Individualising management of severe respiratory failure and the specialist commissioned severe respiratory failure service for England

N Barrett, L Camporota, C Langrish, G Glover, R Beale

Despite the improvement in the survival rate in patients with acute respiratory distress syndrome, there is a cohort of patients with severe hypoxaemia and hypercapnia who offer a significant therapeutic challenge and may require some of the more contentious rescue therapies, including prone positioning, high-frequency oscillatory ventilation and extracorporeal support. It is essential to implement a protocolised pathway for diagnosis and individualised treatment for these patients. In 2011, the English National Specialist Commissioning Service established a number of severe respiratory centres for England including the provision of extracorporeal membrane oxygenation. Early referral is essential for the successful use of rescue therapy as the evidence indicates that the time of mechanical ventilation prior to rescue therapy is a key predictor of mortality. Guy’s and St Thomas’ NHS Foundation Trust has been commissioned as one of the severe respiratory failure services and we describe the process of assessment and management that we have instituted to manage patients with severe respiratory failure.

**Keywords:** adult ARDS; mechanical ventilation; lung injury; recruitment; extracorporeal membrane oxygenation

**Introduction**

The current operative definition of acute respiratory distress syndrome (ARDS) has been well established for the last 15 years.1 Over this time, significant research into the mechanisms and management of patients with ARDS has led to a gradual improvement in patient mortality from 90% in the 1970s, to 40% in the mid-late 1990s, down to 25-30% in the most recent trials.2-4 Besides the general improvement in the standard of care provided in the intensive care units (ICUs), the only specific management that has consistently been shown to reduce mortality in ARDS is the provision of mechanical ventilation with static inspiratory pressures (plateau pressure) of less than 30 cm H2O and low tidal volumes normalised to predicted body weight (PBW) according to a concept known as ‘lung-protective ventilation’ (LPV). This strategy has been shown to reduce ventilator-induced lung injury (VILI), and is linked to improvements in short- and long-term outcomes for the majority of patients.5

Despite this global improvement in survival, there is a cohort of patients with severe hypoxaemia (PaO2/FiO2 ratio <13.3 kPa) and hypercapnia (leading to a pH <7.20) who offer a significant therapeutic challenge. This group of patients, even when managed with optimal recruitment and LPV, have a significantly higher mortality than patients with a higher PaO2/FiO2 ratio or lower PaCO2 for a given minute ventilation.6-8 The identification of a subgroup of patients with ‘severe’ ARDS, has been made more explicit in the new ‘Berlin definition of ARDS’,9-11 allowing for targeted therapeutic interventions and further clinical studies.

Furthermore, this particular cohort of patients may be the group who benefit from some of the more contentious rescue therapies, including prone positioning, steroids, high-frequency oscillatory ventilation (HFOV) and extracorporeal support – such as extracorporeal CO2 removal (ECCO2R) and extracorporeal membrane oxygenation (ECMO).

**A model for severe respiratory failure management**

ARDS is the end result of a series of pathophysiological processes caused by a wide variety of triggering conditions. The pathological hallmarks are diffuse alveolar damage and alveolar-capillary junction dysfunction causing initial egress of fluid into the alveoli (exudative phase), followed by a proliferative phase then either recovery or progressive fibrosis.12 The clinical sequelae consist of significant hypoxaemia, hypercapnia, poor respiratory system compliance and progressive alveolar infiltration on chest imaging, that are not exclusively due to cardiogenic pulmonary oedema. Despite the apparent pathophysiological similarities, ARDS is essentially the final common pathway of a wide range of
known triggering conditions. Each triggering disease has its own natural history, morbidity and mortality and requirement of specific treatments beyond the common ground of the supportive therapies. An acute viral pneumonitis, such as seen in the 2009-2011 influenza A (H1N1) pandemics is a different disease process to a bacterial pneumonia, to an aspiration pneumonitis, to acute pancreatitis, to transfusion-associated lung injury, and so on.\(^\text{13}\) Furthermore, each disease has a slightly different expression in each patient, almost certainly due to the host response having a causative role in the sequelae of ARDS. When considering severe respiratory failure however it is important to remember that, although patients may present with refractory hypoxaemia, poor respiratory system compliance and progressive alveolar infiltrates that are potentially consistent with severe ARDS, the underlying diagnosis can at times be pathologically inconsistent with ARDS (eg lymphangitis carcinoatmosa, primary pulmonary Kaposi’s sarcoma and non-specific interstitial pneumonitis are recent cases managed at our institution). These conditions need to be diagnosed and specific management plans instituted.

