Non-ventilatory treatment of acute hypoxic respiratory failure

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Severe acute hypoxic respiratory failure is uncommon but often fatal. Standard treatment involves high inspired oxygen concentrations, mechanical ventilation and positive end-expiratory pressure. Many other interventions have been used in parallel with conventional treatment or as rescue therapy when it fails, including extracorporeal gas exchange, prone positioning, inhaled vasodilators, exogenous surfactants and drugs which modify the inflammatory process. Nearly all these treatments improve arterial oxygenation or markers of lung injury. However, the relationship between oxygenation and survival in acute hypoxaemic respiratory failure is not established, so improved oxygenation cannot be used as a surrogate for survival. Randomised controlled trials are, therefore, needed to assess the effects of these treatments on mortality. In such trials, extracorporeal oxygenation and extracorporeal carbon dioxide elimination, surfactant, early methylprednisolone, and prostaglandin E, offer no survival advantage over conventional therapy. Prophylactic ketoconazole and pentoxifylline appear to improve mortality in small studies in surgical and oncology patients respectively, and methylprednisolone improves mortality and morbidity in unresolving disease.

Acute hypoxic respiratory failure is an uncommon disease, with an incidence of between 1.5 and 5 cases per 100,000 population per year. Only a limited number of these patients have severe acute hypoxic respiratory failure in which the hypoxaemia is unresponsive to conventional respiratory support with mechanical ventilation, supplemental oxygen and positive end-expiratory pressure (PEEP). Estimates of the incidence of severe hypoxic respiratory failure are difficult to find. A cross sectional study in Berlin identified 3.6% of all patients with acute respiratory failure. The UK APACHE II database shows that only 1% of all intensive care unit (ICU) admissions had a PaO₂ of less than 50 mmHg (6.7 kPa) in the first 24 h of admission. Using these figures leads to an estimate of 1000–2000 cases of acute severe hypoxic respiratory failure in the UK per year, spread over about 250 ICUs. The mortality for this group of patients is probably 40–60%, although a wide
range of estimates have been published. Acute hypoxic respiratory failure is usually secondary to another condition and it is clear that the majority of patients die from the underlying disease rather than pulmonary insufficiency. Estimates of the number of patients dying of (rather than with) acute hypoxic respiratory failure vary between 16% and 40% of all patients with acute hypoxic respiratory failure. Thus the population likely to derive a survival benefit from advanced methods of respiratory support in the UK is between 160 and 800 patients per year, or between 0.02% and 0.1% of all deaths in the UK.

As the patients likely to derive a survival benefit from a new intervention represent a small fraction of those with acute respiratory failure, trials of novel interventions need to be very large to show a survival benefit. Nearly all those cited in this review show no benefit but they are mostly small and the results may merely reflect the limited power of the studies.

The adult (acute) respiratory distress syndrome (ARDS) and acute lung injury (ALI) are both forms of acute hypoxic respiratory failure. ARDS is defined as acute hypoxaemic respiratory failure with a \( \text{PaO}_2/\text{FiO}_2 \) of less than 200 mmHg (26.3 kPa) with bilateral pulmonary infiltrates on chest radiograph in the absence of cardiac causes, ALI is the same but the \( \text{PaO}_2/\text{FiO}_2 \) ratio lies between 300 and 200 mmHg (39.5–26.3 kPa). These definitions are of little practical value, essentially dividing all patients with acute hypoxic respiratory failure into two groups based on oxygenation. There is no clear treatment change or mortality change across the oxygenation threshold. For these reasons the term acute hypoxic respiratory failure will be used in this review.
Fig. 1 The effect of prone position on lung density. This shows a computer-processed cross-sectional CT scan of the lungs of a patient with acute hypoxic respiratory failure in the supine (upper panel) and prone (lower panel) position. The lung density is high in the black areas and lower in the white areas. On turning prone the dependent collapse (high density areas) of the right lung partially re-expands whilst some dependent collapse begins to occur in the left lung. Modified fromGattinoni et al.¹¹.

This review covers non-ventilatory treatment options for acute hypoxic respiratory failure (Table 1), the ventilatory strategies and concomitant treatments such as nutrition and antibiotics are covered elsewhere.

