inappropriate, good communication skills to ensure that the patient (wherever possible) and/or family understand the severity of the condition, possible prognosis, and goals of care are vital.

It is important to consider which patients are unlikely to benefit from critical care, to allow them to make informed decisions about their care. An admission to a critical care unit for a patient with a poor prognosis who is unlikely to respond to treatment may deny the patient the opportunity to fulfil other wishes and priorities at the end of life.

It is not uncommon, however, that the patient lacks capacity to inform the decision. This may be secondary to a reduced level of consciousness or delirium because of their acute illness. Or it may be as a result of coexisting conditions such as severe learning disability, dementia, or a mental health illness. In England and Wales the process of making a "best interests" decision for a patient who lacks the capacity to make a (specific) decision is legally underpinned by the Mental Capacity Act (2005) [17]. A patient may have discussed their wishes with a family member or proxy who can help to guide the discussion, or they may have completed an advance care planning (ACP) document detailing their wishes. Clinicians are legally required to take these wishes into account when making a "best interests" decision.

In other conditions, patients retain mental capacity but are unable to communicate effectively with the attending team. This may be due to preexisting conditions such as advanced motor neurone disease (in which their usual communication tools are not available) or because the dyspnea of the acute illness results in an inability to vocalize. Again, it is important to ask if any advance decisions have been discussed or documented in the past, to support and inform decision-making on critical care.

In situations where the likelihood of response to treatment is *uncertain*, and the patient wishes admission (either expressed by the patient or represented by family or a proxy), it may be appropriate to consider a "trial period" of critical care. This should be clearly described to the patient and family based on whichever measures would determine a response, or a failure to respond, to treatment. This is commonly assessed in relation to response over time (e.g., 48 h of optimal treatment), and may enable patients or their family to adjust to a very acute situation. Similarly, it may be appropriate to set a "ceiling of treatment" whereby there is a trial of treatment and critical care support to reverse the disease process but with recognition that if treatment fails or additional multi-organ complications occur beyond the "ceiling" agreed, this represents a likely un-survivable insult. In both of these scenarios, a plan of transition to providing supportive and end-of-life care in the event of a deterioration or failure to respond should be made clear from the outset.

Ideally, patients with chronic and advanced respiratory conditions should have had the opportunity to discuss advance care wishes before an acute admission. This should be undertaken whenever possible by a clinician who knows the patient, and with family members present, as part of chronic disease management and especially in the context of an illness progressing. These discussions may be communicated in an advance care plan document (e.g., emergency healthcare plan, advance decision to refuse treatment, or ReSPECT form), which can be used to inform acute decisions (as described above) when a deterioration occurs [18]. In practice, the patient and family may find it difficult to decide in advance. But initiation of such discussions is always useful. Sometimes such discussions can be particularly complex, such as in the case of patients with advanced cystic fibrosis who may be close to death but hoping for a rescue lung transplantation [19]. Under these circumstances, palliative measures and some end-of-life discussions are still appropriate even where the disease trajectory may be dramatically altered by transplantation.

When such discussions have not taken place prior to admission to hospital, a further opportunity to discuss wishes may be possible if a patient is stable enough in the emergency department or general ward. Early recognition that a patient may not respond to ward-based care, and discussion regarding the options for escalation (or limitations) of care, should be discussed [20]. Treating clinicians should liaise with the critical care team at the earliest opportunity. Many hospitals have "critical care outreach teams" whose role is to support general ward and emergency department staff to identify and manage patients with a higher level of care. They also provide invaluable support in discussions with patients and families regarding the appropriateness of admission to critical care.

Symptom Control

Critical illness is often associated with distressing symptoms such as pain, breathlessness, and anxiety [3, 4, 7, 8]. The critical care setting can be frightening for the patients and their families with high-technology equipment, noise from monitors, high levels of activity, and bright lighting with some loss of day-night cycles. Many interventions are inherently intrusive and burdensome. It is important to be vigilant for specific symptoms such as pain, agitation, delirium, and distress [21–23]. Relatives and nurses are frequently able to detect and interpret signs of distress or pain, and monitor response to medications given to treat possible causes. Scoring systems, such as the Numerical Rating Scale for awake patients or the Critical Care Pain Observeration Tool for sedated patients, aid staff in delivering effective analgesia. Similarly, the RASS (Richmond Agitation-Sedation Scale) and CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) for agitation and delirium can aid the delivery of an appropriate, pre-prescribed level of sedation [24]. Attention to preexisting conditions which may generate symptoms can be important and may be able to improve comfort without the need for medication. For example a change of position for a patient with arthritis which causes pain in a particular position may relieve symptoms without the need for opioid medication.

Particular attention is needed with interventions that are known to cause distress and pain, such as endotracheal intubation, insertion of central venous or urinary catheters, insertion of nasogastric tubes, and suctioning of the airway [25]. Other procedures, such as turning the patient in bed, have also been identified as causing particular distress. There are often difficulties in assessing symptoms in patients in critical care as many have an impaired level of consciousness and difficulties in communicating their needs when on mechanical ventilation with sedation [2–4, 7]. Many studies show that these patients have distressing symptoms that may be underestimated by the clinical team. Sleep disturbance can lead to disorientation and delirium, and efforts should be made to provide some day-night cycle with reduced lighting and use of clocks to help to orientate the patient in time. Delirious patients often subsequently report having had delusions of being kidnapped and subjected to harm and the symptoms of stress, confusion, and terror are common amongst critical care unit patients [26]. Symptom control, relief of distress, explanation, and reassurance are of paramount importance throughout the whole process of critical care [25].

Recognition of Dying on Critical Care Units

The recognition of dying in a critical care unit may be complex, as it frequently involves the withdrawal, and/or withholding, of life-sustaining treatment(s) [27, 28]. Life-sustaining treatments are any interventions which may prolong life or sustain a condition of permanent unconsciousness without reversing the underlying condition. These include cardiopulmonary resuscitation and defibrillation, mechanical ventilation, inotropic and vasopressor support, renal replacement therapy, as well as less interventional treatments such as antibiotic therapy, nutrition, and hydration. In a critical care setting, where all of these are options immediately available, foresight and planning are required to be able to recognize when a patient is dying and not responding to interventions. The team can then support the patient and relatives to come to terms with this, to prepare them for the withdrawal of life-sustaining treatments and to allow as natural, comfortable, and peaceful a death as possible [28].

At the time of admission to the critical care unit, patients, or their families, may have a discussion about “limitations of treatment” [20], whereby certain treatments may be withheld in the event of continued deterioration in the patient’s condition. Treatment is continued unless the patient deteriorates to the point of requiring a life-sustaining treatment from which it has already been agreed they would not benefit or would not want. In this situation a patient may continue with the present level of support to see if they respond with time, or be recognized as dying at the point where the treatment is withheld. This early identification of the limits of treatment may improve communication in the event that a patient does not improve [29].

When no such limitations have been agreed or identified in advance, patients may be recognized as dying when they deteriorate despite optimal management, or do not improve to be able to survive without organ support, despite optimal management.

Those who deteriorate despite optimal management present a number of challenges. They may deteriorate very rapidly despite escalating levels of treatment and intervention; or there may be a gradual increasing dependency on life-sustaining treatments. Communication with relatives about these changes in condition can support decision-making about future care and enable a limitation of treatment to be agreed, or a point at which withdrawal of life-sustaining treatment ought to be instigated.

Patients who do not "progress" despite optimal management present a different set of concerns. These patients may not require increasing levels of critical care support, but equally do not improve to require less. Patients who are dependent on life-sustaining treatments with no prospect of recovery may be recognized as dying if their prognosis from their underlying condition is poor and they are unlikely to survive their hospital admission [30]. These decisions are complex and require a detailed knowledge of the patient's underlying condition, alongside an understanding of the patient's values and preferences. There are significant variations in practice, including in relation to recognizing dying in this group of patients [31–34]. If dying is not recognized by the critical care team, families may feel the need to make burdensome decisions about stopping life-sustaining treatments themselves [35]. Although it is important to involve patients and relatives in these decisions, ensuring that they understand that the decision lies with the clinician and not themselves relieves what can otherwise be a significant burden.

Withdrawal of Life-Sustaining Treatments

When it is recognized that therapeutic options have been exhausted and that technological interventions are merely prolonging the dying process rather than promoting recovery, a decision is usually made to withdraw such measures [4, 12, 36, 37]. This involves a change in the direction and goals of care with a transition to a focus on relieving symptoms and distress, when recovery is no longer achievable.

Ethics of Withdrawal of Life-Sustaining Treatment

The principles and practice of withdrawing life-sustaining treatments, including artificial nutrition and hydration, have been extensively considered. Guidance has been provided by many authorities including the American Thoracic Society, the American College of Critical Care Medicine, and the General Medical Council in the United Kingdom [3, 4, 37]. There is recognition that continuing treatments and interventions in patients who are dying is not in their best interests. It is acknowledged that such decisions can be difficult and distressing. It is clearly established that patients with mental capacity have a legal right to refuse treatment even where refusal of recommended treatment may result in harm to themselves or their death [17]. Conversely the guidance indicates that where a patient wishes to have a treatment that, in the doctor's considered view, is not clinically indicated, there is no ethical or legal obligation on the doctor to provide it [37]. Decisions about whether to withhold or

withdraw a life-prolonging treatment are the responsibility of the senior clinician in charge of the patient's care, taking account of the views of the patient, or those close to the patient. The aim should be to resolve any disagreements and to achieve consensus between the patient's wishes and the medical team's decisions. In difficult situations, particularly where there is a lack of consensus, it is often helpful to seek a second opinion or to have the case reviewed by an ethics committee. In some rare situations, specialist legal advice may be required to ensure compliance with legal requirements [36, 37]. The General Medical Council also indicates the need to ensure that there is proper care for the dying patient, and recommends the involvement of a specialist palliative care team for patients with complex needs.

Managing the Withdrawal of Life-Sustaining Treatments

When it is recognized that a patient is dying, a clear plan of care must be developed, to determine the treatments to continue (for symptom control) and those to stop, following the principles discussed in Chap. 14. Life-sustaining treatments that are not contributing to symptom control, such as vasopressor and inotropic agents, renal replacement therapy, and assisted nutrition, should be withdrawn.

Particular consideration must be given to the withdrawal of mechanical ventilation in view of its potential to generate specific symptoms, and because its withdrawal may lead to rapid death. In keeping with all end-of-life care, the overriding aim when withdrawing mechanical ventilation is to enable as comfortable and peaceful a death, which is as close to the "natural" process of dying as possible. This requires healthcare professionals to consider the needs of the patient as well as those of the family. In certain circumstances, it may be possible to withdraw endotracheal ventilation so as to allow patients to have some communication with their family. Transfer to noninvasive ventilation may be an option, allowing communication for a period of time while reducing their struggle to breathe. Withdrawal of mechanical ventilation, or other invasive interventions, at this stage, is on the basis that they are not relieving symptoms or distress, or that the patient no longer wants them, rather than on the basis of any intent to hasten death.

There are substantial differences in how critical care is delivered in different countries and different hospitals [30–33, 38]. There are also considerable interclinician variations in practice concerning the withdrawal of mechanical ventilation with some clinicians favoring rapid extubation but others preferring a slower process of weaning and withdrawal [39]. Furthermore, there are differences in practice regarding the removal or not of the endotracheal (ET) tube, with the majority of patients dying with the ET tube in situ [32, 40]. Concerns about removing an ET tube are an association (by clinicians) with the shortening of life, as well as a fear of worsening symptoms of stridor and upper airway secretions [28, 40]. However, the experience of relatives may be improved by the removal of the ET tube, perhaps as death can appear more natural without it and the patient appear more "themselves" without the distortion of facial scaffolding that ET tubes cause [40]. Muscle relaxants are discontinued as they are not helpful in the control of symptoms and risk awareness.

