

17.5 Acute respiratory failure 3867 Susannah Leave

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ESSENTIALS Acute respiratory failure Acute respiratory failure is defined clinically by hypoxaemia ($P_{aO_2} < 8$ kPa, normal range 10–13.3 kPa) with (type 2) or without (type 1) hypercapnia ($P_{aCO_2} > 6.5$ kPa). It is one of the most common problems afflicting critically ill patients and is a common indication for transfer to an intensive care unit. Clinical context—critical illness may be manifest solely as respiratory insufficiency, especially in patients with covert infection. Acute respiratory failure frequently coexists with other organ system failures in the critically ill, and delayed recognition of the condition adversely affects outcome. Clinical features—the signs of critical illness tend to be similar whatever the precipitating cause and are manifest in failure of the respiratory, cardiovascular, and neurological systems. The airway, breathing, circulation, disability, and exposure approach to clinical assessment is advocated. Respiratory rate should normally be 12–20 breaths per minute: a higher or increasing rate is a ‘hard’ sign of critical illness. Full and repeated physical examination may be required to assess the cause and severity of acute respiratory failure and its associated complications, but in severe cases should not delay the instigation of life-saving support and treatment. Investigation—pulse oximetry allows the continuous noninvasive monitoring of arterial oxygen saturation and is useful in all clinical settings. Arterial blood gas analysis confirms the type and severity of acute respiratory failure, and may reveal nonpulmonary organ dysfunction. A full range of imaging modalities, including computed tomography and

echocardiography, may be required for diagnosis. Management—the main steps in treating acute respiratory failure are: (1) Establishing and securing the airway often necessitating (i) endotracheal intubation—the decision to intubate is based on several factors including: (a) inability to maintain the airway, (b) deteriorating physiological parameters despite adequate therapy and often noninvasive respiratory support, (c) reversibility of the underlying condition; (ii) tracheostomy—this may be indicated early in the course of acute respiratory failure in patients likely to require prolonged ventilatory support. (2) Increasing Fio_2 to treat hypoxaemia—oxygen can be administered by a variety of methods depending on the required oxygen concentration. (3) Instituting mechanical ventilation (invasive or noninvasive) as necessary to treat hypoxaemia and hypercapnia—noninvasive positive pressure ventilation involves the delivery of mechanically generated breaths via an interface with the upper airway; usually a tight-fitting nasal or full face mask. In patients receiving mechanical ventilation, the optimum mode depends in part upon the nature of the underlying illness, particularly the presence or absence of pulmonary parenchymal or airway pathology, the phase of the illness (acute or chronic), and the aims of support at the time it is applied. (4) Identifying and managing the precipitating condition. (5) Discontinuing and withdrawing support in stages ('weaning') as the underlying condition improves, or if recovery is no longer deemed possible.

Acute respiratory distress syndrome Acute respiratory distress syndrome results from acute neutrophilic inflammation causing dysfunction of the gas exchange surface of the lung, the alveolar-capillary membrane. Precipitating factors, which may be single or combined, can either primarily affect the lung directly (e.g. pneumonia, aspiration of gastric contents, chest trauma) or act through the circulation, often causing acute respiratory distress syndrome as part of a multiple organ dysfunction syndrome (e.g. severe sepsis and shock). Histological phases have been observed, but these usually overlap and can all coexist simultaneously. The initial phase is characterized by high-permeability pulmonary oedema in which the airspace is filled with proteinaceous neutrophilic exudate. During the subsequent fibroproliferative response, inflammation resolves, and repair and regeneration processes predominate.

Diagnosis—this requires: (1) An appropriate clinical setting, with one or more recognized risk factors. (2) New, bilateral, diffuse, patchy, or homogenous pulmonary infiltrates consistent with pulmonary oedema on chest radiography. (3) No clinical evidence of heart failure, fluid overload, or chronic lung disease.

17.5 Acute respiratory failure Susannah Leaver, Jeremy Cordingley, Simon Finney, and Mark Griffiths

Section 17 Critical care medicine 3868 (4) $\text{Pao}_2\text{:Fio}_2$ ratio of less than 40 kPa (<300 mm Hg) for mild cases, less than 26.6 kPa (<200 mm Hg) for moderate cases, and less than 13.3 kPa (100 mm Hg) for severe cases in the presence of a positive airway pressure of at least 5 cmH₂O.

Investigations—these are aimed at estimating the severity of lung injury and elucidating the precipitating cause. Computed tomography, if practical, may be useful in guiding therapy and detecting complications.

Management and prognosis—aside from other standard supportive measures, low tidal volume ('protective') ventilation, and for patients with severe ARDS managed in experienced centres, managing in prone position for 16 hours each day, has been shown to improve outcome. Overall mortality of patients with acute respiratory distress syndrome is in the range 25–40%, but higher in some subgroups (e.g. sepsis) than others (e.g. trauma). Survivors of acute respiratory distress syndrome may have persistent nonpulmonary functional disability and require long-term follow-up and support.

Acute respiratory failure Definition and epidemiology Respiratory failure is defined by reduced arterial oxygen tension (Pao_2), with or without elevated levels of carbon dioxide (Paco_2), and is one of the most common indications for intensive care unit

(ICU) admission. Traditionally, it has been classified according to rapidity of onset (acute and chronic), and into hypoxaemic and hypoxaemic/hypercapnic subtypes. Chronic respiratory failure is discussed in Chapter 18.15. Type 1 (hypoxic or acute hypoxaemic) is defined by hypoxaemia ($P_{aO_2} < 8$ kPa, normal range 10–13.3 kPa) with a normal or low P_{aCO_2} (normal range 4.8–6.1 kPa). It is attributable to a loss of functioning gas exchange surface and impaired hypoxic pulmonary vasoconstriction in which alveoli are perfused but not ventilated; extrapulmonary shunt may also occur (e.g. in patients with cyanotic heart disease). The less common type 2 (ventilatory or hypercapnic) respiratory failure is characterized by hypercarbia ($P_{aCO_2} > 6.5$ kPa) associated with hypoxaemia ($P_{aO_2} < 8$ kPa). While more severe forms of the same conditions that cause type 1 failure are often responsible, type 2 failure can also be caused by conditions that increase anatomical or physiological dead space or reduce minute ventilation by impairing respiratory drive or respiratory pump function. Common causes of acute respiratory failure are shown in Table 17.5.1. In practice, patients may progress from type 1 to type 2 respiratory failure as the precipitating condition evolves. Moreover, either type of respiratory failure may complicate a wide variety of pathologies. The incidence, prevalence, and attributable mortality is therefore difficult to determine, particularly as acute respiratory failure often coexists with other organ system failures in the critically ill. Nevertheless, recent studies suggest an incidence in the order of 77.6–88.6 cases per 100 000 population per year, with an associated mortality rate of approximately 40%.

