Management of hypoxaemia in the critically ill patient

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Management of Hypoxaemia in the Critically Ill Patient

Key Words:

Hypoxia; Hypoxaemia; Critical Care; Intensive Care; ARDS; Hospital Medicine

Key Points:

Hypoxaemia is defined as a lower than normal arterial blood oxygen level, whilst hypoxia refers to a lack of oxygen at a cellular level.

Hypoxaemia is a common presentation in critically ill patients, with the potential for severe harm if not addressed early.

Determining the nature, cause and severity of hypoxaemia is a key step in enabling effective treatment.

The treatment strategies required will be dependent on the clinical picture and may involve a combination of non-invasive and invasive modalities.

Severely hypoxaemic patients, not responding to initial treatment, should be discussed with critical care and specialist respiratory teams early.

Whilst some specialist centres may use advanced treatment strategies such as extra-corporeal membranous oxygenation (ECMO) in this patient group, further research to support and quantify their effectiveness is still required.
Abstract:

Hypoxaemia is a common presentation in critically ill patients, with the potential for severe harm if not addressed appropriately. The aim of this review is to provide a framework to guide the management of any hypoxaemic patient, regardless of the clinical setting. Key steps in managing such patients include ascertaining the severity of hypoxaemia, the underlying diagnosis and implementing the most appropriate treatment. Oxygen therapy can be delivered by variable and fixed rate devices, and non-invasive ventilation; if patients deteriorate they may require tracheal intubation and mechanical ventilation. Early critical care team involvement is a key part of this pathway. Specialist treatments for severe hypoxaemia can only be undertaken on an intensive care unit and this field is developing rapidly with the trial results becoming available. It is important that each new scenario is approached in a structured manner yet with an open diagnostic mind and a clear escalation plan.

Conflicts of interest

DM – Consultancy and lecture fees from Siemens Healthineers and Edwards Lifesciences
Management of Hypoxaemia in the Critically Ill Patient

**Introduction**

Hypoxaemia refers to a lower than normal arterial blood oxygen level, measured either as oxygen saturation (\(\text{SaO}_2\)) or partial pressure of oxygen (\(\text{PaO}_2\)). It is a common feature of acutely unwell hospitalised patients and can result in substantial morbidity and mortality if not treated rapidly and appropriately. Hypoxaemic patients may require admission to an intensive care unit (ICU), with more than 60% of those that do eventually requiring invasive ventilation. The mortality of hypoxaemic critically ill patients is 27%, rising to as high as 50% in patients with severe hypoxaemia (Grimaldi 2018).

A structured approach to the management of hypoxaemic patients is essential in order to establish a diagnosis and implement the most appropriate therapy. Knowledge of relevant physiology is important when considering both the diagnosis and treatment. Tailoring therapies to individual patients will be necessary, particularly in terms of oxygenation targets.

The aim of this review is to provide a logical framework that can facilitate the management of all hypoxaemic patients. The evidence base in this field is in a constant state of flux and there have been a number of key publications in the past few years that have made us rethink our approach to this problem.

**Definitions and basic physiology**

**Hypoxaemia**

No specific threshold of \(\text{SaO}_2\) or \(\text{PaO}_2\) defines hypoxaemia. Suggested normal values for \(\text{PaO}_2\) are 10.5 – 13.5 kPa, and for \(\text{SpO}_2\) are 94-98% (O’Driscoll 2017). This information can be obtained via arterial blood gas (providing \(\text{PaO}_2\) and \(\text{SaO}_2\)) and pulse oximetry (providing \(\text{SpO}_2\)). It should be noted...
that normal values decline with age and are influenced by the presence of co-morbidities such as chronic lung disease.

Describing the magnitude of hypoxaemia in a patient receiving oxygen can be challenging; from a physiological perspective, knowledge of the alveolar-arterial partial pressure difference (PA-aO₂) or ‘Aa gradient’ can be useful when determining the cause of hypoxaemia. It requires the patient’s arterial partial pressure of carbon dioxide (PaCO₂) to calculate it. Alternatively, the PaO₂ to fraction of inspired oxygen (FiO₂) ratio (PF ratio) may be a helpful guide to quantifying the degree of hypoxaemia and is frequently used in the setting of an ICU (see table 1).