**Prone position**

When patients develop acute hypoxic respiratory failure, their lungs increase in density because of fluid accumulation (non-cardiogenic pulmonary oedema). Lung weight can increase to at least twice normal, whether measured by computerised tomography (CT) or by double indicator techniques. The majority of patients are ventilated lying supine, and in this position the weight of the upper (ventral or anterior) part of the lung compresses the dependent (dorsal or posterior) parts. As the compliance of the dependent part of the lung is effectively reduced, the non-dependent portion receives more ventilation and the dependent areas tend to collapse. The extent of this collapse (as determined by CT scanning) is directly related to the degree of ventilation/perfusion mismatching and hence hypoxaemia. A similar, although less severe, effect occurs after the induction of anaesthesia and the associated reduction in functional residual capacity and has been termed ‘compression atelectasis’.

It has been known since 1977 that the prone position improves oxygenation in patients with acute respiratory failure. This study showed an
initial mean improvement in oxygenation of 9.1 kPa, subsequent investigations showed similar improvements attributable to decompression and opening of atelectatic regions in the previously dependent areas of the lung, and was elegantly demonstrated by Gattinoni et al using computerised tomography (Fig. 1)\textsuperscript{11}.

The re-opening of previously dependent atelectatic areas is accompanied by a gradual collapse of the now-dependent ventral portion of the lung, which may reduce the benefit of the prone position over time. Regular turning of the patient may be the best way to preserve oxygenation. However, there are also good reasons why the prone position \textit{per se}, rather than positional changes, may maintain better oxygenation. Human lungs are approximately triangular in cross section with considerably more lung tissue dorsally than ventrally. Thus, in the supine position, a greater fraction of the lung tissue may be at risk from atelectasis. In addition, the weight of the heart and mediastinal structures may contribute to lung compression in the supine position. In other mammalian species, lung density is more evenly distributed in the prone position, even in the sloth which normally lives supine, implying that the cardiorespiratory system has evolved to function optimally in the prone position\textsuperscript{12,13}.

Clinical studies have nearly all shown an improvement in oxygenation with a change from supine to prone position\textsuperscript{14-18}, but those showing a survival or length of stay advantage have used historical controls and small numbers\textsuperscript{18,19}. A large randomised controlled trial underway in Italy is as yet incomplete\textsuperscript{20}. There are obvious practical risks involved in turning critically ill patients including pressure damage to tissues and dislodgement of therapeutic and monitoring catheters, which must be weighed against the unproved benefit of the prone position.

\section*{Inhaled treatments}

\textbf{Surfactant}

Premature infants are unable to produce functionally active surfactant, leading to a condition known as infant respiratory distress syndrome (IRDS) or hyaline membrane disease. Exogenous surfactant can be used prophylactically to reduce both the incidence and severity of IRDS\textsuperscript{21}, or used to treat established IRDS\textsuperscript{22,23}, and is now a standard treatment for the condition. In 1979, abnormal surfactant function was shown in lavage fluid from the lungs of patients who died from ARDS\textsuperscript{24}, and both functional and biochemical surfactant abnormalities have since been described\textsuperscript{25}. These may be caused by inhibitors present in the alveolar lining fluid, oxidation of the phospholipid or apoprotein moieties of surfactant, or damage to the type II pneumocytes which produce the surfactant\textsuperscript{26}. 

\textsuperscript{168} British Medical Bulletin 1999;55 (No. 1)
The success of trials of surfactant in IRDS and the identification of abnormal surfactant function in acute respiratory failure led to trials of surfactant in adults. Results were conflicting, an improvement in oxygenation being seen in some studies but not all. However, a large \((n = 725)\) randomised controlled trial of aerosolised surfactant to treat adult acute hypoxic respiratory failure failed to show any change in gas exchange or outcome, and so there is no clear evidence this treatment is of value.

**Inhaled nitric oxide**

Nitric oxide is a major endogenous mediator of multiple physiological processes. It is a powerful vasodilator, normally released from vascular endothelium in response to shear stress in order to match vessel calibre to blood flow. Nitric oxide released from the endothelium activates guanylate cyclase in the underlying vascular smooth muscle cells, increasing intracellular cyclic guanosine monophosphate which in turn reduces cytosolic calcium concentrations and causes relaxation. Nitric oxide only acts locally in the circulation, being rapidly inactivated by combining with oxyhaemoglobin to form inorganic nitrates and methaemoglobin.