Table 17.5.1 Causes of acute respiratory failure

Type of cause	Type 1 acute respiratory failure	Type 2 acute respiratory failure
Acute conditions	Pneumonia Acute asthma Pulmonary oedema Acute lung injury/acute respiratory distress syndrome Pneumothorax Lobar collapse Pulmonary contusion (blunt chest trauma) Aspiration Pleural effusion Acute severe asthma Depression of respiratory drive (e.g. drug overdose with narcotic drugs) Upper airway obstruction (e.g. foreign body)	Chronic lung diseases Chronic obstructive pulmonary disease Pulmonary fibrosis Interstitial lung disease Lymphangitis carcinomatosis Pneumoconiosis Bronchiectasis Granulomatous lung diseases Chronic obstructive pulmonary disease Pulmonary vascular diseases Pulmonary embolism Right-left shunts Pulmonary arterial hypertension Fat embolism Neuromuscular diseases Intensive care unit acquired weakness Myasthenia gravis Polyneuropathy Poliomyelitis Acute neuropathies (e.g. Guillain-Barré) Primary muscle disorders (e.g. muscular dystrophy) Primary alveolar hypoventilation Obesity hypoventilation syndrome Brainstem and cervical cord injury Skeletal disorders Chest wall deformities (e.g. kyphoscoliosis, ankylosing spondylitis) Flail chest injury Other Exhaustion from any cause of type 1 respiratory failure

17.5 Acute respiratory failure 3869 While mortality rates for acute respiratory failure alone are probably lower than this, death rates increase with each additional organ failure. Clinical approach History and examination Acute respiratory failure can be caused by extrapulmonary as well as pulmonary conditions. Clinical evaluation must therefore not be restricted to the respiratory system. Early identification of patients requiring organ support is essential, as delayed intervention adversely affects outcome. Clinical assessment aims to identify the cause of respiratory failure, as well as to categorize its severity. Critically ill patients require a flexible approach to clinical assessment. A full history may not be available from the patient. Intervention or resuscitation and crucial investigations (chest radiograph and arterial blood gases) may be required immediately. The airway, breathing, circulation, disability, and exposure (ABCDE) approach incorporated into the Resuscitation Council (UK) Guidelines is advocated. Finally, other issues that

have to be considered immediately include transfer to areas of the hospital where more intensive monitoring is available (usually the intensive care unit), and calling for help from more experienced colleagues. The signs of critical illness tend to be similar whatever the precipitating cause and are manifest in failure of the respiratory, cardiovascular, renal, and neurological systems. Abnormal physiological signs are frequently encountered in patients cared for in general wards, but their charting and recognition are often inadequate. Medical early warning scoring systems, rapid response teams (see Chapter 17.1), and critical care outreach teams have been developed to address this deficiency. Alternatively, critical illness may be manifest solely as respiratory insufficiency. In these circumstances, the history should help to elicit the cause of the clinical deterioration. Thus, central chest pain and breathlessness in a patient with known cardiac disease is suggestive of pulmonary oedema; a history of underlying chronic respiratory insufficiency such as chronic obstructive pulmonary disease (COPD) or asthma, with worsening breathlessness and wheeze, suggests an acute exacerbation of these conditions; and respiratory distress in patients with sepsis, trauma, multiple blood transfusions, or pancreatitis may be caused by incipient acute respiratory distress syndrome (ARDS). Respiratory symptoms may also be a nonspecific indication of increased respiratory demand from a nonpulmonary source, for example, metabolic acidosis associated with diabetic ketoacidosis, poisoning, or acute renal failure. Clinical examination should quantify the signs of respiratory distress (Table 17.5.2). The respiratory rate should normally be 12–20 breaths per minute, and a higher or increasing rate is a ‘hard’ sign of critical illness and a warning that the patient may deteriorate suddenly. The depth of each breath should be assessed, and whether chest expansion is bilateral and symmetrical. Reduced expansion and breath sounds with tracheal shift to the contralateral side are indicative of tension pneumothorax, and the presence of bronchial breathing of pneumonia. An inability to lie flat with pink frothy sputum and bilateral crackles is suggestive of cardiogenic pulmonary oedema. However, clinical examination may be unhelpful and clinical signs absent in conditions such as pulmonary thromboembolism or early acute respiratory distress syndrome. Clinical investigations

Arterial blood gas analysis Arterial blood gas (ABG) analysis confirms the type and severity of acute respiratory failure, but always remember that for interpretation of PaO_2 it is crucial to record the inspired oxygen concentration at the time of sampling and the mode of respiratory support (see Box 17.5.1). ABGs often need to be repeated and the associated pain may warrant insertion of an indwelling arterial catheter. Oximetry, an invaluable aid to monitoring (see next), may be used to minimize the number of arterial punctures required by determining the concentration of inspired oxygen that corresponds to the desired oxygen saturation. Note the oxygen content of blood is primarily determined by the haemoglobin concentration and oxygen saturation rather than SpO_2 . Blood gas analysers provide additional information concerning electrolyte, lactate, and haemoglobin levels. These and other standard haematological and biochemical indices can provide diagnostic information (Table 17.5.3).

Table 17.5.2 Signs of respiratory distress and hypercapnia

General clinical signs of respiratory distress

Indicators of hypercapnia

Respiratory rate $>25/\text{min}$ or $<8/\text{min}$

Bounding pulse

Tachycardia/ bradycardia/ arrhythmia

Warm peripheries

Inability to speak in full sentences

Carbon dioxide retention flap (asterixis)

Cyanosis

Somnolence/lethargy/confusion

Sweating

Decreased consciousness

Obstructed airway/stridor

Headache

Use of accessory muscles of respiration

Intercostal recession

Pulsus paradoxus

Restlessness/agitation

Asynchronous respiration

Inability to lie flat

Paradoxical respiration

Box 17.5.1 Interpretation of arterial blood gases in acute respiratory failure

Steps in interpreting arterial blood gas results:

- 1 Confirm presence of respiratory failure: is PaO_2 less than 8 kPa on room air?
- 2 What is the Paco_2 ? Does the patient have type 1 or type 2 respiratory failure?
- 3 Is the A-a Po_2 gradient high (normal range depends on age, usually <3.5 kPa

(26 mm Hg))? 4 A normal/low A-a gradient suggests that hypoxaemia is due to hypoventilation? 5 A high A-a gradient suggests that hypoxaemia is secondary to ventilation:perfusion (V/Q) mismatch 6 If hypoxia does not correct with oxygen, respiratory failure is due to V/Q mismatch (alveolar perfusion without ventilation). A-a gradient ($PAO_2 - PaO_2$), alveolar-arterial gradient; PAO_2 , alveolar partial pressure of oxygen, obtained from the alveolar gas equation (see Chapter 18.3.1); $Paco_2$, partial pressure of carbon dioxide in arterial blood; PaO_2 , partial pressure of oxygen in arterial blood, obtained from arterial blood gases; V/Q, ventilation/perfusion.

Section 17 Critical care medicine 3870 Screening for infection A full infection screen should be dispatched immediately. This should include samples for blood, sputum, and urine culture, especially if signs of sepsis, or septic shock are present. Ideally samples should be obtained prior to administration of antimicrobial agents, provided this does not delay treatment. Requests for typical and atypical (e.g. viral, legionella, mycoplasma) organisms should be made if clinically appropriate. In patients with pneumonia, urine should be tested for pneumococcal and legionella antigens. Depending upon the immune status of the patient and the presence of underlying pathologies (e.g. malignancy, immunosuppression), evidence of tuberculous and fungal infections should be sought.

Chest radiograph A chest radiograph is an essential investigation in any patient with acute respiratory failure, and not infrequently reveals the cause. Chest radiography is also mandatory following re/placement of central venous catheters, endotracheal tubes, nasogastric tubes, and pleural drains, both to confirm correct positioning and to exclude complications.

Ultrasonography If a pleural collection is suspected clinically or following plain chest radiography, then a diagnostic or therapeutic tap can be performed under ultrasonic guidance and the fluid sent for Gram stain, culture, cytology, pH, and leukocyte count. Removal of moderate quantities of pleural fluid may improve ventilation, perfusion (V/Q) mismatch, oxygenation, and pulmonary compliance.

Computed tomography (CT) Thoracic CT, especially high resolution and contrast-enhanced, can reveal pathologies not detected by a plain chest radiograph, such as pulmonary embolus, abscess cavity, parenchymal infiltrates, or pleural effusions. Transporting critically ill patients to and from the CT scanner is not without risk, but has been shown to identify at least one new significant finding resulting in a change in management in up to 30% of patients.