Weaning to spontaneous ventilation may be possible and would then allow extubation with a period of unassisted or assisted (via noninvasive ventilation) breathing for the patient and loved ones to communicate. If concern exists regarding obstruction of the airway following extubation, placing the patient in the lateral position may improve airway patency and secretion drainage and reduce stridorous noises [41]. Although there is no clear evidence regarding the optimal method of withdrawal of mechanical ventilation for patients or their families, a standardized approach amongst clinicians within a critical care unit reduces confusion and variation of practice for the nurses. It should further be tailored to the specific requirements of the patient.

The symptoms associated with the withdrawal of mechanical ventilation can be managed with medication, to proactively control excessive respiratory secretions, anxiety, and gasping as the ventilation is withdrawn and stopped [28]. Opioids and benzodiazepines may effectively be used to manage the symptoms of respiratory distress, pain, and anxiety while antimuscarinic drugs can reduce airway secretions. Doses should be adjusted in response to the patient's previous exposure to opioids and their renal and hepatic function. Sedation should be titrated, with the aim of ensuring adequate symptom control when extubation occurs (accepting this may result in a semi-unconscious or unconscious state) [28, 40]. Most invasively ventilated patients are sedated. However further planning and explanation may be required for those receiving noninvasive ventilation or those ventilated via a tracheostomy if the patient is not sedated. Drugs should be started in advance of the withdrawal of ventilation and administered as a constant infusion, as well as the administration of a "bolus" dose of the opioid, sedative, and antimuscarinic 30–60 min before withdrawal [28, 40]. Further, titrated bolus doses may be administered and guided by symptom control.

Starting subcutaneous medication may negate the need for further intravenous cannulation for a patient who is dying, and can be considered for almost all symptoms encountered. It may be preferable to switch medication to be given subcutaneously even on the critical care unit to prevent the need for potentially burdensome re-cannulation. Additionally, subcutaneous catheters can be placed to avoid barriers to relatives being able to have physical contact with a patient, an important part of care.

The administration of medication in anticipation of developing symptoms (rather than in response to symptoms) at the end of life is unusual in a palliative care context, but must be considered in proportion to the anticipated symptoms a patient may experience. In addition, because of the severity of the anticipated symptoms, at such a critical point (when there is no time to wait for other, reactively administered, medication to take effect) these drugs are given in larger doses than the initial doses given in usual situations at the end of a patient's life [28].

Integrating Palliative Care into Critical Care Units

Critical care teams are frequently involved in caring for dying patients and their families and have considerable knowledge and experience of managing end-of-life care. It is clear that the palliative care approach is a crucial component at all stages of critical care and that there may be particular issues at the end of life for patients who have been receiving life-sustaining treatments [5]. The need for critical care

clinicians to develop skills in the provision of end-of-life care has been acknowledged in recent years [5], and endorsed by the American College of Critical Care in their consensus statement [3]. The skills, knowledge, and ethos of palliative care are a core component of critical care and should be central to critical care training and educational programs [3, 4].

In recent years, evidence has demonstrated that palliative care integration into critical care teams has reduced patient length of stay on critical care units, without affecting mortality or relatives' satisfaction of care. Additionally, there is evidence that communication can be improved and relatives' anxiety and distress reduced, through the integration of palliative care teams into critical care teams and units [6].

Different models of integration have developed, which may broadly be considered as integrative and consultative [5, 6]. Integrative approaches intend to incorporate the principles and practices of palliative care approaches into critical care teams, through teaching and education. Using this approach, specialist palliative care clinicians rarely provide direct patient care, but may advise in particularly complex cases. In contrast, consultative approaches aim to increase the number of specialist palliative care consultations on critical care units, especially focused on patients at highest risk of poor outcomes [5]. There is no clear evidence favoring either approach in isolation, but consideration of a mixed approach whereby the principles of palliative care are integrated into critical care approaches, with the more complex cases involving the direct involvement of palliative care clinicians, may offer the optimal care for patients and their relatives [5, 6].

The precise role of a specialist palliative care team will depend on the experience of the critical care team and the circumstances of practice in a particular hospital. Sometimes the palliative care team can facilitate the transfer of dying patients from the critical care unit to a general ward, a palliative care unit, or even their home, if that is their wish [42]. In keeping with national priorities in the UK [43], an increasing number of withdrawals of life-sustaining treatments in both level 2 and 3 critical care patients are occurring in their homes. This requires a significant amount of collaborative work between the palliative, critical, and primary care teams to facilitate a safe, timely transfer home with appropriate equipment and medications in place and highly trained members of the nursing and medical teams.

Patient and family satisfaction with communication, symptom control, relief of distress, and end-of-life care are key outcome measures for critical care units. Although there remains a significant variation in practice between units in the UK and internationally, there is evidence that a high level of palliative care can be achieved in this setting [2, 9]. Further research may be able to direct improvements in care, especially concerning the optimal way of achieving symptom control following the withdrawal of mechanical ventilation.

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Lung Transplantation

13

Maria McKenna and Stephen C. Clark

Lung Transplantation

Lung transplantation is a life-prolonging therapy appropriate for a highly selected group of patients with end-stage respiratory failure most commonly secondary to idiopathic fibrotic lung disease, emphysema and cystic fibrosis. In those successfully undergoing surgery, quality of life, in particular exercise tolerance, is substantially improved with a significant proportion of recipients being able to return to work.

Successful lung transplantation became commonplace in the 1980s, with the availability of new and effective immunosuppressive agents such as cyclosporine. In 2017–2018, 214 adults received a lung transplant in the United Kingdom (UK) which represented a 20% increase on the previous year. The vast majority of these were bilateral lung transplants supplemented by 23 single-lung and 12 heart-lung transplants. However the waiting list exceeds the number of transplants performed by a significant margin due to the shortage of suitable donor organs. The number of adult patients on the UK lung transplant waiting list in 2017 is the highest at any point this decade at 368 [1].

Patients appropriate for transplantation usually have a life expectancy of less than 12–24 months but necessarily have minimal co-morbidities and are highly motivated with good social support. The aim of the transplant team is to select a point in time during the disease trajectory for listing when survival is significantly reduced and warrants the risks of such major surgery. It is important to appreciate that continuing deterioration whilst the patient is listed is likely and in due course may render the patient no longer suitable for transplant surgery as an operation

M. McKenna (✉)
Department of Palliative Medicine, Freeman Hospital, Newcastle Upon Tyne, UK
e-mail: Maria.Mckenna@nuth.nhs.uk

S. C. Clark
Department of Cardiothoracic Surgery, Freeman Hospital, Newcastle Upon Tyne, UK

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would then be futile. This period of time is commonly referred to as the transplant window and may last a variable length of time, depending on an individual patient's circumstances, from weeks to years.

The median waiting time for a lung transplant in the United Kingdom is 282 days, though there is great variation depending on factors such as blood group, recipient size, and degree of immunological sensitization. For example based on blood group alone, a patient with blood group A may wait a median of 153 days whilst a patient with blood group O (competing with many other patients on the waiting list) will wait a median of 472 days for a transplant. Overall only 54% of actively listed patients will have received a lung transplant within 2 years, with 29% having died or become too ill to be transplanted [1].

The mismatch between donor organ availability and waiting recipients has increased, with the modest rise in lung transplantation activity overshadowed by marked growth in the transplant waiting list over the past decade. Currently in the UK, only 20% of multiorgan donors actually undergo retrieval of thoracic organs to benefit those on the waiting list. Many are excluded through pre-existing respiratory disease or dysfunction, aspiration, ventilator-acquired pneumonia or other conditions that cause the thoracic organs to be declined. The disparity between donor and recipient numbers is particularly great in the UK due to a general national donor shortage. Recent national initiatives have the aim of improving this situation through a number of measures to increase organ donation rates in the population. This has already met with some success but there is much more to do to rival other European nations and North America.

New donor optimization polices on intensive care units and new technologies in organ preservation may bring benefits in future. Ex vivo lung perfusion (EVLP) is one promising technology to increase the number of organs available for transplantation, whereby lungs deemed functionally unsuitable for transplantation are retrieved from the donor and placed into an extracorporeal circuit at the transplant centre. This permits perfusion of the lungs at controlled hydrostatic pressure with high oncotic pressure perfusate designed to reduce pulmonary oedema. Lungs can also be subjected to bronchoscopy and recruitment manoeuvres to mitigate against areas of collapse or atelectasis. Studies have shown that lung function can be significantly improved to allow the organs to be transplanted after a period of 2–4 h with excellent clinical results. Further research is ongoing looking at additives to the perfusate and modified gases for ventilation (such as hydrogen) to further increase the yield using this technology.

In the absence of a transplant, the progressive nature of advanced organ failure means that clinical deterioration is common during the transplant waiting period. Table 13.1 describes the clinical outcomes, 6 months and 3 years after registration on a UK lung transplant waiting list. Notably around a third of potential lung transplant candidates had not undergone surgery after 3 years. By 3 years, more than one in five had died whilst waiting for a transplant, with an additional significant number removed from the waiting list due to clinical deterioration past the point where a successful operation could be expected. The finite pool of donor organs must be utilized in a manner most likely to achieve a good outcome, hence the significant

Table 13.1 Outcome for patients registered on a UK lung transplant waiting list [1]

	Outcome at 6 months (%)	Outcome at 3 years (%)
Death on the waiting list	12	21
Removed from waiting list	1	6
Still waiting	48	8
Transplant	39	65

proportion of patients removed from the transplant waiting list due to deterioration in their condition when the risks of transplantation then outweigh the likelihood of success.

In those fortunate enough to receive matching donor lungs, there are a variety of possible lung transplant operations that can be undertaken. Bilateral (double) lung transplantation is most commonly performed and whilst mandatory in septic lung conditions such as cystic fibrosis and bronchiectasis to avoid retention of infected tissue in a patient who will be immunosuppressed post-operatively, it is increasingly used in all forms of lung disease as short- and long-term survival is improved when two lungs rather than one are implanted. Single-lung transplantation is now reserved for the sickest patients on the waiting list, often with fibrotic lung disease where survival is better than having no transplant at all and the lung disease is often associated with rapid decline.

The transplant surgery itself is a substantial undertaking requiring median sternotomy or clamshell or bilateral thoracotomies and may be performed using cardiorespiratory support with either extracorporeal membrane oxygenation or cardiopulmonary bypass. Surgery will typically take 4–8 h with explantation of the recipient's own lungs often being complex and time consuming, as a result of adhesions from infections or previous surgical procedures such as pleurodeses. Implantation of the donor lungs involves anastomosis of the bronchus, pulmonary artery and a left atrial cuff into which the two pulmonary veins drain. Reperfusion of the lungs in the recipient may bring primary graft dysfunction where florid pulmonary oedema occurs as a result of neutrophil infiltration and oxygen free radical generation. Some patients may require extended support post-operatively as a result and the syndrome is more prevalent if the ischaemic time of the lungs after retrieval from the donor is prolonged for more than 6–8 h.

The operation itself carries a 15–20% mortality risk and potentially fatal post-operative complications other than primary graft dysfunction include the development of donor- or recipient-acquired infections in the now immunosuppressed patient, acute rejection and anastomotic dehiscence particularly of the bronchus.

The current median age of a UK lung transplant recipient is 53 years (IQR 38–60), 62% of recipients are male and the range of primary respiratory disease is illustrated in Fig. 13.1. A lung transplant recipient is typically not in hospital immediately prior to transplant (85%) and is most commonly (48%) functionally categorized as NYHA class III [1].