Hypoxaemia may result from a multitude of pathologies; however, the basic physiology underlying these can be split into: hypoventilation, ventilation-perfusion (VQ) mismatch (either an increased or decreased VQ ratio), right to left circulatory shunting of blood, impaired diffusion of oxygen across the alveolar membrane and a reduced FiO₂ (Sarkar 2017). Respiratory failure is a broad term that describes inadequate gas exchange that either consists of hypoxaemia alone (type 1) or in combination with hypercapnia (type 2).

**Hypoxia**

The term hypoxia generally refers to a lack of oxygen at a cellular level. Severe hypoxia can affect the production of ATP by mitochondrial oxidative phosphorylation, threatening cellular integrity. Non-oxygen dependent bioenergetic pathways are referred to as anaerobic metabolism; they are short-term inefficient systems that are unable to sustain life for prolonged periods of time in humans. A brief summary of the causes of hypoxia can be seen in table 2.

One of the challenges in critically ill patients is that cellular oxygen levels cannot be measured. Anaerobic metabolism produces lactate as a biproduct; however, this generally indicates poor organ perfusion (ischaemic hypoxia) rather than a lack of oxygen.

**Acute Respiratory Distress Syndrome (ARDS)**

Management of hypoxaemia in the critically ill patient
ARDS is defined as: “The presence of new or worsening respiratory symptoms within 1 week of onset of symptoms; bilateral opacities on chest imaging not fully explained by effusions, atelectasis or nodules; respiratory failure from lung oedema not fully explained by cardiac failure or fluid overload; and oxygenation impairment. The degree of oxygenation impairment is defined by the following PF ratios: mild 40.0–26.8 kPa; moderate 26.7–13.4 kPa; severe ≤13.3 kPa.” (ARDS definition task force 2012).

ARDS can present in a broad range of patients and have a multitude of causes. The incidence in UK ICUs was estimated to be 12.5% (Summers 2016) and data from a worldwide multi-centre study suggested an in-hospital mortality of up to 40% (Bellani 2016). The pathophysiology that underlies ARDS is likely secondary to acute lung inflammation, resulting in increased vascular permeability, pulmonary oedema and worsening surfactant function. The culmination of this results in worsening gas exchange, shunt formation and worsening V/Q mismatch (Pham 2017). When severe this leads to extreme hypoxaemia. The complex pathophysiology behind ARDS means multiple treatment strategies have been suggested and trialled, often with little effect on mortality.

**Initial approach to the hypoxaemic patient**

**Clinical Assessment**

As with any acutely unwell patient, it is important to adopt the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach to assessment and management. During this it is essential to look for any life-threatening causes of hypoxaemia (e.g. pneumothorax) so these can be treated swiftly. The degree of hypoxaemia and nature of respiratory failure should be determined early, and appropriate monitoring implemented to evaluate deterioration and effectiveness of treatment. On ICU this usually consists of continuous \( \text{SpO}_2 \), intermittent ABGs and careful documentation of \( \text{FiO}_2 \). It
is also important to ascertain any past medical history suggestive of chronic cardiopulmonary
disease as this will aid in differentiating between worsening of chronic disease or acute pathology.

**Investigations**

It is important to try and identify the underlying cause of hypoxaemia so that an appropriate
treatment may be initiated. Table 3 summaries the common causes of hypoxaemia by pathology. A
routine panel of blood tests is indicated in most cases, with more specific tests (e.g. d-dimer and
cardiac enzymes) to be performed as clinically indicated. If infection is suspected then blood
cultures, an atypical pneumonia screen, sputum samples and HIV tests may also be relevant.
Depending on the clinical presentation it may also be appropriate to consider diagnoses such as
mycobacterium tuberculosis, pneumocystis pneumonia and vasculitis. Intubated patients may
benefit from a bronchoscopy +/- bronchoalveolar lavage, as this can be both a beneficial diagnostic
and therapeutic tool.