Nonpulmonary causes of acute respiratory failure may also be revealed by CT examination of extrapulmonary sites.

Electrocardiography and echocardiography An electrocardiogram (ECG) is necessary to identify arrhythmias and reveal evidence of cardiac ischaemia. Echocardiography is the investigation of choice for the bedside diagnosing of acute massive pulmonary embolism (PE). The presence of right ventricular dilatation and haemodynamic instability are indications for thrombolysis (Chapter 16.16.1). It is also helpful in differentiating between cardiac and high-permeability pulmonary oedema in cases of suspected ARDS.

Fibreoptic bronchoscopy Fibreoptic bronchoscopy with directed bronchoalveolar lavage is useful for obtaining samples for microbiological and cytological examination. It may be indicated therapeutically for the alleviation of endobronchial obstruction, or for localizing sources of bleeding or sites of trauma. However, bronchoscopy should only be performed once the patient is stabilized and the airway secured, the only exception being when a bronchoscope is required to aid difficult endotracheal intubation.

Respiratory monitoring

Arterial oxygen saturation (Sao_2)/pulse oximetry A pulse oximeter allows the continuous noninvasive monitoring of arterial oxygen saturation by spectrophotometric analysis of the relative proportions of oxygenated and deoxygenated haemoglobin. This is useful in all clinical settings, during transfers, and in the ICU, reducing the need for regular ABG analysis. Oxygenation is usually regarded as acceptable if the Sao_2 is above 90%. A sudden drop in arterial

oxygen saturation should prompt an immediate and full re-evaluation of the patient. However, it should be remembered that pulse oximetry is unreliable in several circumstances, especially if there is poor peripheral perfusion, nail polish has been applied, or if there is excessive movement or high ambient light. It does not measure arterial carbon dioxide levels and cannot be used in patients with a variety of (rare) conditions, including carbon monoxide poisoning and methaemoglobinemia. Indwelling arterial catheter Insertion of an arterial line not only provides invasive blood pressure monitoring, but permits repeated ABG analysis. Estimation of lung function In mechanically ventilated patients the efficiency of gas exchange can be quantified by the alveolar-arterial (A-a) P_{O_2} gradient or the P_{aO_2} /fractional inspired oxygen concentration (F_{IO_2}) ratio. Most machines used to apply ventilatory support via an endotracheal tube provide breath quantification of tidal volume, respiratory rate, minute volume (the product of tidal volume and respiratory rate), airway pressure, and compliance. The latter is an index of the pressure-volume relationship of the respiratory system (elasticity) and is high when the lungs are distensible (e.g. in emphysema) and Table 17.5.3 Blood tests used in the assessment of patients with acute respiratory failure Investigation Utility Full blood count Anaemia contributes to tissue hypoxia; polycythemia is indicative of chronic hypoxemia. May suggest acute infection. Coagulation screen Altered in disseminated intravascular coagulation. Electrolytes, renal function, liver blood tests, C-reactive protein Guide to associated complications, underlying causes, and premonitory conditions. Phosphate and magnesium Low levels aggravate respiratory failure. Serum amylase/lipase Pancreatitis is a cause of ARDS. Thyroid function tests Hypothyroidism is a rare cause of hypoventilation. Creatine kinase and Troponin I Biomarkers of recent myocardial infarction. A high creatine kinase with a normal troponin may indicate myositis. ARDS, acute respiratory distress syndrome.

17.5 Acute respiratory failure 3871 low when they are stiff (e.g. in ARDS). Compliance may also be decreased by chest wall or abdominal pathology. In self-ventilating patients, serial measurements of peak expiratory flow rate (PEFR) may be useful to assess therapeutic response to bronchodilators. Serial estimations of vital capacity are a useful indicator of deterioration in patients with neuromuscular problems involving the respiratory muscles, such as Guillain-Barré syndrome. Capnography A continuous measurement of exhaled/end tidal carbon dioxide ($ETCO_2$) concentration mirrors P_{aCO_2} and is therefore a useful indicator of alveolar ventilation in patients without significant airflow limitation. A large difference between $ETCO_2$ and P_{aCO_2} suggests an increase in alveolar dead space. Portable machines are available and should always be used to confirm endotracheal tube placement when continuous capnography is unavailable. Management The main steps in treating acute respiratory failure are: • Establishing and securing the airway • Increasing F_{IO_2} to treat hypoxemia • Instituting mechanical ventilation (invasive or noninvasive) as necessary to treat impaired oxygenation and hypercapnia • Identifying and managing the precipitating condition • Discontinuing and withdrawing support in stages ('weaning') as the underlying condition improves or if it is decided that recovery will not occur. Airway management Ensuring airway patency and an adequate oxygen supply is a priority in all circumstances. Simple techniques such as head positioning (jaw thrust or head tilt) and removal of obstructions (e.g. dentures, secretions in the oropharynx) may be life-saving. However, insertion of a nasopharyngeal or oropharyngeal airway, which lifts the tongue off the posterior pharynx, and the application of positive pressure ventilation using a self-inflating bag valve mask apparatus may be required. Continuing respiratory support can be delivered by several devices, ranging from face masks to deliver oxygen to positive pressure ventilation administered noninvasively (via nasal or

full face mask) or invasively (via endotracheal tube or tracheostomy). Endotracheal intubation is a task that should be undertaken only by those experienced in the technique. The decision to intubate is based on several factors including:

- Inability to maintain and protect the airway—endotracheal intubation is almost always indicated in patients with a Glasgow Coma Score of 8 or less.
- Exhaustion—elective intubation is considerably safer than an emergency procedure.
- Deteriorating physiological parameters (specifically arterial gas tensions, acid base status, and respiratory rate more than 35 or less than 10 breaths/minute) despite the provision of adequate therapy.
- Reversibility of underlying condition—intubation and mechanical ventilation are not therapeutic interventions and supporting respiration in this manner may be inappropriate in patients with irreversible pathology. The equipment, sedative, and neuromuscular blocking agents required, and the exact techniques employed are beyond the scope of this chapter, however.

Tracheostomy Tracheostomy is a useful intervention in patients who require airway protection and toilet, or prolonged periods of assisted ventilation. A tracheostomy is better tolerated than prolonged endotracheal intubation, allowing sedation to be decreased. Resistance to airflow is reduced and dead space diminished, thereby aiding weaning. Tracheostomies facilitate communication, oral nutrition, removal of secretions, and prevent the nasal, laryngeal, and pharyngeal complications associated with prolonged translaryngeal intubation. As with endotracheal tubes, cuff pressure should be measured regularly and maintained between 24 to 30 mm H₂O. However, recent high quality trials have reported that early tracheostomy (within 72 hours of intubation) does not reduce mortality and a high proportion of patients randomly assigned to late tracheostomy recovered without undergoing the procedure. Mini-tracheostomy (3.5–4 mm diameter, uncuffed) can be used in patients with an ineffective cough or neurological impairment who require regular suctioning for sputum clearance, however, being uncuffed a mini-tracheostomy does not protect against aspiration and is too narrow to allow use of a wide bore suction catheter.

Oxygen therapy Oxygen is administered by a variety of methods depending on the required oxygen concentration (Table 17.5.4). Systems used for the delivery of oxygen can be broadly classified into fixed and variable performance devices. The flow rate of gas supplied, the volume of the mask itself, and the presence of holes or other entrainment systems determine into which category the device fits.