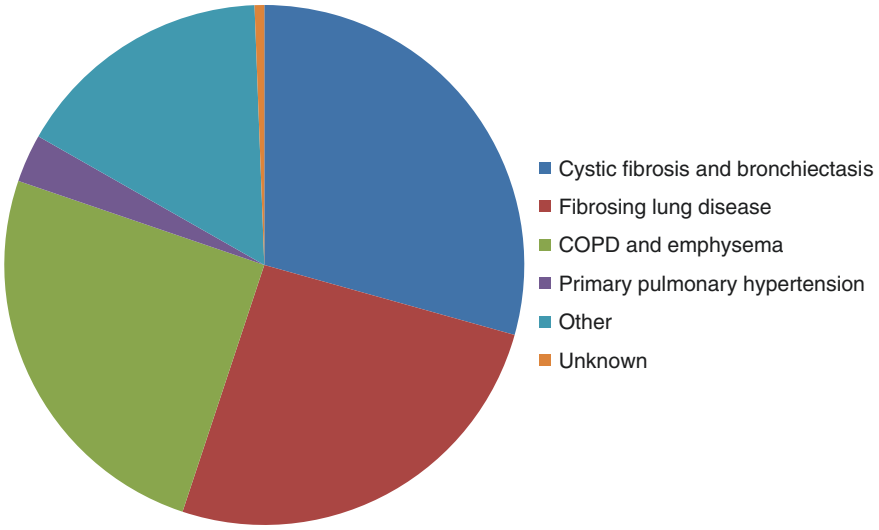

Fig. 13.1 Indications for lung transplantation (2016–17)

In terms of long-term survival in the UK, 5- and 10-year survival rates are 57% and 32%, respectively, for lung transplant recipients [1] which is comparable to internationally reported registry data.

Bridging to Lung Transplantation

Patients are increasingly being offered transplantation from critical clinical situations as technology improves and patients deteriorate on the waiting list, as donor organs are not available. Lung transplantation in patients who have worsened to the point of mechanical ventilation is associated with very poor outcomes and so is seldom practised. However in selected individuals, respiratory support can be offered through the use of extracorporeal membrane oxygenation (ECMO) or membrane oxygenators such as Novalung.

ECMO is most commonly utilized and can easily be instituted through the insertion of a dual-lumen cannula (Avalon) into the jugular vein which is advanced into the right atrium. Venous blood is withdrawn and oxygenated through a membrane oxygenator and this is then returned to the right atrium where it is directed through the tricuspid valve and into the pulmonary circulation. This can effectively oxygenate the patient and remove carbon dioxide allowing the patient to remain conscious and able to rehabilitate while waiting for donor lungs to become available. Complications however increase after a period of around 2–4 weeks of support and include bleeding from the necessary heparinization required, embolism and sepsis.

The Novalung Interventional Lung Assist (iLA) device is a membrane ventilator that allows for oxygen and carbon dioxide gas exchange to occur by simple

diffusion, connected as a passive low gradient shunt between the femoral artery and vein. The iLA consists of a plastic gas exchange module with diffusion membranes made from polymethylpentene treated with a heparin coating to provide a biocompatible and non-thrombogenic surface. Blood flows over the exterior surface of the device's fibers and oxygen flows inside, somewhat mimicking the native lung. In the arteriovenous portion of this pumpless shunt carbon dioxide exchange is the primary function due to arterial inflow blood, while a veno-venous attachment, which requires the support of a mechanical pump, additionally allows full oxygenation support.

In 2016/2017 nearly 5% of lung transplants were undertaken in patients receiving extracorporeal support [1] and this figure seems certain to rise with additional palliative care input into the management of these patients required both for those waiting for an organ that may not come or those suffering complications from the institution of this advanced technology.

Post-lung Transplantation

Life following heart or lung transplantation involves indefinite immunosuppression, frequent follow-up and a high rate of treatment-related complications such as acute rejection, infection, development of malignancy, diabetes and renal dysfunction. Chronic rejection develops in half of lung transplant recipients in the 5 years following transplant and this condition is associated with significant morbidity and mortality [2]. The attrition rate after transplantation from both acute and chronic long-term complications is therefore appreciable.

Considerable improvement has been made in the management of acute rejection post-lung transplantation, augmenting and refining immunosuppressive regimens leading to an improvement in short-term outcomes.

Chronic rejection (chronic lung allograft dysfunction, or described as the most common histological subtype obliterative bronchiolitis (OB)) is the main challenge to long-term outcomes in patients receiving a lung transplant. Bronchiolitis obliterans syndrome (BOS) is manifest by a sustained decline in a patient's best post-transplant lung function [3]. BOS involves progressive airflow obstruction, often affecting distal airways in a patchy distribution [4]. Chronic rejection and indeed BOS encompass a heterogeneous group of processes and clinical conditions, with variability in onset and clinical course, significantly limiting long-term survival and quality of life post-lung transplantation [5].

BOS tends to develop insidiously and is usually identified during routine post-operative monitoring as an outpatient. BOS is most often diagnosed 16–20 months after lung transplantation, with identification of irreversible decline in FEV_1 of at least 20% from the baseline value [4]. Early symptoms may include dry cough, breathlessness, wheeze and fatigue. Development of BOS within 2 years of transplantation carries a particularly poor prognosis, with a median survival of 1.47 years, compared with 2.51 years for the remainder of the cohort [3]. Similarly, patients with early-onset BOS have greatest reduction in FEV_1, higher oxygen requirements

and worse functional ability to mobilize [4]. The cause of death for the majority of patients with BOS is respiratory failure (58%), but infection (23%), malignancy (8%) and cardiac events (4%) are also significant [3].

Treatment options for chronic rejection offer limited hope of slowing the rate of deterioration, but include augmentation and/or modification of immunosuppression and total lymphatic irradiation. Augmentation with corticosteroids and a switch from cyclosporine A to tacrolimus may be advocated. Radiotherapy is usually delivered twice weekly to the three major lymphatic areas, the mantel, para-aortic and inverted-Y fields, with a total dose of 8 Gy. This treatment is of benefit to around 36% of patients, in particular those with a longer duration since transplant, higher FEV_1 and an absence of infection. Azithromycin therapy suppresses inflammation and inhibits *Pseudomonas aeruginosa*, and may therefore be used to improve pulmonary function in BOS. Early fundoplication surgery is known to slow the development of BOS and extend survival in those with gastro-oesophageal reflux disease, especially with pulmonary fibrosis or cystic fibrosis. Finally, there is no increased risk of recurrent BOS following re-transplantation; therefore lung re-transplantation may be considered as a rare treatment option for this patient group, on a case-by-case basis [4].

The Palliative Care Need

Palliative care aims to maximize the quality of life of a patient with a life-threatening condition and their family, through careful symptom assessment and attention to holistic care. In the UK, palliative care is well established as a service working alongside curative or disease-modifying treatments, particularly in the cancer setting. Prognosis can be unpredictable for patients with advanced respiratory disease, though we know that the cohort deemed appropriate for transplant are thought to have a life expectancy of less than 12–24 months. In recent years, UK specialist palliative care teams have moved towards a needs-based approach to patient care, rather than focusing only on prognosis.

It has been suggested for many years that the symptom burden and distress associated with non-malignant disease, such as respiratory failure, may be greater than that in cancer patients [6]. A comparison of 100 patients living with either advanced respiratory disease or lung cancer, who had a similar performance status, found significantly higher rates of clinically relevant psychological morbidity (90% vs. 52%) and worse quality of life ($p < 0.05$) in the group with non-malignant disease [7]. This has been described in relation to a range of respiratory conditions already within this book and is equally applicable to the pre-transplant population.

In addition to the palliative care needs common to all patients with advanced respiratory failure, there are issues unique to those patients involved in lung transplantation. These include the uncertainty associated with being on the transplant waiting list and the altered focus of care for this patient group. Transplantation has been described as the gold standard, or a curative treatment for organ failure; however some have declared this as akin to desiring a lottery win in order to achieve

prosperity [8]. An in-depth cross-sectional study of patients on the transplant waiting list suggested that the lack of control and uncertainty central to life on the waiting list are associated with a high level of psychological distress, likely to have a detrimental impact on the quality of life [9].

Life following a lung transplant is commonly associated with a significant symptom burden. The lung transplant recipient cohort is known to have increased levels of anxiety and depression, alongside a low sense of mastery and coping [10]. For example, 28% of patients post-lung transplant have clinically significant levels of anxiety; this is a reduction from 44% of the pre-lung transplant cohort, but remains significant [11]. Addressing psychological symptoms through medications and psychological therapies can help maximize quality of life and functional ability, as well as support the management of co-existing physical conditions [10].

The group of patients who develop chronic rejection or BOS display a rapid deterioration in quality of life [5]. This cohort struggle functionally with limited mobility and are subject to frequent hospitalizations (range 1–34) [2]. Symptomatically, patients with BOS are commonly troubled by breathlessness, cough and fatigue. BOS is a progressive condition and the associated heavy symptom burden is known to increase in severity over time [12].

Death and Dying Within the Transplant Journey

Patients within the transplant process are at significant risk of deterioration and death throughout their journey, from pre-transplant whilst on the waiting list, perioperatively at the time around their complex surgery, to post-transplant with the associated risks of acute and chronic rejection.

Retrospective review of the care provided to patients who died during a 5-year period, whilst involved in the lung transplantation journey, found recognition of the dying phase to be very late for this group of patients. In 80% of cases, end of life appeared to be acknowledged only in the 24 h before death; this was associated with late introduction of medication focused on palliation of symptoms [13]. The cohort of patients involved in lung transplant are commonly mechanically ventilated around the time of death, highly likely to die in hospital (68–81%), commonly die on the intensive care unit (33–45%) and are unlikely to participate in discussions about end-of-life care (15%). This is true whether the patient dies on the transplant waiting list, perioperatively or post-transplant [14–16].

One study utilizing data gathered through family interviews described the experience of patients with respiratory failure during their last week of life, both pre- and post-lung transplantation. The authors reported multiple distressing symptoms in over 80% of patients, namely breathlessness, pain, anxiety and fatigue. The majority felt that breathlessness was the most distressing symptom and there was no significant difference in experience whether pre- or post-transplant. Symptoms are frequently felt to be poorly assessed and managed, leading to the perception amongst many bereaved carers that it is not possible to control these symptoms [14].

The Challenges

The challenge of providing palliative care to patients involved in the cardiopulmonary transplant journey is complex, often involving misperceptions and avoidance by clinicians, patients and families.

Effective communication is particularly important in the context of palliative care as it is accepted that how information is framed and presented by their clinician, about any service or intervention, impacts a patient's response [17]. Evidence suggests that the majority of transplant clinicians are unaware of the palliative care services available within their unit [15] and over 40% of clinicians surveyed incorrectly felt that palliative care is only indicated for those who are imminently dying [18]. Transplant physicians describe broaching the topic of palliative care as challenging, often citing a preference to preserve hope and focus on active treatment [15, 19, 20]. Difficulty with prognostication may also explain avoidance of palliative or end-of-life discussions. A study of hospital physicians found that this group markedly overestimate their patient's prognosis, by a factor of greater than five. Factors relevant to transplant clinicians, such as non-oncological medical subspecialty training and longer length of patient-physician relationship, increase the propensity to overestimate [21].

Culturally, Western society is known to often avoid the consideration or discussion of death. Within transplantation and critical care, a strong belief in the value of hope and hard work to a positive outcome is commonplace [19]. The time and energy invested by transplant clinicians, through prolonged operating times, lengthy intensive care unit stays and a sense of responsibility to the families of organ donors, may impact the ability of a clinician to recognize the deteriorating patient. The misapprehension that palliative care is analogous with end-of-life care is likely to act as a barrier to palliative care referral. This appears to be the case within cardiopulmonary transplantation and provides some explanation for delayed identification of the dying patient and late or absent referral to palliative care teams.

Published data exploring patient and family views indicate that misperceptions are common and personal experiences are important, such that palliative care is largely viewed as a service for cancer patients in the last days of life. Patients and carers describe a fear of palliative care, believing that contact with a palliative care team would bring death closer. In contrast transplantation was viewed as a cure or solution, explaining why palliative care was considered unnecessary. Commonly palliative care and transplantation were felt to be mutually exclusive [22].

It is well recognized within the transplant process that there is difficulty balancing hope for a positive outcome with the need to contemplate the possibility of a poor outcome. Patients and families hope for a successful outcome and value a positive attitude in achieving this goal. Advanced lung disease commonly involves life-threatening exacerbations, and the experience of surviving these episodes consolidates the value of a positive attitude and a sense of immortality [22]. A prospective survey of 122 patients with advanced non-malignant illness demonstrated the propensity patients have to overestimate their prognosis; this overestimation is

especially marked in younger ambulatory patients, the cohort most likely to be involved in the transplant pathway [23].