**Imaging**

Chest X-rays and ultrasound scans can be performed quickly and easily at the bedside and maintain a
high level of sensitivity and specificity across a broad range of pathologies. More complex cases may
require cross-sectional imaging in the form of computerised-tomography +/- pulmonary
angiography. Echocardiography is also a useful and quick bedside diagnostic tool; particular
attention should be paid to right ventricular function and pulmonary artery pressure, as this may aid
diagnosis of acute or chronic pathologies (e.g. pulmonary emboli or pulmonary hypertension) and
help guide treatments thereafter.
Non-invasive treatment strategies

Some general strategies can be used when approaching almost all ward-based hypoxaemic patients. It is important all such patients are managed in high-acuity wards, with constant pulse oximetry, regular clinical reviews and if appropriate, blood gas analysis.

Management of Type 1 Respiratory Failure

This is defined as hypoxaemia without hypercapnia. Firstly, simple strategies such as optimising patient positioning by sitting them upright, physiotherapy and upper airway suctioning in patients with abundant or thick secretions may aid ventilation. Variable performance oxygen masks and nasal cannula may be appropriate initially; however, their design prevents accurate or high concentration oxygen delivery. Patients with severe hypoxaemia may require high-flow oxygen, delivered via fixed performance masks with a precise FiO₂. Venturi masks fit these criteria and are available for 24 to 60% oxygen. Anaesthetic breathing systems such as the Water’s circuit also use high-flow oxygen and can deliver up to 100% oxygen. A non-rebreath mask requires 15 l/min of oxygen and can deliver up to 80% oxygen.

If traditional oxygen delivery systems fail to adequately oxygenate a patient, continuous positive airway pressure (CPAP) ventilation may be beneficial (BTS 2012). CPAP improves oxygenation by preventing the collapse of alveoli and small airways at the end of expiration and lessening VQ inequality via redistribution of fluid within the lungs (Mas 2014). Low levels of end-expiratory pressure can also improve cardiac function in the presence of left ventricular failure (by reducing the afterload) or right ventricular failure (by reducing the preload) (Sin 2000, Agarwal 2005). Administering CPAP requires specialist skills and frequent patient observations and review.
An alternative is high-flow nasal oxygen (HFNO), which provides flow rates of up to 60 litres per minute and delivers precise humidified oxygen concentrations up to 100%. It has been associated with significant improvement in acutely hypoxaemic patients in ICU (Sztrymf 2012). Proposed mechanisms of action include: positive airway pressure generation, flushing of dead space gas and benefits from humidification and heating of the oxygen delivered through the circuit (Ashraf-Kashani 2017).

Management of Type 2 Respiratory Failure

Type 2 respiratory failure is hypoxaemia with associated hypercapnia and is common in patients with chronic obstructive airways disease (COPD). The approach to managing a patient with hypercapnic respiratory failure (T2RF) is similar to T1RF, with the avoidance of severe hypoxaemia remaining key. The first step in treating these patients is the initiation of oxygen via a fixed performance device. A sub-group of patients with COPD are at increased risk of T2RF due to a combination of worsening VQ mismatch (following the loss of hypoxic pulmonary vasoconstriction), the Haldane effect and decreased minute ventilation (Hanson 1996). In such patients supplemental oxygen must be carefully titrated using fixed performance, with acid / base balance, neurological status and carbon dioxide levels closely monitored. It is important to emphasise that the risk of severe hypoxaemia in these patients outweighs that of hypercapnia.

If hypoxaemia and / or hypercapnia persists, non-invasive ventilation should be considered. Bi-level positive airway pressure (BIPAP) is the appropriate intervention; its benefit over CPAP for these patients is the addition of an inspiratory pressure to augment their tidal volume. The rise in minute ventilation that results from this should reduce PaCO₂. It is important these patients are reviewed regularly and their BIPAP settings adjusted according to their response. The British Thoracic Society / Intensive Care Society joint guidelines currently advise starting at an inspiratory pressure of 15
CMH\textsubscript{2}O and positive end expiratory pressure (PEEP) of 3 CMH\textsubscript{2}O, with the view to up titrate over 10-30 minutes until adequate ventilation is reached (targeting an SpO\textsubscript{2} of 88-92\%). If inspiratory pressure reaches >30 CMH\textsubscript{2}O or PEEP >8 CMH\textsubscript{2}O then expert review is advised. Contraindications to BIPAP include airway obstruction, recent upper gastrointestinal or cranio-facial surgery, facial / airway burns, high risk of aspiration and untreated pneumothoraces (Davidson 2015).