Fixed performance devices These are designed to provide a constant and predictable inspired oxygen concentration, irrespective of the patient's ventilatory pattern. Oxygen is passed through a jet in the mask, which entrains air through ports in the side. The total flow rate of gas to the mask should be 10–15 L/min. The flow rate of oxygen should be adjusted to achieve the required Fio₂.

Table 17.5.4 Oxygen delivery systems

Method of delivery	Fio ₂ achieved	Type of patient
Nasal cannula	0.24–0.30	Stable patients
Venturi mask	0.24–0.50	Type 2 respiratory failure and COPD
Partial rebreathing mask	0.60–0.80	Acute type 1 respiratory failure (e.g. pneumonia, asthma, and acute pulmonary oedema)
Non-rebreathing reservoir mask	Up to 0.90	Severely hypoxic patients
Nasal high flow	Up to 1.0	Acute type 1 respiratory failure
Anaesthetic face mask or endotracheal tube	Up to 1.0	Patients requiring intubation

COPD, chronic obstructive pulmonary disease; Fio₂, inspired oxygen concentration.

Section 17 Critical care medicine 3872 exceed the peak inspiratory flow rate of the patient at rest. Examples of fixed performance devices include the Venturi, Hudson, and medium concentration (MC) masks. Variable performance devices These provide an inspired oxygen concentration (Fio₂) which varies according to the gas flow rate and patient's ventilatory pattern. Most patients require only a modest increase in Fio₂ to overcome the combined effects of mild hypoventilation,

diffusion hypoxia, and some degree of ventilation/perfusion mismatch. In these circumstances a Fio_2 of 0.3 is usually adequate, which is achieved by supplying a flow rate of 4 litres/min to any of the variable performance devices. However, in patients with COPD and/or type 2 respiratory failure, ventilatory drive may be stimulated by hypoxaemia. If this is relieved by the administration of oxygen in an uncontrolled fashion (e.g. applying a large increase in Fio_2 via a variable performance device), then arterial oxygen tension rises and respiratory drive is depressed. This leads to reduced entrainment of room air, an increase in the proportion of oxygen inhaled, and respiratory drive is further reduced. In rare circumstances a high Fio_2 is needed. Large capacity systems with an added reservoir bag are required to achieve this. Nevertheless, using these masks, an Fio_2 up to 85% can be achieved using oxygen flows of 10 litres/min or greater. However, considerable CO_2 rebreathing occurs if the oxygen supply fails or is reduced. Rebreathing can be eliminated and delivered Fio_2 increased still further if unidirectional valves are added. Nasal high flow In this mode heated, humidified oxygen is delivered via nasal cannulae at high flow rates of up to 60 litre/min. The high flow generates a low level of positive pressure as well as ensuring the patient receives the set FiO_2 by reducing entrained air. High flow oxygen was recently found to reduce 90-day mortality in patients with acute type 1 respiratory failure when compared to noninvasive ventilation and standard oxygen therapy.

Mechanical ventilation The primary aim of mechanical ventilation is to support adequate gas exchange, while minimizing complications (Table 17.5.5). Modern mechanical ventilators contain sophisticated microprocessors that enable operators to control Fio_2 , tidal volume, airway pressures, respiratory rate, gas flow rates, and the time spent in inspiration and expiration. The optimal mode of ventilation depends in part upon the nature of the underlying illness, particularly the presence or absence of pulmonary parenchymal or airway pathology, the phase of the illness (acute or chronic), and the aims of support at the time it is applied (e.g. initiation of mechanical ventilation or weaning).

Noninvasive ventilation (NIV) Noninvasive positive pressure ventilation involves the delivery of mechanically generated breaths via a tight-fitting nasal or full face mask. Most modern systems deliver gas to preset inspiratory (IPAP) and expiratory (EPAP) positive airway pressures. Noninvasive ventilation also incorporates negative pressure ventilation, such as jacket (cuirass) ventilators, which are now rarely used in adult practice. Box 17.5.2 and Table 17.5.6 show the contraindications to the use of noninvasive ventilation and its limitations. In the acute setting, the evidence base supporting the use of noninvasive ventilation is most complete in patients with acute exacerbations of COPD who do not require immediate endotracheal intubation. Following intensive care unit admission, one good study found that noninvasive ventilation significantly reduced the need for intubation (26% in NIV group vs. 64% in standard group) and thus the associated complications, and length of stay and inpatient mortality were both reduced. A similar study has

Table 17.5.5 Complications associated with mechanical ventilation

System affected	Complication	Comment
Cardiac	Reduced cardiac output	Positive pressure ventilation increases intrathoracic pressure, causing a reduction in venous return and thus stroke volume and cardiac output
Renal	Reduced renal perfusion	Salt and water retention (especially when associated with PEEP)
	As a result of a reduced cardiac output	Due to increased ADH secretion, reduced renal blood flow, and a reduction in antinatriuretic peptide secretion
Respiratory	Ventilator induced lung injury	Pneumothorax Pneumomediastinum Pneumopericardium Subcutaneous emphysema
	Ventilator-associated pneumonia	Due to ventilation with high tidal volumes resulting in overdistension of the alveoli Due to barotrauma
	Early recognition and prompt management of a tension pneumothorax is essential.	This is nosocomial pneumonia developing more than 48 h postintubation. It is partly due to microaspiration of gastric contents or nasopharyngeal secretions

and is associated with increased mortality Gastrointestinal Abdominal distension and ileus Stress ulceration Also associated with the use of opiates The most common cause of gastrointestinal bleeding in ICU. Associated with an increased mortality when compared to patients without bleeding Neurological Critical illness myopathy and polyneuropathy Attributed to immobility, treatment with corticosteroids and paralyzing agents and associated with the systemic inflammatory response syndrome Others Oxygen toxicity Ventilator failure or disconnection High inspired oxygen concentrations can cause reabsorption atelectasis and direct cellular toxicity. It is usual clinical practice to decrease the inspired oxygen concentration to <60% where possible Alarms must be in place to alert the clinicians of ventilator failure or disconnection. A bag valve mask for manual ventilation and oxygen should be available at each bed space ADH, antidiuretic hormone; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

17.5 Acute respiratory failure 3873 supported the use of noninvasive ventilation on medical wards in patients with COPD with mild to moderate acidosis. Other benefits of noninvasive ventilation include the facilitation of ventilation 'breaks' for food and drugs, easier communication, earlier mobilization, more cooperation with physiotherapy, and cough preservation. A trial of noninvasive ventilation can therefore be advocated in patients with acute exacerbations of COPD who have a persistent respiratory acidosis (pH <7.35) despite controlled oxygen therapy and maximal medical treatment. Prior to its institution, however, a decision should be made as to whether the patient will proceed to endotracheal intubation and invasive ventilation if deterioration should occur. In some patients, endotracheal intubation is not appropriate and noninvasive ventilation is employed as a 'ceiling' therapy. It can be delivered on general medical wards if staff have received appropriate training, and provided that monitoring with continuous pulse oximetry and regular arterial blood gas analysis is available. The benefit to patients with more severe acidosis (pH <7.25) is less clear, and in such cases noninvasive ventilation should be administered on the intensive care ward where facilities for endotracheal intubation are readily available. The evidence base concerning the benefits of noninvasive ventilation is less strong for patients with acute respiratory failure secondary to restrictive lung disease, cystic fibrosis/bronchiectasis, ARDS, trauma, and postoperatively. It is probably reasonable to attempt a trial of noninvasive ventilation for hypoxaemic respiratory failure in such cases, but preferably in the ICU setting if the patient is a candidate for endotracheal intubation. If there is no significant improvement in pH, P_{aCO_2} and respiratory rate after 1 to 2 h of noninvasive ventilation, the trial is likely to fail and invasive ventilation must be considered. Noninvasive ventilation is not routinely recommended for the treatment of acute exacerbations of asthma. Noninvasive ventilation has also been shown to be of benefit in some groups of patients to aid weaning and can be used to relieve respiratory distress in patients receiving palliative care for end-stage respiratory disease. Positive end-expiratory pressure (PEEP) By preventing airway pressure returning to atmospheric at the end of expiration, the application of PEEP minimizes alveolar collapse, thereby increasing functional residual capacity and compliance. In addition, recruitment of atelectatic alveoli is encouraged, and V/Q mismatch reduced. Lymphatic drainage may be stimulated, decreasing alveolar oedema and further improving oxygenation. Its main disadvantage is that airway pressures are raised, thereby reducing venous return and impairing cardiac output. The effect on right ventricular afterload, another major determinant of cardiac output, is complex: pulmonary vascular resistance is increased both by atelectasis (low PEEP) and extrinsic compression of pulmonary microvasculature by raised airway pressures (high PEEP). Continuous positive airway pressure (CPAP) This can be delivered either via an endotracheal tube or to a conscious patient