Integrating Palliative Care with Lung Transplantation

Within the lung transplant journey, palliative care should sit alongside active management of the patient and their underlying respiratory disease [24]. Provision of palliative care is dependent on the individual need of the patient and family, which will fluctuate and need close monitoring. This concurrent and integrated model of palliative care is illustrated within Fig. 13.2. Collaborative working between the transplant service and palliative care team is essential to achieve this goal. The intensity of palliative care involvement is individualized according to the needs of the patient or family, but is commonly greatest at times of clinical deterioration, complex decision-making and towards the end of life.

In many situations, the palliative care needs of the patient can be explored, addressed and managed by the multidisciplinary transplant team. This team includes respiratory physicians, transplant coordinators, intensivists, social workers, clinical psychologists and physiotherapists. The clinical team carries considerable skill and wide-ranging expertise, is trusted by the patient and their family and understands the complexities of transplantation. Formal, regular holistic needs assessment may facilitate identification and prioritization of need.

If the transplant team are struggling with any aspect of holistic care, from symptom control to challenging communication or complex decision-making, the specialist palliative care team can provide additional support. A patient within the lung transplant journey is usually closely linked and in frequent contact with their hospital-based transplant team; therefore initial referral to palliative care is most likely to involve the local hospital specialist palliative care team. Ongoing palliative care support may be arranged through the local community or hospice-based palliative care team, according to the patient's situation and preference.

The clinical condition of a patient throughout the transplant journey is often precarious. The patient initially has advanced respiratory disease, is clinically deteriorating and is expected to die in the near future; however alongside this there is often hope for and focus on the possibility of life-altering transplant surgery. Access to a donor organ is unpredictable, whilst this complex surgery risks significant

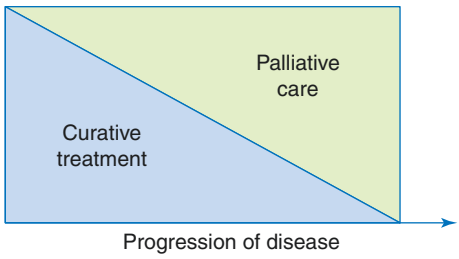

Fig. 13.2 A concurrent, integrated model of palliative care

perioperative mortality, together with the opportunity for improved quality and quantity of life. This dichotomy is challenging for the patient, family and healthcare professionals involved. Palliative care professionals are experts in managing uncertainty and familiar with the concept of "*hoping for the best, whilst planning for the worst*", also known as parallel planning; the transplant journey illustrates this paradox most vividly. Any palliative care team support is flexible and can be intensified or pared back, in keeping with varying clinical need within an uncertain trajectory.

Supporting patients and families to understand the role of palliative care is vital to successful collaborative working and optimizing the palliative care received by transplant patients. Strengthening relationships between palliative care and transplant clinicians improves clinical credibility, and helps transplant colleagues to develop their confidence in discussing the concept and purpose of palliative care with their patients. It is common that patients discuss issues and challenges with other patients and families, directly on the ward, in clinic, or via social media. Recommendation as to the value of palliative care by friends and fellow patients, as well as trusted clinicians, is perhaps the most valuable endorsement of an integrated service. This is one resource providing an honest and comprehensive message about the role of palliative care within lung transplantation, designed for patients and families and openly available through the Transplant TV website: http://transplant.tv/portfolio/palliative-care/. It may appeal to more technologically minded transplant patients, promote insight and reduce misconceptions around palliative care.

Symptom management in the context of a patient within the lung transplant journey is complex and diverse, reflecting this heterogeneous cohort of patients. Challenging or refractory physical symptoms may relate to unresolved psychological problems, or non-physical concerns which have not been addressed. A holistic approach to patients, their current situation and priorities facilitates greater understanding and improved symptom management. The symptoms most commonly encountered by patients within the lung transplant journey are breathlessness, cough, fatigue, anxiety and depression. The approach taken in the initial assessment of any symptom would be to (a) consider reversible causes, (b) explore non-drug strategies and (c) discuss pharmacological treatment options. There is no guidance to direct specific strategies to palliate symptoms within lung transplantation, but disease-specific advice is often available and detail around the general approach to the management of breathlessness and cough can be found elsewhere within this book.

Five key points for provision of effective integrated palliative care within lung transplantation are as follows:

- Utilize the skills of the multidisciplinary transplant team to optimize holistic care for all patients.
- Remember the uncertain trajectory for patients within the lung transplant journey, with the potential for either rapid deterioration or prognosis-altering surgery—consider parallel planning.
- Education of patients, families and transplant teams as to the broad role of palliative care is essential to avoid misperceptions.

AL GRAWANY

- Actively ask about the five most common symptoms—breathlessness, cough, fatigue, anxiety and depression.
- Develop close links with your local specialist palliative care team and utilize their expertise when initial management strategies require additional support.

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Part IV

End of Life Care

End-of-Life Care

14

Paul Paes

To cure sometimes, to relieve often, to comfort always (*Anon. 16th century*)

Introduction

The earlier chapters have looked at specific conditions and the major palliative care issues in each. In progressive respiratory conditions, the focus of care transitions from therapies directed against the disease to palliative management of the effects of the disease process. Often this realisation can feel like a failure of medical treatment and cause clinicians and patients to feel a loss of hope. Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [1]. In doing so, palliative care aims to give some control back to patients and clinicians, by focusing on what can be done to improve the situation and acknowledging those areas which cannot be addressed.

This chapter addresses end-of-life care, incorporating thinking about both the last few days of life and the last year of life. The focus of the first part of the chapter is on identifying those patients who are approaching the end of their life, and planning their care appropriately. For these patients disease-modifying therapies, emergency treatments, palliative care and supportive care must run in parallel. A framework of care across primary and secondary care is set out including key issues

P. Paes (✉)
Department of Palliative Care, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, Tyne and Wear, UK

School of Medical Education, Newcastle University, Newcastle Upon Tyne, UK
e-mail: paul.paes@nhct.nhs.uk

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around communication, anticipatory planning, clinical decision-making and ethics. The second part of the chapter focuses on the last few days of life and practical steps in managing this stage.

Recognizing that a patient is Dying (or is at risk of Dying)

Recognizing that a patient is, or may be, approaching the end of their life is a key skill for those involved in managing respiratory conditions. On a population level, it is relatively straightforward to estimate prognosis, based on the severity of a disease and other measurable factors. However for individual patients, it is difficult to predict prognosis accurately in terms of time, and healthcare professionals are poor at doing this [2].

Two studies looking at recognition of prognosis in respiratory conditions highlight the challenge. In one, 5 days before the death of patients with COPD, doctors were predicting an expected survival probability of 50% at 6 months [3]. In another study, taking place in intensive care units, physicians estimated that only 10% of a group of patients with asthma or COPD would survive more than 6 months when in fact 40% survived [4]. It can be especially difficult to determine whether an acute deterioration will be reversible or whether it may represent the onset of the dying phase.

In the UK, the General Medical Council considers that individuals are "approaching the end of their life" when they are likely to die in the next 12 months [5]. This includes those whose death is imminent (expected within a few days or hours) and those with:

- Advanced, progressive, incurable conditions.
- General frailty and co-existing conditions that mean they are expected to die within 12 months.
- Existing conditions from which they are at risk of dying from a sudden acute crisis in their condition.
- Life-threatening acute conditions caused by sudden catastrophic events.

There are a number of tools designed to help. Earlier chapters have covered some respiratory condition-specific prognostic tools. The UK national end-of-life strategy endorses the use of the gold standards framework which is designed to aid recognition of patients who are in the last 6–12 months of life, and provides a template for their care [6]. It suggests three triggers to identify patients in the last 12 months of life [7]:

1. To ask yourself "the surprise question": "Would you be surprised if this patient were to die in the next few months, weeks or days?" This is an intuitive question, incorporating clinical assessment, knowledge and experience.
2. General indicators of decline: deterioration, increasing need or patients who make the choice not to have further disease-modifying treatments.
3. Specific indicators relevant to the underlying condition.

Examples: Prognostic Indicator Guidance 2016 [7]
Cancer:

- Deteriorating performance status and functional ability due to metastatic cancer, multi-morbidities or being not amenable to treatment—if spending more than 50% of time in bed/lying down, prognosis estimated in months.
- Persistent symptoms despite optimal palliative oncology. More specific prognostic predictors for cancer are available, e.g. PiPS (UK validated Prognosis in Palliative care Study).

Organ failure:
Chronic obstructive pulmonary disease (COPD):
At least two of the indicators below:

- Recurrent hospital admissions (at least 3 in last year due to COPD).
- Medical Research Council dyspnea score 4/5—shortness of breath after 100 m on level.
- Disease assessed to be very severe (e.g. FEV_1 <30% predicted, persistent symptoms despite optimal therapy, too unwell for surgery or pulmonary rehab).
- Fulfils long-term oxygen therapy criteria (PaO_2 <7.3 kPa).
- Required intensive care admission/non-invasive ventilation.
- Other factors such as right heart failure, anorexia, cachexia, more than 6 weeks' steroids in preceding 6 months, requires palliative medication for breathlessness, still smoking.

None of these triggers can accurately predict prognosis in an individual patient and they need to be used judiciously but they are aimed at identifying a group of patients who have advanced disease and are at risk of dying in the next 6–12 months whilst acknowledging that they may well live longer. There are significant disparities between the levels of palliative care provided to patients with different diagnoses [8, 9]. This is partly due to the inherent unpredictability of some lung diseases. However it is necessary to avoid "prognostic paralysis" which can prevent the patient from receiving appropriate supportive end-of-life care. If the needs of these patients can be identified sooner, discussion of the patient's wishes, anticipation of clinical problems and patient-centered planning can be performed in a timely fashion rather than during a crisis.

Example: Mrs. Smith is 75 years of age and she has a long history of COPD. She has been having increasingly frequent hospital admissions for treatment of exacerbations and she is clearly less well than she was 6 months ago.

Although her prognosis is uncertain, it would not be a surprise if she died in the next year. It would therefore be sensible to start having discussions about this with her. If she realises that she may be approaching the end of her life then she will have the opportunity to plan things such as writing a will, visiting people she wants to see or doing particular things she would like to do before she dies. Recognizing that a patient may be at risk of dying in the next 6–12 months does not necessarily mean stopping disease-modifying treatment, or changing the management plan, unless this is clinically indicated or due to patient preferences. Instead, it is about considering the measures that might be taken to improve quality of life now and in preparation for the dying stage.

The End of Life Period

Crucial to delivering good end-of-life care is the recognition that palliative care often runs in parallel with disease-modifying treatment and emergency care. This allows full medical treatment to continue whilst overcoming the current reality of respiratory patients often failing to have their palliative care needs addressed [10].

A number of issues need to be addressed for this group of patients and their families:

- Communication and information needs
- Patients' current clinical needs:
  - Physical symptoms such as breathlessness or pain and psychological symptoms such as anxiety and depression
- Patients' future clinical needs:
  - Anticipate and plan for problems as the condition deteriorates
- Current personal and social care needs
- Future personal and social care needs

The Ambitions Framework for End of Life Care sets out six ambitions for end-of-life care [11]:

1. Each person is seen as an individual.
2. Each person gets fair access to care.
3. Maximizing comfort and well-being.
4. Care is coordinated.
5. All staff are prepared to care.
6. Each community is prepared to help.

These are underpinned by eight foundations that need to be in place on the ground:

1. Personalised care planning
2. Shared records

3. Evidence and information
4. Involving, supporting and caring for those important to the dying person
5. Education and training
6. Access at all times, day or night
7. Co-design
8. Leadership

This is backed up by quality standards for end of life care describing what good care looks like [12].

Palliative Care Registers

It is now common in the UK for primary care physicians to have palliative care programmes or registers, to aid the identification of, and plan the care of patients in this phase of their illness. Placing patients on a palliative care register leads to the planning of their care as well as regular assessments and multi-professional discussions of their needs. Crucial to this are discussions with patients and their families at an appropriate pace and timing, in order to make shared decisions and forward plans.

Respiratory and palliative care teams play a crucial role in the identification and ongoing care of patients on palliative care registers. Informing primary care that a patient is appropriate to go on the palliative care register is a crucial step in highlighting their needs and it may also open up extra services and finances for patients and carers.