**Management of mechanically ventilated patients**

Failure to respond to high-flow oxygen and / or NIV may require a patient to be transferred to an ICU for consideration for invasive ventilation. Early referral to the ICU team will help them to assess the situation and determine the need for transfer. Indications for intubation and critical care referral for hypoxaemic patients include an inability to: maintain their airway; protect their airway from aspiration (e.g. low GCS); ventilate sufficiently; oxygenate sufficiently despite optimisation of non-invasive techniques; or anticipation of a deteriorating clinical picture. Mechanical ventilation in the acutely unwell patient requires sedation and usually neuromuscular blockade to facilitate tracheal intubation.

Not all patients will be suitable for this level of treatment as it comes at risk of multiple organ failure and prolonged ventilation and the possibility of the need for a tracheostomy. The ICU team, in discussion with the primary team, patient and patient’s relatives should establish this as soon as possible. Whilst mechanical ventilation should improve oxygenation and CO\textsubscript{2} clearance, it will not treat the underlying pathology; this will also need to be addressed to promote recovery.

A number of strategies have been used in mechanically ventilated ICU patients with respiratory failure, around 1/3 of whom will not survive (ICNARC 2018). Much of the research to date has focused on patients with ARDS but strategies for this syndrome can be considered in all patients.
with refractory hypoxaemia. What follows is a synopsis of these treatment strategies with the evidence base supporting their use.

**Pharmaceutical approaches**

Over recent years various pharmacological strategies have been trialled to aid management in severely hypoxaemic patients.

1. Neuro-muscular blocking agents (NMBA) are used to improve synchronisation of ventilation between the patient and ventilator, thus hopefully improving oxygenation and carbon dioxide clearance. A reduced mortality and number of days requiring mechanical ventilation has been demonstrated when used in patients with moderate to severe ARDS (Papazian 2010). Current consensus is in favour of their use in patients suffering from moderate or severe ARDS (Griffiths 2019).

2. Corticosteroids may be indicated for specific underlying diagnoses such asthma or COPD, usually in fairly modest doses. In patients suffering from ARDS, high-dose steroid strategies (e.g. 1 g IV methylprednisolone), have a low level of evidence supporting their use, with a possible associated reduction in mortality (Lamontagne 2009). However, the overall evidence pool remains largely equivocal.

3. Inhaled vasodilators (such as epoprostenol and nitric oxide) have also been used, this is based on the theory that they promote selective vascular dilatation in well ventilated areas of the lung, lessening VQ inequality (see fig 1). To date, no mortality benefit has been shown with their use (Griffiths 2019). However, some suggestions have been made supporting their use as a bridging strategy prior to rescue therapies such as extra-corporeal membranous oxygenation (Wright 2015).
**Fluid Management**

Fluid management in hypoxaemic patients is often complex and dependant on the underlying aetiology of the hypoxaemia. The overwhelming opinion is to avoid excess positive fluid balance. This is particularly relevant in cardiogenic pulmonary oedema and ARDS. Trials have demonstrated a decreased mortality associated with a conservative (neutral) vs liberal fluid approach in such patients and therefore this approach is currently advised (NHLBI ARDS Clinical Trials Network 2006, Griffiths 2019).

**Ventilation strategies**

All mechanically ventilated patients should receive lung protective ventilation. This has been defined as a tidal volume (TV) of $\leq 6\ \text{ml/kg}$ and plateau pressure $\leq 30\ \text{cmH}_2\text{O}$ (as per ARDSnet protocol). This has been shown to reduce mortality, and local and systemic inflammation in mechanically ventilated patients (ARDSnet 2000, Wolthuis 2008). Originally recommended for those patients with ARDS, it is now clear that to prevent damage to lung parenchyma lung protective ventilation should be the default whenever mechanical ventilation is required. Thus, the consensus is that most patients should be ventilated with a TV of $\leq 6\ \text{ml/kg}$, unless there is a specific contraindication.