When exogenous gaseous nitric oxide is inhaled, it diffuses into the outer (ablumenal) surface of pulmonary blood vessels, which are adjacent to the alveoli and alveolar ducts. Under physiological conditions this has no effect, as the normal pulmonary vascular tone is very low, but if there is pulmonary vasoconstriction nitric oxide reduces pulmonary vascular resistance. This was first reported in patients with pulmonary hypertension where inhaled nitric oxide was as effective as intravenous prostacyclin at reducing pulmonary vascular resistance, but with no systemic side effects. When inhaled nitric oxide is administered to patients with acute hypoxic respiratory failure, the vasodilator effect is confined to ventilated areas of the lung, improving ventilation/perfusion matching and thereby oxygenation as well as reducing pulmonary vascular resistance. By contrast, intravenously administered vasodilators non-selectively vasodilate the lung, reversing hypoxic pulmonary vasoconstriction and worsening ventilation/perfusion matching.

The effects of inhaled nitric oxide in patients with acute hypoxic respiratory failure were first demonstrated by Rossaint and colleagues who showed a mean increase in the \(\text{PaO}_2/\text{FiO}_2\) ratio of 6.2 kPa and a reduction of 7 mmHg in mean pulmonary artery pressure when patients with acute hypoxic respiratory failure where given 18 ppm (parts per million) inhaled nitric oxide. This finding has subsequently been repeatedly confirmed.

The dose of nitric oxide used appears to be quite important. Increasing the dose administered to 100 ppm causes increasing vasodilatation, but
between 10 and 100 ppm any improvement in oxygenation begins to diminish\textsuperscript{34}. This is probably because at higher doses pharmacologically active doses of nitric oxide reach relatively underventilated alveoli, increasing blood flow through areas with low ventilation/perfusion ratios. This would also explain the limited or paradoxical effect of nitric oxide in patients with chronic obstructive pulmonary disease\textsuperscript{35,36}.

The efficacy of nitric oxide can be increased by simultaneous infusion of pulmonary vasoconstrictors, which augment vasoconstriction in the underventilated lung regions but are antagonised in the better ventilated areas. The most commonly used vasoconstrictor is almitrine\textsuperscript{37}, although phenylephrine and the nitric oxide synthase inhibitor L-NMMA (monomethylarginine) have been used clinically or experimentally. The effects of nitric oxide, prone positioning and almitrine are all additive\textsuperscript{15,38}.

There have been no definitive randomised controlled trials of nitric oxide in adult acute hypoxic respiratory failure published to date. A phase II (dose-ranging/efficacy) study involving 177 patients showed a possible survival benefit with 5 ppm nitric oxide in a post hoc analysis\textsuperscript{39}. A pan-European study was stopped prematurely when 268 patients had been enrolled because of poor recruitment. No survival advantage was seen. The French GENOA study recruited 203 patients and again showed no survival advantage. Both the European and GENOA studies remain unpublished.

All the larger studies and case series published to date have shown that about 60–70\% of patients with acute respiratory failure have a clinically useful increase in their $\text{PaO}_2$ after nitric oxide is administered. Although widely used in intensive care units throughout the world, it is not at all certain that inhaled nitric oxide will eventually be shown to improve outcome. Fortunately, nitric oxide seems to have few serious side effects, the most important being rebound pulmonary hypertension on abrupt withdrawal\textsuperscript{40}.

As with ECMO, the situation with neonates is different. Neonates with hypoxic respiratory failure treated with nitric oxide require ECMO far less frequently than control infants\textsuperscript{41} and, thereby, avoid an expensive, invasive therapy that carries with it the potential for neurological damage. Nitric oxide will probably be licensed first for neonatal use.

Other inhaled therapies

Any drug that is a pulmonary vasodilator, has a short half life in the systemic circulation and can be nebulised should have an effect similar to inhaled nitric oxide. Nebulised prostacyclin has been most studied clinically and appears to have similar efficacy to inhaled nitric oxide in improving oxygenation and reducing pulmonary vascular resistance.
with virtually no systemic effects\textsuperscript{42,43}. The pulmonary selectivity of nebulised prostacyclin is usually attributed to its short half life, drug absorbed by the lungs being significantly metabolised before it reaches the systemic circulation. This is probably not the case, because the prostacyclin analogue iloprost, which has a much longer half life than prostacyclin, has a similar selectivity for the pulmonary circulation when inhaled. In addition, intravenous infusions of prostacyclin cause much greater reductions in systemic vascular resistance for equivalent pulmonary effects when compared with inhaled prostacyclin\textsuperscript{44}. It is probably the high local concentrations in the lungs which confer the pulmonary selectivity. If this is correct, most vasodilators should show pulmonary selectivity when inhaled. Experimental work has shown other prostaglandins and nitro-dilators to also be effective. It is also possible that endogenous pulmonary nitric oxide production is impaired in acute lung injury, and is limited by the availability of the cofactor for nitric oxide synthase, tetrahydrobiopterin (BH\textsubscript{4}). If this is the case, nebulised BH\textsubscript{4} may improve oxygenation in acute respiratory failure\textsuperscript{45}. There are no randomised controlled trials of the effects of any of these treatments on outcome.