Example: Mr. Brown is a 45-year-old man with a long history of smoking who presents to the emergency department in an emaciated state with haemoptysis. He is diagnosed after bronchoscopy and computed tomography as having metastatic non-small cell carcinoma of his lung. His WHO performance status is 2 to 3.

Mr. Brown has a poor prognosis and meets the criteria for the palliative care register. This means that he will be regularly reviewed, to assess and manage any problems that arise, to plan for the future and to provide support for his immediate family. If he were to respond well to anticancer treatment his name could be removed from the register.

The UK General Practice Core Standards for Advanced Serious Illness and End of Life Care [13] set out eight core domains to enable general practitioners to ensure compassionate, safe and effective care:

1. Professional and competent staff
2. Early identification

3. Carer support—before and after death
4. Seamless, planned, coordinated care
5. Assessment of unique needs of the patient
6. Quality care during the last days of life
7. Care after death
8. General practice being hubs within compassionate communities

Communication

Good communication is the key to managing the end-of-life phase well. Patients and their families value honest and open communication. Many patients want to know more than they are currently being told and find healthcare professionals reluctant to talk about their issues [14–16]. A particular concern is a lack of understanding among patients of the severity and prognosis of progressive, non-malignant conditions such as COPD, fibrotic lung disease and advanced bronchiectasis. A systematic review of palliative/end-of-life conversations in COPD indicated that the frequency and quality of palliative care conversations are generally poor. Patients and physicians identified many barriers and important topics were not discussed. Patients and clinicians reported tension between remaining hopeful and the reality of the patients' condition [17]. A majority of complaints about end-of-life care are in relation to communication [18].

Clinicians often want to protect patients from losing hope, or worry that patients may not be ready for key discussions. Sometimes there is a reluctance to acknowledge treatment failure, uncertainty about prognosis or a lack of time and skill to undertake such conversations. One of the goals of this book is to reinforce the concept that active disease-modifying care can run alongside palliative care, and that palliative care is not entirely dependent on an accurate prognosis. Patients often expect healthcare professionals to lead these conversations, and pick up on the professional reluctance to discuss them. Sometimes questions such as "How do you see the situation/future?" "What hopes/fears do you have?" or "What worries you most about the future?" can be useful triggers to such discussions.

Patients and families have mixed requirements for information, sometimes not having enough information and at other times being overloaded. A flexible approach is essential. Opportunities to discuss issues may need to be given repeatedly. Often the style of communication is as important as the words that are said. Key components include:

Exploring understanding

- What does the patient know?
- What are their expectations?
- What do they want to know?
- Do they want anyone else to be present?
- Do they have particular concerns?
- Do they have particular hopes or goals?

Dealing with difficult questions, such as about prognosis

- Is the patient asking the question because they want an answer? Often patients are not after specific answers but want to discuss worries.
- If time was short would they want to know this? What difference would that information make and to whom?
- If time was short, what would the patient want to do or say?
- Where would they wish to be cared for and by whom?
- What would help the situation now?

Example: Mrs. Smith is 75 years of age and she has advanced progressive COPD. She is the main carer for her husband who is older. She has been having increasingly frequent hospital admissions for exacerbations and is less well than previously. She knows that the situation is changing, and asks her doctor about his thoughts on her future.

In addressing this situation, understanding the motivation behind this question is important. Is she worried about the future, either for herself or for her husband? Does she need to make specific plans? What would be helpful for her? Key aspects of communicating include listening as well as talking, recognizing uncertainty and acknowledging anxiety and distress. Patients do not always expect answers, but appreciate an honest acknowledgement of the situation and affirmation that whatever happens they will not be abandoned. Uncertainty about prognosis should not stop discussion—focusing on specific issues and how to address them is often easier than trying to guess the timing of those issues. Communication should occur only at a pace that is appropriate for the individual patient rather than forcing conversations to fit a professional timetable or checklist.

Clinical Management: Adjusting the Focus of Care

As patients approach the end of life, there needs to be a shift in the focus of their care so that treatments are aimed at maximizing quality of life rather than only trying to extend life. This requires recognition from both the patient and the clinical team that the patient is towards the end of their life. The shift required in focus of care will be different for each individual patient but there needs to be acceptance that the aim of treatment is no longer curative.

Mrs. Smith with progressive COPD may be reaching the end stages of her illness. She may have practical or emotional things she wishes to plan for. She may also want to think about how future exacerbations will be managed. She may consider whether she would rather spend time in hospital in the hope of prolonging life, or whether she would rather stay at home and accept that life may be shorter without some treatments. Depending on her precise clinical status the medical team may strongly advocate hospital treatment or conversely may feel that further treatments are unlikely to help the situation. Decisions do not need to be made in one

consultation. This should be an ongoing process. Sometimes it is appropriate to continue with intensive disease-modifying treatment because this can often be a way to relieve symptoms and to maximize quality of life.

Clinical Management: Deciding on Treatments

In patients with advanced disease, decisions have to be made about the appropriate level of treatment. Sometimes this decision is obvious. If a patient presents who is known to have very advanced disease which has now progressed such that the patient is dying, the benefit of burdensome treatments should be questioned. The treating clinician should always identify the intended benefit of the proposed treatment. Patients can be offered treatment to make them *feel* better, but this is not the same as making the underlying condition better. Conversely, patients may have advanced disease but present with an acute complication, such as a pneumothorax, that is reversible, and treatment is likely to relieve distress and may restore the previous quality of life.

Many respiratory diseases, such as COPD, cystic fibrosis or fibrotic lung disease, follow a chronic disease trajectory, characterized by exacerbations and recovery against a background of slow progressive decline. It is possible that one of these exacerbations may be the last one and that the patient may not recover but it can be difficult to tell when this will occur. This is different to some cancer trajectories. Models of palliative care provision which make an artificial divide between disease-modifying treatment and palliative care are usually inappropriate for patients with chronic lung disease. Palliative care providing symptom relief and support needs to run in parallel with disease-modifying treatments and emergency care for acute exacerbations and complications. When it is uncertain whether a deterioration is reversible or not, it is reasonable to offer a trial of treatment, and patients may have clear wishes about how they wish to be treated. Treatment options should be explained, including the option of comfort measures only. If a trial of treatment, such as non-invasive ventilation, is being considered it may be appropriate to discuss the concept of a ceiling or escalation level of treatment.

Example: Mrs. Smith has advanced progressive COPD. She has been struggling to manage at home for several weeks and is now spending much of her day asleep in bed. She presents unwell with another exacerbation. On previous admissions she has made it clear that she does not like being in hospital and is getting tired of life.

Mrs. Smith needs a frank and honest discussion about her understanding of her disease and the treatment options, including the option of no treatment. Because exacerbations make her severely unwell and breathless, she is keen to try treatments but says that if it is clear that they are not working, then she would like her

symptoms managed in alternative ways. She has always made it clear that she would like to die in her own home.

Having that open discussion, including acknowledging the possibility that treatment may not work and she may die, might allow her to express her preferences about end-of-life care.

CPR or DNACPR

In such circumstances it is also appropriate to consider whether cardiopulmonary resuscitation (CPR) would be appropriate in the event of a cardiorespiratory arrest. Making a DNACPR (Do Not Attempt Cardiopulmonary Resuscitation) decision is an area that is emotive as, if not well handled, patients and their relatives may feel that they have been unfairly denied a treatment.

A DNACPR order specifically relates to the one treatment (CPR) and not other forms of treatments and resuscitation, such as fluid resuscitation. Current guidance in the UK comes from a joint statement by the British Medical Association, the Resuscitation Council and the Royal College of Nursing [19]. If no CPR decision has been made and the patient's wishes are unknown, the presumption should be in favour of CPR. The exception to this is in patients in whom attempting CPR would be clearly inappropriate, for example a patient in the final stages of a terminal illness where death is imminent and unavoidable but for whom no formal DNAR decision has been made. CPR under these circumstances is not a realistic treatment option for the patient's condition, and is both futile and inappropriate. If it is felt that CPR would not restart the patient's heart and breathing then CPR should not be attempted.

Two recent court cases in the UK have set out a clear legal position on the involvement of patients and their families in the decision-making around DNACPR decisions. Following the rulings in the Winspear and Tracey cases, healthcare professionals must consult with patients (or relatives and carers if the patient lacks mental capacity) and a failure to do so may breach a patient's right to respect for private and family life, guaranteed by Article 8 of the European Convention on Human Rights and a doctor's common law duties [20]. The only exceptions to this are situations where it is not practicable or appropriate to do so, for example if consultation would cause physical or psychological harm to the patient. Clinical futility is not considered an acceptable reason for not discussing a DNACPR decision.

In clinical terms, this is only one of a spectrum of clinical decisions that need to be thought of. However, it assumes a special significance because in the UK and other countries, CPR is the only potential treatment which requires a documented decision if it is not going to be carried out as well as a discussion. In other treatment consultations, it would not always be necessary to talk about treatments that are not being offered.

These legal aspects should not divert health professionals from compassionate communication. It is not usually helpful to ask a patient "do you want to be resuscitated if your heart stops?" A more useful discussion for patients and families may focus on the severity of their illness, their understanding and expectations. If they

are approaching the end of their life the discussion can look at the focus of decision-making, before discussing specific clinical decisions that are relevant. If the patient is deteriorating progressively and is in the dying phase of their disease, CPR is not likely to be a feasible treatment and should not be offered as an illusory option.

Anticipatory/Advance Care Planning

One of the key reasons to identify that a patient is reaching the end phase of their illness is that it enables us to plan ahead and to deliver care that is consistent with a patient's wishes. Key to this is addressing current problems, but perhaps greater skill is required by the healthcare team to anticipate and plan for future problems. Decision-making in this situation takes a number of forms and must comply with the legal and ethical frameworks of individual countries:

- Patient-driven decision-making tools: advance care planning (ACP)
- Professionally driven decision-making: clinical management plans, emergency healthcare plans, treatment escalation plans

Although these can be patient or professionally driven, they work best when done in partnership.

Advance Care Planning

Advance care planning is a voluntary process through which patients discuss their future wishes [21]. This is done in the anticipation of a future deterioration in a person's condition in case they lose the capacity to make those decisions as they arise. Many patients welcome this discussion, but others will not wish to participate. In the UK the Mental Capacity Act indicates some legal options which patients can take:

Advance decision to refuse treatment (ADRT)—This is a decision to refuse specific treatments. Set out correctly; this is legally binding. Common treatments refused include resuscitation, ventilation, feeding tubes, intravenous fluids and antibiotics [22].

Lasting power of attorney: A patient may appoint someone to make decisions on their behalf in the future. This may be about healthcare issues or more financially based ones.

In addition to the legal options, many patients prefer a less formal approach. Some will be happy simply to discuss what is likely to happen, think about the future and their choices, but not wish to do anything more. Others will prefer to record some of those preferences in the form of an advance care planning document or advance statement.

Advance statement: This is a statement reflecting an individual's preferences and aspirations. It can help health professionals identify how the person would like to be treated and record past, present and future wishes. It is the documented result of an

advance care planning discussion. Crucially it is not legally binding, which means that healthcare professionals need to use their judgement in applying the values and priorities expressed in the document to their decision-making. For patients, this fact overcomes a fear that they may commit themselves to a decision which they may later regret. A powerful aspect of an advance statement is that it enables views to be communicated, checked, clarified and then shared with others.

The sorts of issues that patients might include in an advance care planning discussion are:

- The patient's preferred place of care during the duration of their life
- Where they would like to be if they are dying
- General care preferences
- How active treatment should be if a complication develops
- Decisions about swallowing: nutrition and hydration
- Resuscitation status
- Management of incontinence
- Organ donation
- Any other areas of importance to them

When a patient's condition deteriorates the loss of control experienced can be overwhelming. Involving them in decision-making restores some control over events. Literature in this area suggests that respiratory patients seldom get the chance to have these discussions before emergency situations arise and that they would welcome such discussions [23]. It is important to recognize that advance care planning decisions only apply if a patient loses capacity. While a patient has capacity they should be consulted. Equally patients change their minds, and care should be taken in interpreting plans, and updating them. Useful training modules on advance care planning are included on the e-learning End of Life Care website [24].