The use of high PEEP ($> 10\ \text{cmH}_2\text{O}$) in hypoxaemic patients stems from the idea that it may improve alveolar ventilation by reducing atelectasis and splinting small airways open. Trials looking into the use of high PEEP in patients with ARDS demonstrated that patients who improved following its initiation, then benefitted from its continued use, with no increase in hyper-inflation and barotrauma recorded (Guo 2018). Evidence to date is in support of the use of high PEEP in patients with severe hypoxaemia/ARDS who are initially responsive to high PEEP levels (Griffiths 2019). A degree of PEEP, although not high, is used in the majority of ventilated patients.

**Prone positioning**

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In patients with moderate or severe ARDS a strong evidence base is forming regarding the benefits of ventilating them in the prone position. The prone position improves VQ matching by creating a more homogenous pleural pressure gradient, reducing atelectasis and improving drainage of secretions (see Fig. 2). Meta-analyses have shown a reduction in mortality in patients suffering from ARDS, most significantly so when patients are in the prone position for at least 12 hours (Hu 2014, Park 2015).

**Extra-corporeal CO\(_2\) removal (ECCOR):**

The CO\(_2\) removal provided by this technique allows lung protective and ultra-low TV to be used in acutely hypoxaemic patients, who would otherwise develop severe hypercapnic acidosis (Peperstraete 2017). There is currently ongoing research being performed looking into use of ECCOR in awake patients suffering from COPD in order to prevent intubation. At this time there is no evidence for or against this treatment strategy so further research is required. Other suggested management strategies include permissive hypercapnia, permissive acidosis (pH >7.2) and the use of sodium bicarbonate, however, more research is required.

**Extra-corporeal membranous oxygenation (ECMO)**

A full description of ECMO is beyond the scope of this article. Veno-venous ECMO facilitates oxygenation of severely hypoxaemic patients via an extracorporeal circuit and is only available in specialist centres. It requires the insertion of large cannulae into central vessels, anticoagulation of the circulation and specialist ICU nursing skills. In patients with severe refractory hypoxaemia, referral to a specialist ECMO should be considered early. Criteria for referral to such centres may vary but are generally: severe hypoxaemia (PF ratio <13.3 kPa), severe hypercapnic acidosis (pH <7.20), inability to achieve lung protective tidal volumes, nil improvement with rescue therapies.
such as prone position and significant air leak or broncho / pleural fistula. The evidence surrounding the use of ECMO in patients with ARDS is constantly being re-visited, with a small reduction in mortality suggested historically (Peek 2009). However, the 2018 EOLIA trial looking at ECMO in severe ARDS showed no significant improvement in 60 day mortality, with the trial terminated early for futility (Combes 2018).

**Conclusion**

Management of a critically ill hypoxaemic patient can be a complex and challenging task. It is important to maintain a structured approach, attempt to identify an underlying cause and pay close attention to any signs of deterioration. The degree and nature of hypoxaemia will direct the chosen treatment route. The clinical picture should constantly be re-reviewed, whilst asking one’s self: Is this patient still severely hypoxaemic? Does this patient require escalation to critical care? Does this patient require referral to a tertiary respiratory centre? If the answer to any of these questions is yes, then immediate advice should be sought. In patients requiring invasive ventilation, lung protective techniques should be used in all cases. Treatment strategies such as the prone position, high PEEP, corticosteroid use, NMBA and a conservative fluid balance may be beneficial in patients with moderate to severe ARDS. Whilst ECMO, ECCOR and inhaled vasodilators may also confer some benefit, more research is indicated to support their ongoing use.