**Intravenous vasoconstrictors and vasodilators**

Pulmonary hypertension is almost universal in acute hypoxic respiratory failure\textsuperscript{46}. Some of the increase in pulmonary artery pressure is due to raised intrathoracic and left atrial pressures, but there is also an increase in pulmonary vascular resistance, due to a combination of mechanical damage to pulmonary vessels and vasoconstriction. The pulmonary hypertension increases right ventricular afterload with the potential for right ventricular strain, and may increase lung water. There have been several studies of intravenous pulmonary vasodilators such as nitroprusside, ketaserin, diltiazem, and acetylcholine\textsuperscript{47-49}. These all have shown a reduction in pulmonary artery pressures, usually accompanied by a reduction in systemic pressures. However, the usefulness of these treatments is limited, because they all cause a reduction in \(\text{PaO}_2\) which is the result of worsening ventilation/perfusion matching in the lung\textsuperscript{48,49} probably because of reversal of hypoxic pulmonary vasoconstriction. With the increasing use of inhaled nitric oxide and prostacyclin, which reduce pulmonary artery pressures and improve oxygenation, there is now little place for intravenous pulmonary vasodilators in the management of acute hypoxic respiratory failure.

Pulmonary vasoconstrictors tend to increase \(\text{PaO}_2\) in acute respiratory failure. Almitrine is known to augment hypoxic pulmonary vasoconstriction\textsuperscript{50}, and improves ventilation/perfusion matching in ARDS\textsuperscript{51}, but at the cost of increased pulmonary artery pressure. Almitrine is now
Fig. 2 The arachidonic acid pathway. Note that cyclo-oxygenase inhibitors are highly non-selective.

**Drugs acting on the metabolism of arachidonic acid**

The products of arachidonic acid metabolism, the thromboxanes, prostaglandins and leukotrienes, have all been implicated in animal models studying the pathogenesis of ARDS (Fig. 2). Studying patients undergoing oesophagectomy, Schilling et al\(^{51}\) were able to demonstrate an early increase in pulmonary production of thromboxane A\(_2\) in patients who went on to develop ARDS. Thromboxane is a powerful pulmonary vasoconstrictor which also promotes neutrophil sequestration in the lung. Neutrophil production of the chemoattractant leukotriene B\(_4\) also precedes the onset of respiratory failure\(^{53}\) and prostacyclin levels are reduced in acute respiratory failure\(^{54}\).

Ibuprofen is a non-specific cyclo-oxygenase 1 and 2 inhibitor and decreases the production of both prostaglandins and thromboxanes. Although not studied directly in patients with acute respiratory failure, a large randomised controlled study (\(n = 455\)) of patients with sepsis treated with ibuprofen showed no difference in respiratory complications between treatment and placebo groups. It may be that any beneficial blockade of thromboxane production was offset by the blockade of potentially useful prostaglandins such as prostacyclin and prostaglandin
E_1 which prevent platelet aggregation, cause vasodilatation and down-regulate neutrophil-induced inflammatory responses.

This problem can be avoided by specifically blocking thromboxane synthetase, which reduces thromboxane concentrations but leaves prostaglandin synthesis unchanged. Ketoconazole, an imidazole antifungal agent, is a blocker of thromboxane synthetase and also inhibits leukotriene biosynthesis. A small randomised controlled trial of oral ketoconazole (n = 54) as a prophylactic measure in high risk surgical patients showed a marked reduction in the incidence of ARDS in the treatment group from 64% to 15%. This finding remains to be confirmed.