via a noninvasive interface (e.g. face or nasal mask, and helmet). It is generated either using a bellows/pressure device, or through a flow generator. Gas must be delivered at a sufficient flow rate to ensure that airway pressure does not fall below zero during inspiration, with a PEEP valve fitted to the system. CPAP can be used in a trial of spontaneous ventilation at the end of weaning from mechanical ventilation. In patients with cardiogenic pulmonary oedema that remain hypoxic despite medical therapy, CPAP reduced intubation rates, with a trend towards reduced mortality.

Acute respiratory distress syndrome (ARDS) Definition This syndrome, defined by refractory hypoxaemia associated with high-permeability pulmonary oedema, complicates a wide variety of acute serious conditions, not all of which involve the lung directly (Fig. 17.5.1). The first widely accepted radiological and physiological criteria based definition was developed in 1994 by an American-European Consensus Conference (AECC), which created syndromes acute lung injury and ARDS, which were separated according to the oxygenation deficit. The emergence of these criteria facilitated the design of clinical investigations by permitting direct comparisons between patient groups with widely differing

Table 17.5.6 Limitations of noninvasive ventilation

Limitations

Comment Mask leak and discomfort Can be minimized by correct mask fitting: numerous, different sized, full face, and nasal masks are available Nasal bridge ulceration Protective barrier dressings can be used to reduce this Gastric dilatation and vomiting A nasogastric tube should be inserted, although this may increase leak Lack of airway protection If a patient is unable to protect their airway, an endotracheal tube should be inserted No endotracheal suction Patients often require regular physiotherapy Exact Fio₂ delivered unknown Oxygen is entrained proximally in the circuit or directly into the mask. Pulse oximetry and ABGs are used to guide oxygen enrichment Exact tidal volume and minute volume delivered unknown Due to leak ABG, arterial blood gas; Fio₂, inspired oxygen concentration.

Box 17.5.2 Contraindications to noninvasive ventilation

- Confusion/agitation
- Life-threatening hypoxaemia
- Reduced Glasgow Coma Score/inability to protect airway
- Vomiting
- Recent facial, upper airway, or upper gastrointestinal surgery
- Fixed upper airway obstruction
- Facial abnormalities (e.g. trauma or burns)
- Bowel obstruction
- Excessive secretions
- Haemodynamic instability
- Undrained pneumothorax

Section 17 Critical care medicine 3874 underlying pathologies. However, these definitions took no account of the prognostic significance of the precipitating condition, failed to account for the effect of ventilatory strategy on hypoxaemia, and made no recommendation concerning the interpretation of chest radiographs. In 2011 a panel of experts developed the Berlin definitions for ARDS. Three grades of ARDS were developed based on severity of hypoxaemia, which included a stipulation for the level of PEEP applied, and the term acute lung injury (ALI) was removed (Box 17.5.3). **Aetiology** Susceptibility to ARDS is determined in part by the nature of the underlying condition (Fig. 17.5.1), thus 40–60% of patients with severe sepsis and septic shock develop ARDS, regardless of the anatomical site of infection, but only 16% develop ARDS following trauma. The Lung Injury Prediction Score (LIPS: Table 17.5.7) was derived from large data sets of patients and validated prospectively with a view to using it as a basis for recruiting patients to ARDS prevention studies. Evaluation of the score discriminated between patients who did and who did not develop ARDS. When a cutoff score of greater than 4 points is used, sensitivity of the score for ARDS is 0.69 (95% CI 0.64–0.74), specificity is 0.78 (95% CI 0.77–0.79), positive predictive value is 0.18 (0.16–0.20) and negative predictive value is 0.97 (0.97–0.98). The score demonstrates the ranking of common predisposing conditions as well as comorbidities that influence

susceptibility to ARDS. Finally, genetic polymorphisms and biomarkers have been demonstrated that increase susceptibility to lung injury, but these have currently been useful in research as pointers to pathophysiological mechanisms, rather than having clinical utility. Epidemiology In Europe, the most recent epidemiological data found AECC criteria (pre-Berlin definitions) were met in 15.8% of patients admitted to intensive care for treatment of acute respiratory failure of all causes. Of those who developed ARDS, 65.4% of cases fulfilled the relevant criteria early in intensive care admission and the remainder did so within a median of 3 days. Of those who developed ALI (comparable with Berlin definition of mild ARDS) within the first 24 h, 54.4% evolved to ARDS (comparable with Berlin definition of moderate and severe ARDS). By contrast, only 18.4% of patients with established ARDS had preceding ALI identified. Precipitating cause or risk factors for ALI Genetic factors Co-morbidities Alcoholism Diabetes Smoking Obesity Inflammation Coagulation Altered cell function Tissue injury Fibrogenesis/repair Pulmonary causes Pneumonia Aspiration of gastric contents Inhalational injury Pulmonary contusion Near drowning Hypoxia/reperfusion injury Nonpulmonary causes Sepsis Cardiopulmonary bypass Severe trauma Blood transfusion Drug overdose Acute pancreatitis Infection VALI TRALI fluid overload Fig. 17.5.1

Aetiology of the ARDS. A combination of patient factors (blue: genetic and comorbidities) and iatrogenic factors (red: including ventilator-associated lung injury—VALI) contribute to the pathological processes of ARDS. ALI, acute lung injury; TRALI, transfusion related acute lung injury.