Professionally Driven Decision-Making

Advance care planning is a voluntary process that is dependent on patients wishing to plan for anticipated changes in their condition. Whether that takes place or not, healthcare professionals need to have clear management plans, which anticipate and address potential problems. In the vast majority of cases, this should be done with the full involvement of patients unless doing so would cause considerable distress or the patient has lost capacity (in which case there is clear legal guidance to follow).

Clinical Management/Care Plans

The most straightforward option is to simply have a management plan agreed between the health team and the patient to address some of the following:

- What are the most likely clinical problems? Often these will be about exacerbations of the underlying respiratory condition, symptoms such as breathlessness and potential acute events such as infections or thromboembolic disease.
- What is the best management of these problems? What clinical signs should people look out for? What treatment works for this individual patient? What is the appropriate ceiling of treatment? What can be managed at home and when should an admission to hospital be considered?

In some areas, a number of specific tools are emerging to aid this process:

- Emergency Healthcare Plans

These documents are designed to give a specific plan to address an anticipated clinical problem where the right treatment is required promptly. Such a form is used as part of the Deciding Right initiative, a programme designed to encourage discussion and future planning [25]. These plans are very specific to individuals.

- Treatment Escalation Plans

These decision-making tools are growing in popularity and are designed to be used for patients who are deteriorating and for whom acute problems are anticipated. As a patient's health deteriorates, their ability to benefit from specific treatments lessens. Treatment escalation planning looks at specific treatments and considers whether a patient is likely to benefit. Importantly this needs to be an evolving document as a patient's situation changes. It allows both quick escalations of treatment where that will make a difference (sometimes patients considered "palliative" are undertreated) and ruling out treatments that are no longer effective or desired (sometimes patients considered "palliative" are subjected to burdensome treatments with little chance of success). An example of a Treatment Escalation form can be found in the reference quoted [26].

An Emergency Healthcare Plan is likely to be useful in managing a specific anticipated problem with a specific treatment plan. A Treatment Escalation Plan may be more helpful where a number of potential problems may arise, and guidance is required as to which specific treatments may be of benefit to a patient. Importantly clinical management plans, Emergency Healthcare Plans and Treatment Escalation Plans are advisory plans and should guide clinical assessment and judgement, rather than replacing it. All of these approaches should include patients where possible in joint decision-making and be consistent with any advance care planning discussions.

Example: In our two case examples, Mr. Brown has metastatic non-small cell carcinoma of his lung, and Mrs. Smith has progressive COPD. Both are keen to talk about the future—Mr. Brown has very clear views about how he wants his health managed. Mrs. Smith feels that she would like her doctors to make decisions for her as she does not feel that her knowledge of treatments is good enough to make clear decisions.

Both patients would benefit from advance care planning discussions. Both may benefit from making advance statements if they have particular preferences. If Mr. Brown wishes to make clear decisions to refuse certain treatments, an ADRT form may be helpful. This ADRT may cover most clinical scenarios if well written, but cannot ask for specific treatments. Both patients would benefit from clear clinical management planning. In particular, Mrs. Smith with her frequent exacerbations would benefit from the medical team considering how further exacerbations should be managed. Treatment escalation planning, an emergency healthcare plan or simply a clinical management plan may all be helpful in managing an acute deterioration.

Ethics

There are numerous potential ethical issues that may arise in the palliative management of respiratory conditions. Professional guidelines are useful to guide ethical conduct—in the UK the General Medical Council sets this out for doctors in "Good Medical Practice" [27]. There are multiple ethical frameworks for analyzing clinical issues such as the commonly cited four principles of medical ethics [28]:

- Respect for the **Autonomy** of the patient.
- Acting for their **Beneficence**.
- Avoiding harm: **Non-maleficence**.
- While being fair to others in how we use resources: **Justice**.

All four principles need to be balanced against each other to make a wise decision. Some health organisations have clinical ethics specialists or committees who can help to advise clinicians when faced with particular dilemmas. This section focuses on two specific aspects of ethics.

Withholding, Withdrawing and Futile Treatments

Deciding whether or not to start or stop a treatment that may prolong life can be challenging, especially in a patient with a respiratory illness when their disease trajectory may be difficult to predict. It may seem an easy decision to try to treat everything but this has serious consequences in dying patients, and especially for their families. This is discussed more fully later in the chapter. It can sometimes feel easier to never start a treatment than to stop it at a later date.

Example: Mr. Brown is a 45-year-old man with metastatic non-small cell carcinoma of his lung. His WHO performance status is 2 to 3.

Although Mr. Brown has a new diagnosis of lung cancer and is relatively young, he has a poor performance status and it is uncertain if he will tolerate or benefit from

palliative chemotherapy. Is it ethically better to start chemotherapy and then stop it, or not start it at all?

The decision should remain a clinical one, rather than be influenced by his young age or emotions about withholding a treatment. If he meets the standard criteria to receive chemotherapy then it should be offered to him. As with all patients he should have the intended benefits explained to him, alongside likely adverse effects and alternative options (including the option of no chemotherapy). It should be made clear that the treatment is with palliative, rather than curative, intent. If he wishes, the treatment should be started and his response to treatment gauged. If it is clear that chemotherapy is providing no benefit, that the adverse effects outweigh any benefits or that his cancer is progressing despite the treatment then it would be appropriate to stop treatment.

The alternative would be to withhold chemotherapy from Mr. Brown. This would mean not offering him the option of chemotherapy, rather than him declining the treatment. To do so would be to deny him the chance of a treatment that may prolong his life and reduce his symptoms. If he is clinically well enough to receive it and meets the relevant criteria, then he should be offered chemotherapy.

The situation would be different if he was clearly within the last few days or weeks of life. In these circumstances, chemotherapy is unlikely to provide any benefit but instead gives him the burden of adverse effects. This may prevent him from doing things he needs to do and seeing people he wants to see before he dies. In this situation it would be appropriate to withhold chemotherapy, but it would be being withheld because this is the appropriate clinical decision rather than Mr. Brown being denied a potentially beneficial treatment.

Doctrine of Double Effect

A concern that is sometimes raised in the management of patients with advanced disease is that use of medications such as opioids or benzodiazepines might hasten death, even though the intention is to alleviate symptoms. The doctrine of double effect is an ethical term that is sometimes used where the intention of treatment is good (symptom control), but the treatment may have foreseeable but unintended consequences (for example, respiratory depression). It is culturally sensitive, depending on the law and societal attitudes to intentions; for example euthanasia would be a good intention or outcome in some countries.

The doctrine is overused and often inappropriately to describe poor practice. The same level of rigor should be applied to the use of opioids and benzodiazepines as with drugs such as insulin. Insulin has the potential to cause harm if used inappropriately but the doctrine of double effect would never be used to defend such practice. In a similar way it should not be used to defend inappropriate use of symptom control medication. Symptom control medication should be gradually titrated upwards from small doses. A dose of opioids or benzodiazepines should never be so big as to affect the patient's respiratory function. Pain (even when treated) remains a respiratory stimulus and antagonizes opioid-induced respiratory depression [29].

If a dose is given that is large enough to affect the patient's respiratory function it does not suggest that the doctrine of double effect is required to justify the prescriber's actions. Rather it suggests that the dose is inappropriate [30].

Psychological and Spiritual Issues

Patients with chronic lung disease who suffer from shortness of breath often exhibit anxiety or depressive symptoms [31]. Emotional reactions tend to peak at key points such as at the time of diagnosis of a serious illness, when the disease progresses and when an acute crisis occurs. It is important to distinguish between normal reactions to stress and more persistent signs of adjustment disorders, anxiety or depression. Many patients with chronic lung disease suffer greater psychological morbidity than those with cancer [18, 32]. Interventions range from supportive listening to psychological treatments such as cognitive behavioral therapy and medications such as antidepressants and anxiolytics.

Spiritual issues are harder to define, but relate to people's values and their search for meaning or purpose. The European Association for Palliative Care defines spirituality as: "The dynamic dimension of human life that relates to the way persons (individual and community) experience, express and/or seek meaning, purpose and transcendence, and the way they connect to the moment, self, to others, to nature, to the significant and/ or the sacred" [33]. Spiritual domains may be the key component in bringing together the physical, psychological and social issues of a patient. Towards the end of life, many people start to review their life and seek:

- Affirmation and acceptance of their life, choices and decisions
- Forgiveness and reconciliation of areas of their life where they feel they have unresolved issues
- Discovery of meaning and direction

Indicators of spiritual distress include:

- Sense of hopelessness, meaninglessness, powerlessness, becoming withdrawn or having suicidal thoughts
- Intense suffering: can't endure anymore, what's the point in going on? Loneliness, isolation, vulnerability
- Change in beliefs, loss of faith/culture, anger towards God, church, etc.
- Sense of guilt or shame: being punished, deserving to be ill
- Unresolved feelings about death, worries about going to sleep, the dark, etc.

Example: Mr. Brown is a 45-year-old man with metastatic non-small cell carcinoma of his lung. His symptoms of breathlessness and pain have previously been well controlled. Recently his pain has been unbearable and the team feel that he has been responding differently to them.

The expression of physical symptoms should not be attributed to non-physical causes without good reason, and in most situations the interaction between physical and spiritual is complex. However, intense suffering and changes in the way people behave are often warning signs. Without addressing spiritual issues, physical symptoms can sometimes be difficult to treat.

In Mr. Brown's case, during a hospital admission one of the healthcare assistants finds him crying in the bath. He has two young children and having been told there is nothing that can control the cancer, the reality is dawning on him that time is very short with them. The thought of not being there for his children is unbearable, but he also wants to prepare them for his death. He distances himself from them gradually, so that they turn more to his wife and others. It has been over this time that his pain has got much worse, and when he talks it is obvious that although the distancing plan was well intentioned, it is causing him great distress. His family are the driving force in his life, and emotionally he cannot just close down that side of his life, without it leaving a profound gap. Bringing these issues out into the open makes the problem more explicit, even if there may be no easy solution.

A skill in addressing spiritual and emotional issues is to avoid the desire to answer every question or seek to find solutions—some questions and reflections about life have no answer or ready solution. People often need to find their own resolutions over time. Sometimes sharing human frailty and acknowledging uncertainty can be more powerful than providing inappropriate or false answers. Religion may also form a key component of a person's spiritual being, and may be an important element to address for individuals.

Identifying the Last Days of Life

Identifying the dying phase can be difficult. Some respiratory conditions such as lung cancer, fibrotic lung disease and neuromuscular conditions may follow more predictable trajectories. Conditions such as COPD and cystic fibrosis are inherently more difficult as the disease trajectory is characterized by exacerbations and remissions.

Pragmatic criteria for recognizing the last days of life in a patient with respiratory disease include having a known terminal or life-limiting diagnosis and:

- Reaching the end of their anticipated life expectancy having progressively deteriorated with no reversible cause or
- An acute deterioration with no reversible cause or
- The treatment of a potentially reversible cause would be futile or
- Treatment for a potentially reversible cause has failed or
- The patient does not want treatment for a potentially reversible cause.

Where there is doubt about whether deterioration is reversible, active treatment is appropriate but care needs to be taken in the communication with patients and

family members so they are clear about the potential outcomes. Treatment needs to be carefully monitored so that there is a regular review until it is clear whether the patient is likely to survive this episode, or deteriorate and die.

Signs and symptoms that suggest a person may be in the last days of life include [34]:

- Signs such as agitation, Cheyne–Stokes breathing, deterioration in level of consciousness, mottled skin, noisy respiratory secretions and progressive weight loss
- Symptoms such as increasing fatigue, reduced desire for food and fluid and deterioration in swallowing function
- Functional observations such as changes in communication, deteriorating mobility or performance status, or social withdrawal

The decision that a patient is dying can sometimes be incorrect. In a patient who is thought to be dying, an open mind should be kept and decisions reviewed if there is a stabilization or improvement in the patient's condition.