Although a conventional, evidence-based management strategy which limits tidal volume, plateau pressures and fluid administration, and aims to optimise PEEP have been demonstrated to impact upon the progression of the lung injury\(^\text{14-16}\) the best course of management for patients with refractory and life-threatening hypoxaemia or hypercapnia despite LPV remains unclear. The options include the administration of nitric oxide, LPV in prone position, HFOV, and LPV with ECCO\(_2\)R or ECMO. Although these modalities have a well-demonstrated benefit on improving gas exchange, the data supporting their benefit on mortality outcomes are still limited and often conflicting.\(^\text{20}\) Each treatment has a different risk profile, degree of invasiveness and resource utilisation. In addition, the level of expertise and training required dictate and limit their availability. There is also no evidence supporting the use of a particular ‘rescue’ therapy over any other for an unselected patient population. Given the heterogeneous population of patients with severe respiratory failure, how does one choose which therapy will best suit an individual patient?

At Guy’s and St Thomas’ Hospitals (GSTT) we have developed a pathway for the management of severe respiratory failure (Figure 1). The key elements of the pathway are protocolised diagnostic investigations, optimisation of LPV and haemodynamics, and a graded approach to therapy, based around the complexity of the intervention, likelihood of response to that intervention and the individual patient’s risk profile suggested by their co-morbidities.

**The GSTT severe respiratory failure pathway – diagnosis**

The diagnosis of the triggering disease in patients presenting with severe respiratory failure can be relatively straightforward and based upon the presenting history, physical examination and the initial investigations. However, it is not always so. We use a multimodal diagnostic pathway incorporating radiology, broncho-alveolar lavage (BAL) and serology to attempt to delineate the underlying diagnosis (Table 1). All patients with severe respiratory failure routinely have a high resolution chest CT as early as possible in their admission, usually as they are being retrieved into our institution from referring centres. The CT is subsequently considered at our respiratory radiology multi-disciplinary meeting, along with any previous radiological investigations that are available. There is early and sustained microbiology, virology and rheumatology involvement in the management and investigation of patients.

All patients also undergo an early screening trans-thoracic echocardiogram (TTE) and when necessary more detailed cardiac investigation. Routine TTE has significant advantages in this population, giving guidance on filling status with inferior vena caval compressibility and the appearances of the left ventricle as well as assisting in the diagnosis of valvular disease, ventricular failure and the presence of intracardiac shunts. Bronchoscopy is routinely used for this patient cohort. Although it may introduce temporary physiological instability, it can allow both investigations (cultures and cytology from broncho-alveolar lavage) and management (the identification and removal of inpsissated secretions) to be addressed. This

---

**Table 1** Initial routine investigations performed. More targeted investigations are requested based on history and initial investigations.

<table>
<thead>
<tr>
<th>Investigations</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular screen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune screen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV and HSV viral load</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary pneumococcal and Legionella antigens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broncho-alveolar lavage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory virus PCR panel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV/HSV inclusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB screen and culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening transthoracic echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional echocardiography or coronary angiography as appropriate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Breakdown of diagnoses by form of rescue support. Five patients had more than one support, all eventually requiring ECMO.
approach has allowed for the early diagnosis and appropriate treatment of a number of patients with significant underlying disease processes that were not recognisable from the presenting history (Table 2).

Of the last 50 patients with severe respiratory failure admitted to our service, all presented with features consistent
with acute bacterial or viral lung infections or with a history suggestive of aspiration pneumonitis and although, in the majority of cases, the initial diagnosis was confirmed by the described protocolised approach, in some cases alternative diagnoses have been found (malignancy, interstitial lung disease and primary cardiac pathology) which required specific interventions and were not compatible with the denomination of ARDS.