Box 17.5.3 Berlin definition of ARDS • Appropriate clinical setting with one or more recognized risk factors • New (within 1 week of known clinical insult), bilateral pulmonary infiltrates on chest radiograph not fully explained by lobar/lung collapse • Respiratory failure not solely due to heart failure or fluid overload. Objective assessment (e.g. echocardiography) required to exclude cardiac failure if no risk factor present • In patients with a PEEP/CPAP 5 cmH₂O: • Mild ARDS PaO₂:FiO₂ ratio of less than 40 kPa or less than 300 mm Hg • Moderate ARDS PaO₂:FiO₂ ratio of less than 26.6 kPa or less than 200 mm Hg • Severe ARDS PaO₂:FiO₂ ratio of less than 13.3 kPa or less than 100 mm Hg FiO₂, inspired oxygen concentration; PaO₂, arterial partial pressure of oxygen; PAOP, pulmonary artery occlusion pressure. Table 17.5.7 The Lung Injury Prediction Score (LIPS)

Predisposing conditions LIPS

points Risk modifiers LIPS

points Shock 2 Alcohol abuse 1 Aspiration 2 Obesity (BMI >30) 1 Sepsis 1 Hypoalbuminaemia 1 Pneumonia 1.5 Diabetes mellitu -1 High-risk surgery Chemotherapy 1 • Orthopaedic spine 1 FiO₂ >0.35 or >4 2 • Acute abdomen 2 litres/minute • Cardiac 2.5 Tachypnoea RR >30 1.5 • Aortic vascular 3.5 SpO₂ <95% 1 High-risk trauma Acidosis (pH <7.35) 1.5 • Traumatic brain injury 2 • Smoke inhalation 2 • Near drowning 2 • Lung contusion 1.5 • Multiple fractures 1.5

17.5 Acute respiratory failure 3875 In North America, a prospective, population-based cohort study in 21 hospitals over 14 months, also using AECC criteria, found an incidence of 78.9 per 100 000 population. This increased with age (16 per 100 000 for patients 15–19 years; 306 per 100 000 for those aged 75–84). Overall, this study suggested there are around 190 000 cases of ARDS per year in the United States of America, with 74 500 deaths and some 3.6 million hospital days taken up by such patients. Pathogenesis ARDS is caused by intense inflammation affecting the gas exchange surface of the lung—the alveolar-capillary membrane. Increased permeability of this barrier is associated with an exudate in the airspace, the physico-chemical nature of which causes inactivation of surfactant and atelectasis of lung units. Inflammation in the vascular space counteracts hypoxic pulmonary vasoconstriction, partly by causing dysregulation of the production of

vasoactive mediators including prostanoids, endothelins, and nitric oxide. The refractory hypoxaemia that characterizes ARDS is attributable to the combination of loss of lung units and hypoxic pulmonary vasoconstriction. Loss of pulmonary vasculature caused by lung destruction and intravascular coagulation causes increased dead space ventilation and carbon dioxide retention. Dysregulation of pulmonary vascular tone is associated with increased pulmonary vascular resistance which is exacerbated by the use of high airway pressure mechanical ventilation. Rarely, right heart failure may develop, usually in the presence of very severe type 2 ventilatory failure.

Pathology The pathological appearances of ARDS are termed 'diffuse alveolar damage', although the same features are seen in distinct clinical conditions like acute interstitial pneumonia. Histological phases have been observed, but they usually overlap and can all coexist simultaneously, particularly in the later stages. Three overlapping phases are recognized that correlate loosely with the clinical evolution of the disease: the exudative phase of oedema and haemorrhage, the proliferative phase of organization and repair, and the fibrotic phase. Eosinophilic hyaline membranes, composed of plasma proteins and cell debris, are characteristic features of the neutrophil predominant exudate that fills the airspace in early ARDS. The proliferative phase is characterized by organization of intra-alveolar and interstitial exudates with the formation of granulation tissue and regeneration of the alveolar epithelium with undifferentiated cuboidal cells. Total lung collagen is increased in ARDS patients surviving more than 14 days, and there is a progressive increase in lung collagen with the duration of the disease. This probably represents a normal healing response: in most cases this provisional matrix remodels, but in a few fibrosis becomes fixed and progressive, manifesting clinically as low lung compliance and prolonged ventilator dependence. These patients have a poor outcome.

Clinical features and differential diagnosis The clinical features of ARDS will be largely determined by the underlying cause and are nonspecific to the syndrome apart from the degree of hypoxaemia being out of proportion to the pulmonary oedema compared with cardiogenic causes. Considering alternative diagnoses is important because many conditions that cause respiratory failure and pulmonary infiltrates have specific treatments (Table 17.5.8).

Clinical investigations Initial investigations should be aimed at defining the extent of lung injury and accompanying organ failures, and elucidating the precipitating causes. Subsequent investigations detect complications and guide therapy. CT of the thorax is increasingly used in patients with ARDS because it has greater sensitivity for detecting pneumothoraces, pleural collections, abscess, and lung infiltrates than plain chest radiography. Typically, areas of dense opacification are apparent in dependent lung regions, with ground glass shadowing elsewhere (Fig. 17.5.2), this pattern being more often seen in indirect or blood-borne causes of ARDS like sepsis, rather than direct causes where the original lung pathology is often evident (e.g. lobar pneumonia). Fibreoptic bronchoscopy is often used to obtain microbiological samples and bronchoalveolar lavage cytology may reveal unexpected diagnoses (Table 17.5.8). A panel of investigations has been developed for patients with the severest forms of ARDS. Close coordination with local microbiologists and public health experts is vital because of the annual changes in prevalent causative organisms of pneumonia and the constantly developing molecular means of detecting pathogens, for example, 16S polymerase chain reaction based assays. Treatment of both the precipitating conditions and managing generic complications of critical illness and its support, most notably nosocomial infection, are essential in the care of patients with ARDS. A management algorithm is shown in Fig. 17.5.3.

Ventilatory management The pathophysiology of ARDS encourages the use of high airway pressures to re-aerate ('recruit') collapsed lung but also results in extreme sensitivity to ventilatory-associated lung injury. Most patients with ARDS require invasive mechanical ventilation to maintain adequate

gas Table 17.5.8 Conditions that mimic or cause ARDS but have a distinct pathology, clinical course, and treatment Pneumonia Bacterial Miliary tuberculosis Viral Cytomegalovirus Herpes simplex Hantavirus Fungal Pneumocystis carinii Others Strongyloidiasis Cryptogenic Acute interstitial pneumonia Cryptogenic organizing pneumonia Acute eosinophilic pneumonia Malignancy Bronchoalveolar cell carcinoma Lymphangitis Acute leukaemia Lymphoma Pulmonary vascular disease Diffuse alveolar haemorrhage Sickle lung

Section 17 Critical care medicine 3876 exchange. While some studies have indicated that a significant proportion of patients with mild ARDS are successfully managed outside intensive care with NIV, most cases require endotracheal intubation. While the application of extreme ventilatory parameters to normal lungs can cause ARDS, the use of 'normal tidal volumes (10 ml/kg predicted body weight)' causes ARDS in patients at risk and kills patients with established ARDS when compared to 6 ml/kg predicted body weight. As a result, ventilatory strategies now aim to limit the shear forces applied to the lung parenchyma and reduce the cyclical recruitment and collapse ('derecruitment') of alveolar units. Thus, tidal volumes are set at lower levels than have traditionally been thought necessary, the so-called lung protective approach. This reduces CO₂ clearance, often resulting in a respiratory acidosis. A large multicentre trial in the United States of America demonstrated a convincing reduction in mortality (from 40% to 31% $p = 0.007$) associated with this approach (using tidal volumes of 6 ml/kg ideal body weight and plateau pressure (end inspiratory pressure) <30 cm H₂O) compared to conventional (12 ml/kg and plateau pressure <50 cm H₂O) ventilation. Positive end-expiratory pressure High levels of positive end-expiratory pressure (PEEP) can also be used to ensure recruitment and retention of damaged lung units. Customarily, PEEP is increased transiently in a stepwise manner to high levels (e.g. 20–30 cmH₂O) before a similar graded reduction to a maintenance level above the lower inflection point of the pressure-volume curve. CT tomograms taken during such manoeuvres (a) (b) Fig. 17.5.2 Plain chest radiograph (a) and CT (b) of patient with ARDS. Note greater detail provided by CT and dependent distribution of consolidation. ARDS by Berlin defining criteria Identify & manage precipitating cause Initial resuscitation (especially if septic) Ventilatory support (consider NIV) using protective strategy Adjunct assessments & monitoring (eg CT chest, echocardiography, infection screen) Act on findings (eg drain pneumothorax, start, inotropes/pressors) Initiate nutritional support, optimize fluid balance Yes Yes Oxygenation satisfactory ($SaO_2 > 88\%$) Stabilize 48 hr Consider weaning No Success Outpatient follow up Re evaluate precipitating cause, re assess with CT No Consider ECMO Consider prone positioning Consider inhaled nitric oxide Consider steroids Fig. 17.5.3 Protocol for management of patients with ARDS. NIV, noninvasive ventilation; P:F, PaO₂:FiO₂; PEEP, positive end-expiratory pressure; NMB, neuromuscular blockade; ECMO, extracorporeal membrane oxygenation.