In respiratory conditions, the diagnosis of dying may not be clear. An easier diagnosis may be that the patient is "sick enough to die" allowing both treatments designed to prolong life alongside good symptom control, psychological care and communication of the severity of the situation.

Example: Mrs. Smith has progressive COPD. She has been struggling to manage at home for several weeks and spending much of her day asleep in bed. On previous admissions she has made it clear that she does not like being in hospital and is getting tired of life. She presents unwell in respiratory failure with a further exacerbation.

Mrs. Smith now needs a further discussion about her treatment options, including the option of no treatment. As she feels so unwell with shortness of breath and cough she is keen to try antibiotics and non-invasive ventilation but says that if it is clear that they are not working she would like her symptoms managed in alternative ways. She has always made it clear that she would like to die in her own home. To achieve Mrs. Smith's wishes requires a dual approach of active medical treatment of the exacerbation of her COPD but also acknowledgement that she may die during this episode. A trial of treatment is usually the most appropriate option. If treatment fails, a decision needs to be taken so that if she wants to die at home, this can be achieved.

Failure to recognize the last days of life may lead to the patient and family:

- Being unaware that death is imminent
- Losing trust in the clinical team as the condition clearly deteriorates without any acknowledgement of this
- Getting conflicting messages from the team

- Being more likely to die with uncontrolled symptoms and less likely to be in the place of their choice
- Having inappropriate cardiopulmonary resuscitation at death
- Not having their psychological, cultural and spiritual needs met
- Having complex bereavement problems

When it is clear that a patient is dying, discussion and decisions need to be made about how this process will be managed:

- Where does the patient/family want to be, and what is possible? For those patients who want to be at home, it should be possible to organize care to meet their needs. Others may prefer the safety of an inpatient or care home environment.
- Making clear decisions about escalations of treatment; resuscitation, fluids, antibiotics, stopping routine observations, investigations, etc.
- Addressing symptom, psychological and spiritual needs.
- Communicating with other healthcare professionals to let them know what is happening.

These decisions should be developed in collaboration with the dying person, those important to them and the multi-professional team, developed into an individualized plan.

Place of Care

Figures for where patients would prefer to die in the UK are quoted as being approximately at home 60%, in hospital 15%, in a hospice 15% and in a care home 0%. These figures need to be treated with some caution because most studies in this area have looked at patients who have incurable conditions but prior to them experiencing the dying phase. As patients approach death, their preference for being at home drops significantly and the preference for a hospice-type environment increases to about 40% [35]. Patients with respiratory disease have the highest rate of dying in hospitals (69%) and the lowest rate of dying in their own home (13%) compared to other conditions [36].

Internationally, the data suggests that most people would prefer to die at home [37]. In COPD and interstitial lung diseases, co-morbidities and deprivation independently increase the chances of dying in hospital [38]. There is now a drive to improve end of life care services in the community. This should not be at the expense of end of life services in hospital where a large proportion of patients will continue to die. In most areas there are teams based in the community to deliver care at the end of life, and to facilitate rapid transfer of patients from hospital to their home when dying. The earlier this is planned, the less the likelihood of delays due to issues such as waiting for oxygen or equipment.

Keeping people at home depends on:

- Having services/equipment in place.
- Making clear clinical decisions: What could go wrong? What problems could lead to a hospital admission? How would we manage deteriorations? What is the escalation or ceiling of treatment?
- Appropriately skilled healthcare professionals who can assess and manage unexpected situations 24 h a day.

Keeping people at home requires patients and families to feel secure there, physically and emotionally. This can be achieved through access to skilled and competent help at any hour of the day or night [39].

For other patients, either their clinical situation or preference leads to an inpatient admission, either to a palliative care setting or to a hospital ward. Many respiratory patients have long-standing relationships with their specialist care teams and may want their end of life care to be delivered on a respiratory ward. Ensuring that there are appropriate facilities for dying patients and their families continues to be an important aspect of hospital care.

Clinical Decision-Making

When a patient is dying problems should be anticipated and planned for in accordance with the patient's wishes. As well as anticipating symptoms, healthcare professionals should anticipate acute changes. Patients who are actively dying may experience a "cardiopulmonary arrest" as a normal part of dying. Attempts at cardiopulmonary resuscitation are unlikely to be successful, but likely to be started if an active "Do Not Attempt Resuscitation" order has not been made. Plans should be made to deal with possible problems such as infection, bleeding, falls or acute symptoms. Although the goals of management are comfort care, often the most effective way of dealing with symptoms is to address the underlying cause. Where more burdensome treatments are used, their effectiveness should be closely monitored and the treatment withdrawn if it is not effective. Involving the patient in decision-making is crucial. Certain treatments such as intravenous antibiotics, being for active resuscitation and consideration of ventilation (even if limited to non-invasive ventilation) are likely to require a hospital admission. For patients who wish to stay at home, an active decision needs to be taken about withholding these treatments, and managing the problem in a different way.

Physical Care

Careful attention to personal care and any nursing needs is essential. Routine observations and investigations should stop unless they will support or change the plan of care. Active assessment and management of symptoms and care issues need to continue. This includes assessing the cause of any symptoms.

When a patient is dying, swallowing and absorption of drugs become problematic. Drugs are given parenterally, usually subcutaneously for comfort (or intravenously if people have long-term intravenous access that is being used). Medication is given on an as-required basis, unless the patient is already taking the medication regularly. If a patient requires a drug more than once a day or has been on a regular oral dose, the drug should usually be prescribed on a regular basis using a continuous syringe driver.

Current medications should be reviewed to see whether they are clinically appropriate in the last days of life. There may be specific drugs used for respiratory conditions, such as oxygen or nebulized bronchodilators that continue to provide symptom relief. In addition, there needs to be anticipation of potential problems that may arise. All new issues should be assessed and managed, reversing problems where appropriate (for example a catheter for urinary retention rather than a painkiller). Management of key problems tends to rely more on medication as people become less able to manage non-pharmacological treatments. Common symptoms in the last days of life include the following:

Pain

- Morphine and diamorphine are usually the most appropriate strong opioids to manage most pains at this stage.
- Patients who have not previously had pain often get pain in the last days of life from musculoskeletal causes. Other analgesic options include rectal paracetamol, and rectal or injectable non-steroidal anti-inflammatory drugs.

Breathlessness

- Treat any reversible issues such as pulmonary oedema. Use simple measures such as a fan to increase airflow.
- Strong opioids such as morphine or diamorphine reduce the perception of breathlessness.
- Benzodiazepines such as midazolam relieve anxiety associated with breathlessness.

Agitation and Delirium

- Agitation is common and can be associated with confusion. Causes are multifactorial, including biochemical abnormalities, infection and hypoxia. Treat any reversible causes.
- Benzodiazepines such as midazolam and antipsychotics such as haloperidol or levomepromazine can be helpful, as well as maintaining a calm environment and reassurance.

Nausea

- The same problems that lead to agitation often lead to a chemical nausea.
- Cyclizine, haloperidol or levomepromazine are commonly used.

Respiratory Secretion "Death Rattle"

- These build up when a patient is no longer able to clear normal respiratory tract secretions.
- The noise produced can be distressing to relatives although patients are not usually affected. Sometimes an explanation and reassurance are enough.
- Positioning of the patient in a semi-prone state allows postural drainage.
- Anticholinergic drugs such as hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium are used to reduce secretions.

The Appendix, at the end of the book, contains recommended starting doses of common drugs used at the end of life, and conversions of commonly used opioids to parenteral preparations. These drugs need to be titrated according to effect. Please note that these are guidelines and advice should be taken for individual patients.

Other key components of physical care include bladder and bowel care, reviewing nutrition and hydration, mouth care, and skin and hygiene needs.

Nutrition and Hydration

Loss of interest in food and drink and a reduction in the need for food and fluids are features of somebody who is naturally dying. Patients should be supported to eat and drink naturally for as long as they are able to and wish to. Artificial fluids may be beneficial if a patient is experiencing uncontrolled thirst, or symptoms due to dehydration. However thirst can be due to other causes and therefore effectively managed in other ways—good mouth care (keeping the mouth clean, moist and free of infections such as thrush; adjusting the temperature of the room; and avoiding situations which exacerbate thirst such as high blood glucose levels). Clinically assisted nutrition, such as nasogastric tube feeding, may be indicated for those who are experiencing uncontrolled hunger but this is very rare in dying patients. In the last days of life, the goal of any treatment is comfort. Giving too much fluid or nutrition may induce symptoms as the body struggles to cope with large volumes. Vomiting and bowel disturbances or fluid retention and excess respiratory secretions can be problems in these patients.

Families and healthcare professionals may be concerned that the patient is dying because of lack of hydration or nutrition, rather than the underlying disease process. It is important to establish that patients are dying from an underlying disease, and that eating and drinking less is a symptom of this process, rather than the cause. Care should be particularly taken where the patient appears to stabilize or improve,

or where the process of actively dying takes longer than expected. If there is doubt, decision-making should err towards preserving life and considering the use of fluids and nutrition. A second opinion may be helpful if there is disagreement over these decisions.

Psychological and Spiritual Care

Crucial to exploring these areas is making sure that a patient's language and communication abilities have been maximized. This may need the addition of equipment or a translator. Exploring patients' understanding, their concerns, hopes, coping strategies, fears, feelings, beliefs and values is crucial to good end-of-life care. Often unresolved, apparent physical symptoms are due to non-physical problems that have not been addressed. Most issues can be dealt with by the clinical team trusted by the patient. There may be times when specialist input from psychology, chaplaincy or palliative care is indicated, but for most patients being listened to by a person they trust is the key. The importance of simply being there, rather than always needing to do something, should not be underestimated. Patients appreciate not being abandoned, even if the healthcare professional does not always feel they are achieving something.

Exactly the same issues face families and informal carers. Care needs to be taken to ensure that consent has been given by the patient to talk about health details. However caring for those around the dying patient becomes increasingly the goal of end-of-life care as death approaches.

Communication

The emotional and communication needs of patients and families increase as patients approach the end of their life. The quality of care and symptom burden that patients face will have a marked impact on the experience relatives have, and their subsequent bereavement. At the very end of life communication needs can evolve rapidly. Clinical teams need to adapt quickly and to offer regular opportunities to discuss issues, but in a way that is subtle and avoids being intrusive. Family members require communication to be as clear and unambiguous as possible. In addition they need to be able to access healthcare professionals readily, especially if they are at home. Communication between clinical teams is essential so that care is coordinated.

Care After Death

As well as ensuring that the patient's care before death is well planned and appropriate, it is also important to ensure that this continues after the patient's death. There may be discussions that can be had prior to the patient's death so that both the patient and their family know what to expect.

Verification of Death

The death of the patient needs to be verified by someone qualified to do this. Traditionally this was a doctor, but in the UK this role has now been extended to nurses (with suitable training). The person verifying the death need not have met the patient when they were alive.

Certification

In the UK, a death certificate must be issued before the death can be registered and funeral proceedings commence. This needs to be issued by a doctor who has previously met the patient and seen them alive within the last 2 weeks. If a patient dies at home this may pose difficulties. If the general practice team knows that the patient is dying and has been notified by the hospital that the patient is being transferred home for end of life care, they are able to visit that patient, to attend to the patient's needs, but also to ensure that a death certificate could be provided without undue complication. If a patient dies without being seen by a doctor in the preceding 2 weeks, in England their case must be discussed with the coroner.

Post-mortem Examinations and Coroner Referrals

If a patient dies of a possible occupationally acquired illness the death must be referred to the coroner and a post-mortem is likely to be undertaken. In other situations a hospital post-mortem may provide useful information. It is helpful to make families aware of these issues as early as possible, before death if appropriate.

Practical Tasks

After a patient dies there are many practical tasks for the family to remember to do. The death certificate must be obtained and the death registered. The funeral must be organized—often patients who know that they are dying have specified some wishes that they want to incorporate into the funeral. Health- and social-care professionals involved in the patient's care must be notified and any equipment in the house returned. UK agencies such as the Department for Work and Pensions must be notified so that pensions and benefits are appropriately dealt with. Because there is so much to remember at such a difficult time in life, booklets are available to guide the family through the process, for example: "What to do after a death in England and Wales" [40].