Replacing prostaglandins has also been attempted in patients with acute hypoxic respiratory failure. The use of prostacyclin (prostaglandin I_2) has already been described under inhaled treatments. Prostaglandin E_1 is an anti-inflammatory prostaglandin which inhibits platelet aggregation and vasodilates. It should, therefore, reduce the severity of ARDS. Two randomised controlled studies have failed to confirm this. The first studied 100 patients; no difference between control and treatment groups were seen. The second study used a liposomal preparation of prostaglandin E_1 (n = 25) because the effects of the liposomes and prostaglandin on neutrophils are additive. This showed a reduction in the time of mechanical ventilation and a more rapid improvement in oxygenation. No survival benefit was demonstrated, but the control group only contained 8 patients so the power of the study was very limited.

**Extracorporeal gas exchange**

The development of safe cardiopulmonary bypass systems for cardiac surgery, and especially membrane oxygenators which did not cause the haemolysis associated with bubble oxygenators, inevitably led to their use in the treatment of acute respiratory failure. The first patient who survived long term extracorporeal oxygenation was reported in 1972. Two main concepts have evolved since then, extracorporeal membrane oxygenation (ECMO) and extracorporeal CO_{2} removal (ECCO_{2}R).

ECMO is, in essence, identical to the cardiopulmonary bypass used for cardiac surgery. Blood is removed from the cavae or right atrium, passed through a pump and a membrane or hollow fibre oxygenator (artificial lung), and replaced either in the arterial system (veno-arterial ECMO) or back into the venous circulation (veno-venous ECMO). About half to two-thirds of the patient's cardiac output has to pass through the membrane lung to allow adequate oxygen uptake, so in veno-arterial ECMO the pulmonary blood flow is reduced, whereas in veno-venous ECMO it is maintained.
Following reports of uncontrolled series of 150 and 215 patients treated with ECMO with 10–15% survival, the only randomised control of ECMO was reported in 1979\textsuperscript{57}. Ninety patients were studied, no survival benefit was demonstrated. The study has been criticised because the veno-arterial bypass would have caused pulmonary hypoperfusion, the ventilator settings used for the patients on ECMO were not reduced to allow 'lung rest', ECMO was instituted late, and many of the patients had a particularly virulent viral pneumonia. In spite of these objections the study has never been repeated. Since 1979, many case series of patients treated with ECMO have been published\textsuperscript{58,59} claiming better results than conventional treatment but all were uncontrolled, or used historical controls. As the mortality of patients with ARDS treated without ECMO is improving\textsuperscript{60}, the interpretation of studies without concurrent controls is almost impossible, and adult ECMO remains an unproved, speculative treatment.

This situation only applies to adults with respiratory failure. Neonates with severe respiratory failure clearly benefit from ECMO, the mortality from the condition is nearly halved\textsuperscript{61}. The use of ECMO in neonates is outside the scope of this review and has been covered in a previous edition of the \textit{British Medical Bulletin}\textsuperscript{62}.

A totally different approach to extracorporeal gas exchange was pioneered by Gattinoni in Italy in the early 1980s. They reasoned that ventilation, whilst initially life saving, worsened lung damage in the long term and that this damage could be reduced by limiting lung movement. To limit ventilator induced lung damage, they employed pressure-limited ventilation at 3–4 breaths/min. In this situation, oxygenation can be maintained by apnoeic oxygenation. To avoid the otherwise inevitable hypercarbia, CO\textsubscript{2} was removed in an extracorporeal circuit. As membrane lungs can remove virtually all the CO\textsubscript{2} from blood passing through them, the total CO\textsubscript{2} production can be removed with extracorporeal blood flows of only 20–30% of cardiac output. The technique was termed LFPPV-ECCO\textsubscript{2}R (low frequency positive pressure ventilation – extracorporeal CO\textsubscript{2} removal). An initial case series of 43 patients showed good survival rates compared with the ECMO study published 7 years previously\textsuperscript{63}. However, a subsequent randomised controlled trial\textsuperscript{64}, scheduled to recruit 60 patients but terminated at 40 patients after interim analysis, showed no survival benefit when compared to conventional treatment.

Two other techniques of non-pulmonary gas exchange have been described. The IVOX (intra vena caval oxygenator or intravenous oxygenator) is a bundle of hollow fibres inserted into the vena cavae via the femoral vein, through which oxygen is drawn. Gas exchange takes place between the gas in the lumen of the fibres and the blood around the fibres. The risks of an extra-corporeal circuit can be avoided, but in their current configuration the devices are inefficient and cannot
exchange enough gas to make them clinically useful. Carbon dioxide can also be eliminated as bicarbonate in dialysis systems, but to date there are no reported trials of this technique.