17.5 Acute respiratory failure 3877 have demonstrated recruitment of atelectatic regions, especially in dorsal areas of the lung, which remain inflated after the PEEP is reduced with an associated improvement in gas exchange. However, while higher PEEP may result in better oxygenation and possibly less ventilator-associated lung injury, circulatory depression and overdistension of recruitable lung units may also occur. The relationship between potentially recruitable lung (indicated by CT) and effects of PEEP has been explored in patients with ARDS and appropriate controls (healthy patients with unilateral pneumonia). Those patients with greater recruitability had greater calculated lung weight, poorer oxygenation, and respiratory system

compliance, higher dead space, and higher rates of death. Thus, in this patient population the percentage of recruitable lung is variable, but strongly associated with level of PEEP. Despite such knowledge, the application of varying levels of PEEP in clinical trials has not influenced outcome favourably. When patients with ARDS were randomized to low or high levels of PEEP using preset FiO_2/PEEP (levels achieved in the two groups were 8.3 and 13.2 cmH₂O, respectively), none of the study endpoints (mortality, days of unassisted breathing, inflammatory markers) differed between the two groups. A meta-analysis of three large recent randomized controlled trials found higher levels of PEEP in a subgroup of patients with ARDS, defined as a $\text{PaO}_2:\text{FiO}_2$ ratio of 200 mm Hg or less (equivalent to moderate ARDS with the new Berlin definition), conferred a mortality benefit. In contrast, a recent international trial, in which the majority of patients were recruited in Brazil, reported increased mortality when a protocol using recruitment manoeuvres and titrated PEEP was compared to a conventional low PEEP strategy. Further research is needed to elucidate the optimum strategy for PEEP in patients with ARDS.

Prone positioning Mechanical ventilation in the prone position is frequently employed in the management of patients with ARDS, around 60% of whom respond to this manoeuvre with significant improvements in gas exchange that may persist even after they are returned to the supine position. Since response cannot be predicted, a trial period is often used to identify those patients who are likely to benefit. While a large (>300 patients) study carried out in Italy demonstrated no survival benefit in response to at least 6 h prone ventilation per day, more prolonged 'proning' (e.g. 17 h per day) applied early to patients with more severe lung injury may reduce mortality. Moreover, a systematic review and meta-analysis of published randomized controlled trials enrolling nearly 2000 patients suggested this manoeuvre reduces mortality in those with the most severe hypoxemia. The results of a recent randomized control trial in patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg with positive end-expiratory pressure of at least 5 mm Hg and FiO_2 of >0.6) comparing early prone positioning (at least 16 hours a day) with nursing patients in the supine semi-recumbent position showed a significant reduction in both 28-day (16% versus 32.8%) and 90-day mortality (23.6% versus 41%). Both groups were ventilated with tidal volumes of around 6 ml per kg ideal body weight. All the ICUs in which the trial was conducted had routinely used prone positioning for more than five years. Turning critically ill patients from the supine to prone position and back is not without risk and requires experienced staff to perform safely. An instructional video made by the investigators is available, which accompanies the trial publication (<http://www.nejm.org/doi/full/10.1056/NEJMoa1214103#t=article>).

High-frequency ventilation High-frequency ventilation (HFV) employs rapid respiratory rates (>4 times those used in conventional techniques). Tidal volumes are reduced, and are often smaller than the anatomical dead space. The two modes of HFV most widely used are high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV). HFJV involves the intermittent delivery of high pressure gas jets into the endotracheal tube, but optimal gas warming and humidification are difficult to achieve, which leads to problems with airway secretions and debris that, when coupled with a reliance on passive expiration, can lead to air trapping. HFOV involves the delivery of a continuous distending pressure to the endotracheal tube, which is then modified by the movement of a vibrating loudspeaker. Humidification and warming of the fresh gas flow are easier to achieve, and an active expiratory phase leads to less gas trapping. The only randomized controlled trial of HFJV in patients with severe acute respiratory failure did not show a significant improvement in gas exchange or a survival benefit. However, recent evidence suggesting that low tidal volumes reduce ventilator-associated lung injury, and that high levels of continuous airway pressure (PEEP) improve recruitment and retention of lung units, have led to renewed interest in HFOV. Two randomization

controlled trials have been published comparing HFOV with conventional ventilation in patients with moderate and severe ARDS ($P:F \leq 200$ mm Hg (26.6 kPa). The OSCILLATE investigators compared the use of early HFOV with conventional ventilation using a low tidal volume and a high PEEP strategy. The trial was stopped early as HFOV was associated with higher in-hospital mortality than the control group (47% and 35%, respectively). The OSCAR study group found no difference in 30-day mortality between HFOV and usual ventilator care. As a result, HFOV cannot be recommended as standard treatment in patients with moderate and severe ARDS and at most should be reserved for use by experienced operators in cases with refractory life-threatening hypoxaemia when conventional therapies fail and extracorporeal support is not an option.

Extracorporeal gas exchange Extracorporeal gas exchange is performed using a variety of techniques (e.g. venovenous or venoarterial bypass) either to completely replace or more commonly to accompany mechanical ventilation. Two historical randomized controlled trials of extracorporeal membrane oxygenation (ECMO) reported no survival advantage, but they did not take advantage of the main benefit of the technique by failing to decrease mechanical ventilation. A third recently completed study using more advanced technology found a 16% survival benefit without severe disability among patients transferred to an ECMO centre compared to those who remained at the referral hospital and continued conventional ventilatory support. During the 2009 Influenza (H1N1) pandemic, ECMO was used to support patients who developed severe rapidly progressive ARDS and refractory hypoxia despite conventional ventilation with good results. A case series from Australia and New Zealand found 71% of those who received ECMO survived to ICU discharge. A UK-based cohort study in adult patients with suspected or confirmed H1N1 associated ARDS found those who were referred and transferred to an ECMO centre had a lower mortality than matched patients who were not referred for ECMO. This led to national commissioning of ECMO services in the United Kingdom with standardized

Section 17 Critical care medicine 3878 referral and exclusion criteria (Box 17.5.4). By contrast, a recent French study found receiving ECMO for H1N1 associated ARDS conferred no mortality advantage over matched controls treated conventionally.

Pharmacotherapy Fatty acids and antioxidants Initial research suggested that feeds rich in certain fatty acids and antioxidants may be of benefit in ARDS, presumably via changes in the host immune response. Eicosapentaenoic acid modulates production of proinflammatory eicosanoids, and γ -linoleic acid may suppress production of leukotrienes while itself being metabolized to prostaglandin E₁. However, while one recent randomized controlled trial of eicosapentaenoic acid/ γ -linoleic acid supplemented feeds in patients with ARDS showed improvements in oxygenation and shorter periods of ventilation and ICU stay, a more recent randomized controlled trial found no benefit from enteral feed supplemented with n-3 fatty acids, γ -linoleic acid and antioxidants in patients with ARDS: further investigation is required.