Bereavement

Grief is natural and to be expected in bereavement. It may present in different ways. Some people feel numb, shocked and unable to function normally. Others need to

carry on with normal activities to try to maintain a structure to their life. There is no right or wrong way to experience grief, and it should be recognized as an individual process.

When a patient has a life-limiting illness the bereavement process may start prior to their death as the family start thinking about the future. They may wish to plan things to help future memories and the grieving process, and this should be encouraged. This may include activities, seeing loved ones or developing memory boxes. Memory boxes are a way for the patient to collect memories to pass to another member of the family, for example cards or items of special personal importance.

Grief persists for a long time after the patient dies and should not be expected to resolve quickly. Factors that influence the grief reaction include circumstances leading up to the patient's death, meaning of the relationship with the deceased, personal vulnerability and availability of social support [41]. Most individuals are resilient and can cope with bereavement without professional intervention. Evidence suggests that bereavement counselling only makes a difference to those with high levels of vulnerability and may be harmful to those who are resilient [42]. UK guidelines describe a three-tier approach to bereavement [43].

1. Most people manage without professional intervention, but may require information about the bereavement process.
2. Some people may require a formal mechanism to explore their experience. This can be done without involving professionals, for example with self-help groups, volunteer befrienders and community groups.
3. Some people, including children and young people, will require specialist intervention. In different areas, this may come from psychology, mental health or palliative care services.

Role of the Palliative Care Team

In many situations, the palliative care needs of patients with lung disease can be met by their primary care and respiratory teams. If teams are struggling to control a patient's symptoms and need help with psychological care, communication, difficult social situations or decision-making, the palliative care team can provide help and support. This may be in the form of advice or direct assessment. A referral to palliative care services is based on need, not on diagnosis or prognosis.

Whether a patient is in hospital or at home, there will be a hospital, community or integrated palliative care team available for advice or to assess a patient. This team has nurse specialists, consultants and often social workers, physiotherapists and occupation therapists, often available at any hour of the day or night. They have access to inpatient palliative care where more intensive palliative care or end-of-life care is required. Inpatient facilities come in the form of hospices or palliative care units within hospitals. Most can admit patients at any time of the day or night for emergencies. Day hospices play an important role for respiratory patients. In these settings, patients can attend a day service once a week with a group of other patients

to receive symptom management, psychological care, specific interventions, rehabilitation and peer support.

Final Thoughts

Managing the final stages of an illness requires active decision-making and compassionate communication. Addressing physical, psychological, social and spiritual issues greatly enhances a person's quality of life and this in turn impacts the bereavement of their families. Most end-of-life care is delivered within families and communities, sometimes at home or in hospital. Specific palliative care services have an important role to play where the situation becomes more complex. Good end-of-life care is less about dying, and more about helping people to live as well as possible until they die. Rather than focusing on the endpoint, it should focus on the path to get there. Sometimes by acknowledging and affirming patients' greatest fears and hopes, we can liberate individuals to cope and even flourish towards the end of their life.

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Appendix: Respiratory Palliative Formulary

Abbreviations

CSCI Continuous subcutaneous infusion by syringe driver over 24 h
IR Immediate release (suspension, capsules, or tablets)
MR Modified release (tablets, capsules, or granules)

Pain

Opioid Analgesic Conversion Tables

In all opioid conversions the convention is to describe the existing daily dose in terms of "24-hourly oral morphine equivalent" and then calculate the appropriate dose of the new drug from the conversions below (Tables A.1, A.2, and A.3).

Table A.1 Oral–oral or transdermal

	Potency ratio with morphine	Dose equivalence to 30 mg morphine
Codeine	1/10	300 mg Codeine
Dihydrocodeine	1/10	300 mg Dihydrocodeine
Tramadol	1/10	300 mg Tramadol
Oxycodone	1.5	20 mg Oxycodone
Hydromorphone	5	6 mg Hydromorphone
Fentanyl (transdermal)	100	0.3 mg (i.e., 300 μg) fentanyl in 24 h (12 μg/h)

Table A.2 Oral–subcutaneous

Oral	Divide by	Subcutaneous
Morphine (60 mg)	2	Morphine (30 mg)
Morphine (60 mg)	3	Diamorphine (20 mg)
Oxycodone (40 mg)	2	Oxycodone (20 mg)
Morphine (60 mg)	3	Oxycodone (20 mg)

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Table A.3 Subcutaneous–subcutaneous

Subcutaneous	Divide by	Subcutaneous
Morphine (30 mg)	1.5	Oxycodone (20 mg)
Morphine (30 mg)	1.5	Diamorphine (20 mg)

Gabapentin Dosing

	Cautious	Usual
Day 1	100 mg at night	300 mg at night
Day 2	100 mg twice daily	300 mg twice daily
Day 3	100 mg three times daily	300 mg three times daily

Then titrate up at similar increments to maximum 900 mg three times daily, depending on symptoms and side effects

Cough and Secretions

Cough Enhancement

- Nebulized saline 0.9% 5 mL four times daily
- Nebulized DNase 2500 units (2.5 mg) once to twice daily (cystic fibrosis only)
- Carbocisteine (capsules or suspension) 750 mg three times daily, orally

Central Cough Suppressants

- Codeine linctus 15 mg (5 mL) four times daily (opioid naïve), orally
- Morphine IR suspension 2.5–5 mg 4 hourly, orally
- Methadone linctus 2 mg (5 mL) 12 hourly
- Equivalent pain rescue dose if already on strong opioid for pain
- Gabapentin 100 mg at night, titrated incrementally to maximum 900 mg twice daily

Peripheral Cough Suppressants

Simple linctus 5 mL four times daily.

Removal of Secretions

- Hyoscine hydrobromide patch: 1 mg transdermal 72 hourly
- Glycopyrronium: 200 μg orally, up to three times daily, titrated up every 2–3 days to 1 mg three times daily if needed

Hemoptysis

Tranexamic Acid

- 1–1.5 g three times daily, orally or
- 500 mg–1 g slow intravenous injection (over 5–10 min) three times daily or
- 25–50 mg/kg by intravenous infusion over 24 h

Breathlessness

Opioids

Opioid Naïve

- Codeine phosphate 15 mg 6 hourly as required
- Morphine IR susp 1–2.5 mg 4 hourly as required
- Morphine MR tabs 5 mg twice daily

On Opioids Already

- Usual IR rescue dose 4 hourly as required
- *End of life*: morphine sulfate 2.5 mg subcutaneously hourly as necessary. Commence CSCI if two or more doses needed in 24 h

Benzodiazepines

1. Dyspnea associated with panic, requiring rapid palliation: lorazepam 500 μg sublingually 6 hourly as required
2. End-of-life respiratory palliation: midazolam 5 mg/24 h CSCI titrated upwards as necessary

End of Life (Prescribing)

For all of the end-of-life symptoms, as-required dosing only is recommended, initially, if not already on the drug regularly. If two or more rescue doses are needed in 24 h, then commence CSCI as below.

Pain

If *already on opioids*: Convert 24-h oral morphine equivalent to appropriate dose given over 24 h by continuous subcutaneous infusion (CSCI). Rescue dose = 1/10–1/6 CSCI dose hourly as required.

Escalate dose if two or more rescue doses in 24 h (by 1/3–1/2).

Opioid naïve: Start with morphine sulfate 2.5 mg or diamorphine 2.5 mg hourly as required. Commence CSCI: 10 mg/24 h if two or more rescue doses in 24 h.

Agitation

	CSCI: 24 hourly	Rescue
Haloperidol	1–3 mg (starting)	1.5 mg
Midazolam	5–10 mg (starting)	2.5–5 mg
Levomepromazine	50 mg	12.5–25 mg

Nausea and Vomiting

If already on an antiemetic, then convert to CSCI at the same total oral dose.
Otherwise:

- Cyclizine 50 mg subcutaneously 6 hourly as necessary, max 150 mg in 24 h, or
- Haloperidol 1.5 mg subcutaneously 6 hourly as necessary, max three doses, or
- Levomepromazine 6.25 mg subcutaneously 6 hourly as necessary.

Death Rattle

	CSCI (24 hourly)	Rescue
Hyoscine hydrobromide	1.2–2.4 mg	400 μg
Hyoscine butylbromide	60–120 mg	20 mg
Glycopyrronium	600 μg–1.2 mg	200 μg

Licensed Drugs Prescribed in an Unlicensed (Off-Label) Way in Palliative Care

Drug	Off-label use
Alfentanil	Subcutaneous
Amitriptyline	Neuropathic pain Bladder spasm
Baclofen	Hiccup
Carbamazepine	Neuropathic pain
Clonazepam	Neuropathic pain Restless leg syndrome Terminal restlessness
Dexamethasone	Appetite stimulant Bowel obstruction Dyspnea Nausea and vomiting Bone and nerve compression pain Spinal cord compression

Drug	Off-label use
Diamorphine	Painful skin lesions—topical Dyspnea
Erythromycin	Pro-kinetic agent
Etamsylate	Prophylaxis and control of hemorrhages from small blood vessels
Fentanyl	Subcutaneous
Fluoxetine	Anxiety
Gabapentin	Malignant bone pain Restless leg syndrome
Glyceryl trinitrate spray	Smooth muscle spasm pain
Glycopyrronium	Hypersalivation Nausea and vomiting associated with bowel obstruction Smooth muscle spasm Sweating associated with cancer Terminal secretions Unlicensed subcutaneously
Granisetron	Nausea and vomiting—drug induced and cancer related, refractory Unlicensed subcutaneously
Haloperidol	Delirium Nausea and vomiting Unlicensed subcutaneously
Hyoscine butylbromide	Nausea and vomiting associated with bowel obstruction Smooth muscle spasm—colic Sweating Terminal secretions Unlicensed subcutaneously
Hyoscine hydrobromide	Hypersalivation Smooth muscle spasm—colic Sweating Terminal secretions
Ketamine	Refractory chronic pain Unlicensed subcutaneously Unlicensed orally Incident pain
Ketorolac	Short-term management of cancer pain Unlicensed subcutaneously
Levomepromazine	Unlicensed indications Psychosis (by injection) Nausea and vomiting (tablets)
Lidocaine patch	Post-thoracotomy pain Post-mastectomy pain Localized neuropathic and muscular pain
Loperamide	Bowel colic Reduction of stoma output (topically on mouth ulcers)
Lorazepam	Dyspnea Unlicensed sublingually
Medroxyprogesterone	Anorexia and cachexia
Methylphenidate	Cancer-related fatigue Depression

(continued)

Drug	Off-label use
Midazolam	Dyspnea Epilepsy Hiccup Major hemorrhage Myoclonus Status epilepticus Terminal agitation or anxiety Unlicensed subcutaneously
Mirtazapine	Appetite Nausea and vomiting Pruritus
Morphine	Painful skin lesions—topical Mucositis—topical Cough Dyspnea
Nifedipine	Smooth muscle spasm pain Intractable hiccup
Olanzapine	Nausea and vomiting Delirium Terminal agitation (refractory to conventional treatment)
Ondansetron	Nausea and vomiting Pruritus(opioid induced, cholestatic, uremic) Unlicensed subcutaneously
Oxycodone	Dyspnea
Phenobarbital	Terminal agitation (in patients not controlled conventionally) Unlicensed subcutaneously
Pregabalin	Malignant bone pain, sleep improvement
Risperidone	Delirium, antiemetic (refractory nausea and vomiting) Major depression
Sodium valproate	Unlicensed subcutaneously
Sucralfate	Surface bleeding
Tranexamic acid	Prophylaxis and control of hemorrhage from small blood vessels Bleeding from wounds (topical)
Zoledronic acid	Bone pain

Unlicensed Drugs in Palliative Care

Cyclizine	Unlicensed—suppositories available
Gabapentin	Unlicensed liquid available
Glycopyrronium	Unlicensed tablets available
Hydromorphone	Unlicensed—injection
Ketorolac	Unlicensed liquid available
Levomepromazine	6 mg tablet—unlicensed
Midazolam	Epistat—unlicensed buccal liquid

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