The treatment of severe hypoxaemia is likely to continue to evolve as more research and trials are performed. Nevertheless, as clinicians it is important we approach each new scenario with a reliable structure, an open diagnostic mind and a clear escalation plan.
Figures

Figure 1. Poorly aerated regions of lung result in VQ mismatch, as blood to these areas is poorly oxygenated. Inhaled vasodilators result in dilatation of vasculature surrounding healthy lung units, with increased blood flow, oxygenation and thus reduction in V/Q mismatch and shunting.
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Figure 2. When supine, gravity and the weight of the heart result in compression of dependant dorsal areas of lung and thus hypoventilation. In the prone position, the alveoli become more homogenous and the weight of the heart is instead on the sternum. This leads to increased perfusion of dorsal lung segments with reduced V/Q mismatch. Perfusion in the lung is remains largely dorsal in both the supine and prone position. Note red shading indicates most perfused lung regions.

(Diagram adapted from Scott JB ‘What’s New About Proning?’ Rush University)
### Tables

<table>
<thead>
<tr>
<th>Arterial partial pressure of oxygen (PaO2) (mm Hg)</th>
<th>Fractional inspired oxygen concentration (FiO2)</th>
<th>SEVERITY OF HYPOXAEMIA According to P:F Ratio</th>
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<td>0.21 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00</td>
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</table>

Table 1. PaO2 to FiO2 ratio association with severity of hypoxaemia.
### Table 2. Causes of hypoxia (a lack of oxygen at the cellular level)

<table>
<thead>
<tr>
<th>Cause of Hypoxia</th>
<th>PaO₂</th>
<th>Common causes</th>
<th>Treatment strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic</td>
<td>Low</td>
<td>Altitude</td>
<td>Supplementary oxygen</td>
</tr>
<tr>
<td>Anaemic</td>
<td>Normal</td>
<td>Bleeding and anaemia</td>
<td>Blood transfusion and address underlying cause of anaemia</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>Normal</td>
<td>Embolism, thrombus</td>
<td>Treat underlying cause by increasing blood flow to target organ</td>
</tr>
<tr>
<td>Histotoxic</td>
<td>Normal</td>
<td>Cyanide poisoning</td>
<td>Reverse / address causal agent, [increasingFiO₂ is not beneficial]</td>
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### Table 3. Common causes of hypoxaemia

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Speed of onset and symptoms</th>
<th>Examination findings</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Pneumonia</td>
<td>Days to weeks, infective symptoms, check travel Hx</td>
<td>Pleuritic chest pain, systemic signs of infection, possible crackles/bronchial breathing on auscultation</td>
<td>CXR, sputum samples, CT may be required if complex</td>
<td>As per local sepsis and antimicrobial guidelines, supplementary oxygen often required</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>Acute if new event. If inpatient, check fluid balance and preceding history</td>
<td>Peripheral signs of heart failure if cardiogenic, bilateral crackles, peripheral oedema</td>
<td>CXR, ECHO, ultrasound</td>
<td>If acute event – as per ACS treatment, diuresis, CPAP to be considered</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Commonly acute</td>
<td>Pleuritic chest pain, reduced air entry, increased resonance on percussion</td>
<td>CXR, ultrasound scan, CT may be required if complex</td>
<td>If tension Px – needle decompression and chest drain insertion, otherwise as per BTS guidelines dependant on size and PMH</td>
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<tr>
<td>Pulmonary embolism</td>
<td>Commonly acute, can present as chronic – Hx often reduced mobility or pro-coagulant state</td>
<td>Pleuritic chest pain, tachycardia, tachypnoea, possible circulatory collapse</td>
<td>CTPA as gold standard, ECHO for R heart strain, V/Q scan if CTPA not possible</td>
<td>If circulatory collapse and nil contra-indications – thrombolysis as per guidelines. Otherwise anti-coagulation as per BTS</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Acute or chronic</td>
<td>Reduced air entry at site of effusion, stony dull to percuss</td>
<td>CXR, ultrasound, CT scan is complex</td>
<td>As per BTS management, if significant or possibly infective then pleural tap +/- drain insertion</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>Commonly acute, often associated with trauma</td>
<td>Reduced air entry, dull to percuss, may have signs of trauma</td>
<td>CXR, ultrasound, CT scan</td>
<td>If indicated – surgical chest drain insertion</td>
</tr>
</tbody>
</table>
References


Management of hypoxaemia in the critically ill patient