Nitric oxide Nitric oxide (NO) is an endogenous vasodilator which can be given by inhalation at concentrations of up to 20 parts per million. It has been shown to improve oxygenation in patients with ARDS through effects on ventilation/perfusion matching, and to decrease pulmonary vascular resistance. However, only two-thirds of patients with ARDS benefit from inhaled nitric oxide (iNO), and randomized controlled trials of iNO in ARDS have failed to show an improvement in mortality or a reduction in the duration of mechanical ventilation. Moreover, improvements in oxygenation are only transient, disappearing after 24 h of iNO therapy. Prostacyclin (PGI₂) is another endogenous vasodilator that may have beneficial effects in ARDS. Like iNO it is thought to redistribute pulmonary blood flow to ventilated lung units, thus improving ventilation/perfusion matching. A sequential trial of iNO and PGI₂ in patients with ARDS

showed the two treatments to have identical effects on oxygenation and shunt flow, but as PGI₂ is easier to monitor and deliver than iNO, it is frequently used in its place. Surfactant administration

Surfactant supplementation has proved effective in neonatal re- spiratory distress syndrome, and surfactant deficiency and dys- function has been demonstrated in adult patients with ARDS. However, several randomized controlled trials have failed to dem- onstrate an effect on mortality, or length of ventilation or intensive care unit stay in adults. A recent small trial has shown a survival benefit following use of bovine surfactant, but further large-scale trials are necessary.

Neuromuscular blockade While neuromuscular blockade is frequently required to prevent ventilator dysynchrony in patients with ARDS, the use of paralyzing agents have been limited due to concerns about causing or worsening long-term muscle weakness. However, a recent randomized con- trolled trial found the early use (within 48 hours) of cisatracurium in patients with moderate or severe ARDS (PF ratio, 150 mm Hg) in- creased time off the ventilator and improved 90 day survival without causing an increase in muscle weakness. Further trials are required to determine whether this is a reproducible class effect.

Other pharmaceutical interventions Adult respiratory distress syndrome has considerable clinical and financial significance. While recently the association between prehospital treatment with anti-inflammatory agents (e.g. aspirin) and the incidence of ARDS has been explored, most investigations have evaluated the potential of both supportive and pharmaco- logical interventions in the established syndrome. Most of these interventions have targeted cellular and mediator-driven inflamma- tion. Although evaluated in large, randomized, placebo-controlled trials, all have failed to show a survival benefit.

Corticosteroids Steroids have been used to treat ARDS since its first description in the 1960s. However, several multicentre trials in the 1980s failed to show a beneficial role for steroids either in the prevention of ARDS in at-risk groups, or in the treatment of established ARDS. Indeed, recent meta-analyses have concluded that steroids do not improve mortality in sepsis—a major group at risk of ARDS. However, des- pite this evidence, there has been a recent resurgence in enthusiasm for the use of steroids in the late (fibroproliferative) phase of ARDS. Early controlled data that appeared to support such therapy ran- domized patients on day 7 of ARDS to receive methylprednisolone or placebo for a further 32 days. A much larger randomized, double- blind trial compared corticosteroids to placebo in severe, late phase ARDS (7–14 days). There were two objectives; firstly, to determine if the administration of corticosteroids (methylprednisolone) in severe late-phase ARDS would reduce mortality and morbidity; and secondly, to evaluate the effects of steroids on markers of in- flammation and fibroproliferation. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days in association with an improvement in oxygenation, re- spiratory system compliance, and blood pressure, with fewer days of vasopressor therapy. There was no increase in the rate of infectious complications, but steroid therapy was associated with a higher rate of ICU-acquired weakness. These results do not support the routine use of steroids for persistent ARDS despite the improvement in car- diopulmonary physiology. In addition, starting methylprednisolone therapy more than 2 weeks after the onset of ARDS might have in- creased the risk of death.

Antioxidants Oxidative stress is thought to be central to the pathogenesis of ARDS. Alveolar macrophages and recruited activated neutrophils

Box 17.5.4 Indications and contraindications to the use of ECMO

Referral criteria Acute, severe, potentially reversible, respiratory failure Lung injury score above 3 or hypercarbia, such that the pH is less than 7.20 despite optimized conventional mechanical ventilation

Exclusion criteria Contraindication to limited anticoagulation (e.g. intracranial haemorrhage) Duration of high pressure and high FiO₂ ventilation for over seven days (relative contraindication)

17.5 Acute respiratory failure 3879 release highly reactive oxygen species which cause injury through interactions with proteins, lipids, and DNA. It is thought that excessive production of reactive oxygen species in ARDS overwhelms the endogenous antioxidant systems that normally regulate redox state within the lung. Attempts have therefore been made to introduce antioxidants to redress this balance, in particular using N-acetylcysteine, but none has shown a survival benefit or a reproducible effect on pulmonary physiology. Anti-inflammatory agents Ketoconazole is an imidazole used primarily for its antifungal effects, but which also has immune modulating functions which may be of benefit in preventing the development of ARDS. Although a large multicentre trial showed that ketoconazole had no effect on mortality or duration of ventilation in patients with established ARDS, two smaller studies in critically ill surgical patients demonstrated a significant reduction in the incidence of ARDS. β -Agonists Experimental studies suggest that β -agonists might be beneficial in ARDS through several mechanisms, including the acceleration of alveolar fluid clearance. However, recent randomized controlled trials found no benefit from either nebulized albuterol (salbutamol) or intravenous salbutamol over placebo in patients with ALI/ ARDS, hence β -agonists cannot be recommended in this patient population. General supportive measures Pulmonary oedema in ARDS is caused by increased pulmonary vascular permeability in the face of apparently normal pulmonary capillary pressure. Several studies have shown an association between a persistent positive fluid balance and poor outcome in ARDS, but it is not clear whether this represents administration of unnecessary fluid or greater haemodynamic instability in a group with a pre-existing poor prognosis. However, in a recent study of the safety and efficacy of 'fluid conservative' vs. 'fluid liberal' management strategies, applying interventions based on measurements of central venous or pulmonary artery occlusion pressures made at least every 4 h, the primary endpoint (death at 60 days) did not differ between strategies. Advantages in ventilator-free and organ failure-free (cardiovascular and central nervous system) days in favour of the fluid restricted group have to be balanced against suggestions of worse neurocognitive function at later follow-up. Transfusion of blood products, particularly those delivering large amounts of plasma from multiparous women, can cause ARDS—probably by preformed donor antibodies. Similarly, all blood products confer an increased risk of ARDS, nosocomial infection, and death on the recipient. Hence, the use of these products should be minimized. Wherever possible, feed should be administered via the enteral route, and the use of prokinetic drugs, avoidance of agents that impair gastric emptying (e.g. dopamine), and the use of postpyloric feeding tubes can all help achieve this aim. Prognosis and outcome Death rates attributable to ARDS are difficult to interpret, in that prognosis is determined in part by the nature of the precipitating illness. Thus, the mortality associated with ARDS complicating the sepsis syndromes is typically higher (40–60%) than that with trauma (14%), or following surgery using cardiopulmonary bypass (15%). Most patients with the established syndrome who die succumb to multiple organ dysfunction rather than as a direct result of respiratory insufficiency. Recent controlled trials of putative therapeutic interventions in patients with ARDS have identified mortality rates of 25–40% in the control arms. Using the Berlin definition stages, mild, moderate, and severe ARDS were associated with mortality of 27%, 32%, and 45%, respectively. Survivors of ARDS have persistent functional disability five years after discharge from the intensive care unit despite normal or near normal lung function. Most patients have extrapulmonary conditions, with muscle wasting and weakness being most prominent. FURTHER READING Acute Respiratory Distress Syndrome Network (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*, 342, 1301–8. British Thoracic Society

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