Currently there are no data to support the use of extracorporeal gas exchange in acute hypoxic respiratory failure except as part of a controlled trial.

**Modifying the inflammatory response**

*Steroids*

The early stages of acute hypoxic respiratory failure are characterised by neutrophil margination and sequestration in the lungs, with release of proteases, reactive oxygen species, hypohalites and free radicals. *In vitro*, at least some of the response of neutrophils to activating stimuli can be inhibited by corticosteroids. However, in a clinical setting, acute hypoxic respiratory failure does not respond to early high dose corticosteroid treatment with methylprednisolone. A randomised controlled trial of 99 patients with acute hypoxic respiratory failure failed to show any benefit either in gas exchange parameters or 45 day mortality when given four doses of 30 mg/kg methylprednisolone at the beginning of their illness. Methylprednisolone also had no value as a prophylactic measure to reduce the risk of acute hypoxic respiratory failure in high-risk surgical patients.

The acute respiratory distress syndrome has three phases, an early exudative phase, an inflammatory phase and a later fibroproliferative phase beginning after 7 or more days. Experimental evidence suggests the later, fibrotic phase might be attenuated by corticosteroids. There is limited evidence from case series that healing of the lung might be accelerated by corticosteroids in the later phase of the disease, although the mortality from these series are within the expected range. A recent randomised controlled trial showed both a survival advantage and an improvement in morbidity (days on ventilation and other organ dysfunction) in patients with acute hypoxic respiratory failure given a tapering course of methylprednisolone for 32 days starting 8–9 days into their illness. This improvement in outcome was not associated with an increase in infections. Although statistically sound, the study design resulted in very small numbers with only 8 patients in the control group, so the matching of confounding factors between the control and treatment groups may not have been ideal.
Modulation of neutrophil function

The pulmonary damage that occurs in acute hypoxic respiratory failure may result from neutrophil sequestration in pulmonary vessels, followed by activation and migration of the neutrophils into the lung. This results in the dense neutrophilic infiltration of the interstitium seen on histological section, neutrophils in lavage fluid and an increased concentration of proteolytic enzymes in lavage fluid. The trigger for the neutrophil activation and chemotaxis may be interleukin-8, which is present in high concentrations in the blood and lavage fluid of patients with acute hypoxic respiratory failure. Neutrophils induce tissue damage by oxidative damage and proteolysis, leading to the changes seen in the lungs of patients with acute hypoxic respiratory failure.

Pentoxifylline is a phosphodiesterase inhibitor which increases red cell deformability and so improves capillary flow. It has been used to treat peripheral vascular disease, but it also has a major inhibitory effect on neutrophils, reducing their adherence and superoxide and proteolytic enzyme production. In experimental models it reduces the severity of acute hypoxic respiratory failure. A study of cancer patients at risk from acute respiratory failure showed both the severity and mortality of the respiratory failure was reduced by prophylactic use of pentoxifylline, there are no data available on its efficacy in established respiratory failure.

Antioxidants can be given to reduce the oxidative damage done by neutrophils. The only compound studied in detail is N-acetylcysteine, commonly used to treat paracetamol poisoning. In a randomised controlled trial of 42 patients, N-acetylcysteine did not alter the severity of acute hypoxic respiratory failure. Another small study compared N-acetylcysteine, L-2-oxothiazolidine-4-carboxylate (another anti-oxidant), and placebo in a total of 46 patients and found a slight benefit in terms of speed of recovery with both the anti-oxidants, although mortality was unchanged. Superoxide levels can be reduced by giving exogenous superoxide dismutase. Although this has been evaluated in neonatal respiratory failure there are no reports in adults.

Conclusion

There are many observational studies of non-ventilatory treatments using short-term pathophysiological changes as outcome measures in patients with acute hypoxic respiratory failure. However, there are very few randomised controlled studies using mortality as an endpoint and many of these may be considerably underpowered because of an overestimation of the population likely to benefit. Extracorporeal oxygenation and extracorporeal CO₂ elimination, surfactant, early methylprednisolone,
and prostaglandin E₁ provide no major survival advantage over conventional therapy. Prophylactic ketoconazole and pentoxifylline appear to improve mortality in small studies in surgical and oncology patients, respectively, and unresolving disease may respond to a long course of methyprednisolone. The mainstays of treatment of acute hypoxic respiratory failure are still appropriate treatment of the precipitating disease and careful ventilatory support.

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