For patients unresponsive to mannitol, the barbiturate thiopental (thiopentone) may be effective and seems to improve survival, but controlled trials are lacking.[1] The use of thiopental is limited by systemic hypotension which may require vasoconstrictive agents to maintain perfusion pressure. Consequently, patients must be closely monitored for cardiovascular complications.

Furthermore, as thiopental is usually metabolised by the liver careful monitoring of thiopental concentrations is also required.[1]

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Treatment of severe hypoxia relies on supportive therapy

The management of severely hypoxaemic patients remains a clinical challenge. Positive pressure ventilation, administered either noninvasively or through intubation, continues to be the main supportive measure. Adjunctive therapies including fluid management and vasopressor treatment aim to optimise oxygen supply and extraction, and improve the prognosis of critically ill patients with severe hypoxia. However, despite improved ventilator strategies and supportive care, mortality remains high.[1]

Many conditions linked with hypoxia

Acute respiratory distress syndrome (ARDS), acute lung injury (ALI), sepsis and septic shock are conditions that may lead to hypoxic respiratory failure. These conditions are described by a set of symptoms with a wide variation of patient risks, rather than being well-defined diseases (see table 1). ARDS is associated with a greater severity of hypoxaemia than ALI, the distinguishing factor between the conditions. Sepsis is the most common risk factor for ARDS, accounting for approximately half of the cases.[2,3]

Fluid therapy often needed

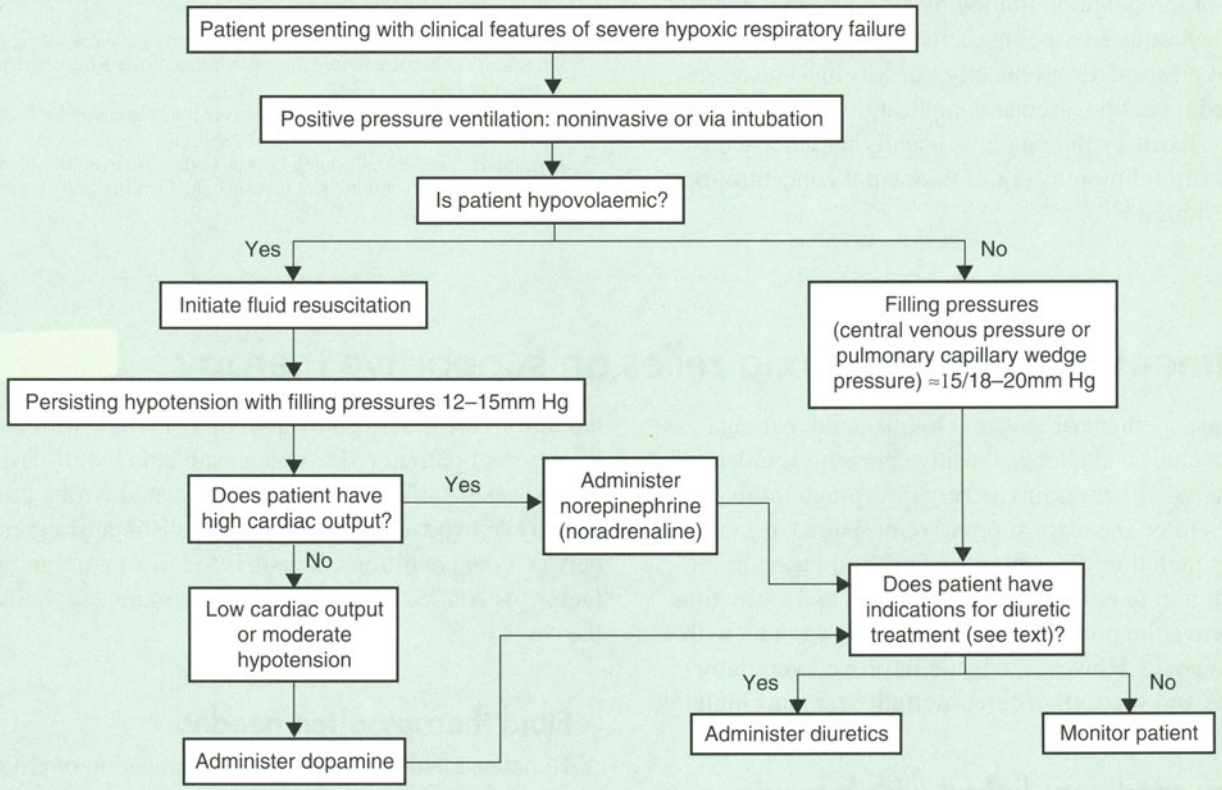
Hypotension often develops after intubation of critically ill patients as a result of septic shock or relative hypovolaemia in ARDS.[4] In hypotensive patients with possible hypovolaemia, aggressive fluid therapy should be initiated as early as possible, combined with vasopressors to

Table 1. Illnesses associated with severe hypoxic respiratory failure[1]

Disease	Diagnosis
Acute respiratory distress syndrome	Bilateral infiltrates on chest x-ray PaO_2/FiO_2 <27 kPa No evidence of pulmonary capillary or left atrial hypertension
Acute lung injury	Bilateral infiltrates on chest x-ray PaO_2/FiO_2 <40 kPa No evidence of pulmonary capillary or left atrial hypertension
Sepsis	Systemic response to infection, with ≥2 of the following: • temperature >38°C or <36°C • heart rate >90 beats/min • respiratory rate >20/min • white blood cell count >12 × 10^9/L or <4 × 10^9/L or >10% band forms
Severe sepsis	Sepsis plus organ dysfunction, hypoperfusion or hypotension
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation with systolic blood pressure <90mm Hg or ≥40mm Hg decline plus 1 of the following: • elevated lactate levels • oliguria (<0.5 ml/kg/h) • acute alteration in mental status

Abbreviations: FiO_2 = fraction of inspired oxygen; PaO_2 = arterial oxygen tension.

Patient care guidelines



Approach for treatment in patients with severe hypoxic respiratory failure and acute respiratory distress syndrome, acute lung injury or sepsis[1]

maintain adequate end-organ perfusion (see *Patient care guidelines*). Recent reviews recommend crystalloid (normal saline or lactated Ringer's solution) rather than colloid (plasma, albumin, hydroxyethyl starch or dextran) solutions.[5-8] Synthetic colloids have been recommended for patients who need rapid volume expansion, but cannot tolerate larger amounts of crystalloids, require prevention of thrombus formation or leukapheresis.[5,9]

How much?

The rate of fluid infusion depends on the clinical situation. For example, in young intubated patients with sepsis, several litres of fluid per hour may be needed.[1] On the other hand, in elderly patients with possible pre-existing heart failure, 1 L/hour may be a safer choice. Patients should be checked for signs of volume overload (tachypnoea, jugular distension) during fluid resuscitation. However, because of capillary leakage, large amounts of crystalloids (up to 20 L/day) may be necessary to achieve the following goals of volume therapy:[1]

- warm skin
- normal sensorium
- urine output >1 ml/kg/hour
- reversal of lactic acidosis.

Vasopressors for adequate organ perfusion

Most patients with septic shock will require vasopressor therapy in order to maintain adequate organ perfusion. Vasopressors should be reserved for patients remaining haemodynamically unstable after volume replacement or showing signs of persistent tissue hypoxia (e.g. increased lactate levels) because of the often unpredictable effects of these drugs in critically ill patients.[1]

The vasopressor of choice in severe hypotension with low systemic resistance is norepinephrine (noradrenaline), whereas dopamine is often used in mild hypotension. Higher dosages of dopamine (>10 μg/kg/min) have

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Differential features

Comparison of some features of vasopressors used to treat septic shock[1]

Features	Dobutamine	Dopamine	Epinephrine (adrenaline)	Norepinephrine (noradrenaline)	Phenylephrine†
Dosage (μg/kg/min)	2.5–10	1–10/10–20	1–10 μg/min	0.05–2	2–10
Effect on haemodynamics:					
• arterial blood pressure	0 to ↑	↑/↑↑	↑	↑↑	↑↑
• cardiac output	↑	↑/↑↑	↑↑	↑↑	↓
• systemic vascular resistance	↓↓	0 to ↑/↑↑	↑	↑↑↑	↑↑↑
• pulmonary capillary wedge pressure	↓↓	↑/↑↑	0 to ↑	↑	↑

† Parenteral phenylephrine is not available in Spain.
Symbols: ↑ = slight increase; ↑↑ = moderate increase; ↑↑↑ = strong increase; ↓ = slight decrease; ↓↓ = moderate decrease; 0 = no effect.

greater haemodynamic effects than lower dosages and may increase splanchnic oxygen requirements.[10] Both norepinephrine and dopamine may mask hypovolaemia by increasing central venous pressure and therefore fluid resuscitation should be continued.[1] Some relevant features of vasopressors used in the treatment of septic shock are shown in the *Differential features* table.

Use diuretics to avoid overfilling

Once haemodynamic stabilisation is achieved, loop diuretics such as furosemide (frusemide) are used to obtain the lowest fluid volume for adequate organ perfusion. Clinically, it is often difficult to determine when to start diuretic therapy, although indications may include:[1]

- stable vasopressor requirements
- reversal of lactic acidosis
- pulmonary congestion on x-ray
- adequate or increased filling pressures.

Patients usually respond quickly to low doses (5 to 10mg) of intravenous furosemide, but if boluses up to 80mg are ineffective, a continuous infusion (up to 500 mg/day) might achieve negative fluid balances.[11] Alternative drugs include metolazone† (5mg) or low-dose dopamine (2 μg/kg/min). Patients not responding to these treatments are either still hypovolaemic, have a postrenal obstruction or are in acute renal failure.[1]

Additional options helpful

A number of additional treatments have been used in patients with severe hypoxaemia and ARDS or sepsis with the aim of optimising oxygen delivery, reducing oxygen consumption or modulating the inflammatory response.[1] Despite promising data for the efficacy of some treatments, more experience is needed to determine which patients will have the greatest benefit.

† Metolazone is not available in France and Spain; epoprostenol is not available in Germany.

Nitric oxide may improve oxygenation

Inhalation of low-dose nitrous oxide frequently improves oxygenation in patients with ARDS and ALI. However, there is controversy regarding the effects of nitrous oxide on clinical outcome,[12] and 2 randomised trials found no benefits of this treatment in patients with ARDS.[13,14] A trial of nitric oxide with or without a pulmonary vasoconstrictor (such as almitrine) is justified in patients requiring oxygen concentrations of 100% and with arterial oxygen tension (PaO_2) <12 kPa.[15] However, since nitrous oxide inhalation has potentially harmful effects, therapy should be discontinued if no clear benefit is present.[1]

Corticosteroids for serious cases

Corticosteroids may be useful in the late phase of ARDS: it has been suggested that therapy should be considered in patients showing no signs of improvement after 7 days.[1]

Some treatments lower oxygen consumption

Oxygen consumption can be lowered by treating fever with paracetamol (acetaminophen) and physical cooling or, occasionally, by inducing deep sedation using a combination of an opioid (most often morphine or fentanyl) and a benzodiazepine (lorazepam or midazolam). In the presence of renal or hepatic insufficiency, propofol is a valid, although expensive, alternative. Paralysis with pancuronium or vecuronium has been associated with critical illness polyneuropathy and is used only as a last resort.

More evidence needed for some strategies

Treatments such as surfactant, prostaglandins (alprostadil, epoprostenol†) and β_2-agonists have been shown to improve oxygenation in patients with ARDS, ALI or sepsis, although there is currently no evidence that they improve outcome.[1]

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Antibacterial-induced nephrotoxicity in the newborn can be avoided

Antibacterials are the leading cause of drug-induced kidney disease in all age groups. Although systematic epidemiological data on the incidence of drug-induced acute renal failure in the newborn are not available, an increase (up to 8-fold in the last 10 years) in the involvement of drugs in neonatal acute renal failure has been observed, both in infants and the newborn.

Haemodynamic abnormalities and/or electrolyte derangements may contribute to renal damage in seriously ill neonates receiving antibacterials

For some antibacterials (aminoglycosides and vancomycin), nephrotoxicity occurs very frequently in patients of all ages but is generally reversible upon discontinuation of the drug. However, the development of acute renal failure with these agents is possible and its incidence in neonates seems to be increasing. Antibacterials are frequently used in the neonatal period and exposure to antibacterials may be extremely widespread in very low birthweight neonates.

A knowledge of the nephrotoxic potential of antibacterial agents and appropriate strategies for minimising the risks for renal damage are essential in providing quality care for the newborn.

Direct toxicity most common cause

Antibacterials bring about renal damage via 2 main mechanisms: direct and immunologically mediated (see table 1).[1] Direct or toxic damage is the most common type of antibacterial-induced nephrotoxicity seen in neonates.

Often reversible

Nephropathy caused by antibacterials is often reversible upon drug discontinuation.[1] However, renal damage may alter the pharmacokinetics of the antibacterials, reducing renal excretion and creating a vicious cycle. Drug toxicity may then affect other organs (e.g. the inner ear, where toxicity is rare but the consequences can be irreversible).[2] Furthermore, the development of acute renal failure is possible.[2]

Early detection important

Traditional laboratory parameters of nephrotoxicity (e.g. serum creatinine level, blood urea nitrogen and urinalysis) are abnormal only in the presence of substantial renal damage. Therefore, the use of early noninvasive markers of renal damage (urinary microglobulins, enzymes and growth factors) is of importance. These markers are valuable not only in the identification of renal tubular damage (during the course of antibacterial therapy) but are also helpful in establishing its extent and monitoring its time course.[1]

In infants receiving aminoglycoside treatment, a rise in trough serum aminoglycoside concentrations may be the first indicator of nephrotoxicity. Therefore, therapeutic drug monitoring (TDM) may assist in detecting possible renal damage.

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