**The GSTT severe respiratory failure pathway - management**

The aim of our severe respiratory failure pathway is firstly to optimise conventional ventilation using the established evidence base then attempt to offer the optimal rescue therapy (Figure 1). Choosing which form of support to use can be a very difficult decision.

The first step is to assess patient recruitability, in other words the possibility of obtaining improvement in gas exchange and lung mechanics following a 'high pressure' strategy as a consequence of increasing the proportion of aerated lung. Patients only undergo recruitment assessment strategies if there is demonstrable hypoxaemia on the current ventilatory regime and rescue strategies are being considered. Although the benefit of a recruitment manoeuvre remains unclear and may entail risk of both hypotension and acute desaturation, given the relative risks of rescue therapies, we find that this can assist in identifying patients who will be able to be managed with less aggressive therapies. Recruitability is also assessed using changes in lung mechanics in response to recruitment manoeuvres (RM) modelled on the protocol byGattinoni et al, which involves a lung CT scan at two levels of PEEP 5 and 45 cm H2O. This is only performed if, in the judgement of the consultant managing the patient, the patient is stable enough to tolerate the manoeuvre. Anecdotally we have found that there is a correlation with patients who recruit well on CT and subsequently recruit well on HFOV and we have been using this while considering our initial rescue strategy. More recently, we have been measuring end-expiratory lung volume at two PEEP levels pre- and post-RM using the nitrogen wash-out/wash-in technique to quantify lung recruitability, and electrical impedance tomography (EIT) to assess at the bedside the regional distribution of ventilation and change in regional compliance post RM. If patients are demonstrated to be 'recruitable' then patients may persist with either conventional LPV with higher PEEP or HFOV. If patients with refractory hypoxaemia are 'non-recruitable' they are fast-tracked to ECMO.

If patients are 'recruitable', we measure trans-pulmonary pressure using oesophageal manometry to titrate plateau pressure and PEEP to ensure lung protection with an open lung strategy. If the inspiratory plateau trans-pulmonary pressures are >25 cm H2O, patients are treated with either HFOV or consider LPV with extracorporeal CO2 removal (ECCO2R) to further reduce tidal volumes until the trans-pulmonary inspiratory pressure is <25 cm H2O. If the patient responds well to HFOV (ie, relative increase in PaO2/FiO2 ratio by more than 38%) then they are predicted from our analysis of 102 cases to respond to HFOV and they remain with this support. If however the PaO2/FiO2 and PaCO2 have not improved we convert them to ECMO. A small number of patients do improve their oxygenation sufficiently on HFOV or LPV but have significant refractory hypercapnia. In this group we do arterio-venous ECCO2R for these patients in combination with HFOV or LPV. The optimal role of ECCO2R is however currently unclear and although it may be of benefit to use it earlier as an addition to conventional ventilation, further studies are required to support this.

Prone positioning is not a clear step within our guidelines. Prone positioning has had a number of studies over the years, many of which have demonstrated significant physiological benefit. A recent meta-analysis byGattinoni et al has demonstrated a mortality benefit associated with prone positioning in severe respiratory failure. We also use conventional ventilation or HFOV in prone position in those patients with severe ARDS and with lung recruitability, but large regional inhomogeneities as suggested by CT or EIT, especially with a significant basal distribution of disease. If there is limited or no improvement, we convert to other forms of support within 24-48 hours.

Neither inhaled nitric oxide, nor inhaled prostacyclin are steps within our guideline due to the evidence for physiological improvement without mortality benefit associated with these approaches. We do however use nitric oxide in cases where there is pulmonary hypertension and right ventricular failure after the correction of hypoxaemia and hypercapnoea. Whether this approach confers a mortality benefit for patients is unknown.

Using this approach in the period December 2011-March 2012 we have admitted 26 patients with severe respiratory failure. Ten patients underwent ECMO, nine HFOV, three Novalung and four patients had conventional ventilation in the prone position. Overall 20/26 survived (77%), 8/10 ECMO, 7/9 HFOV, 1/3 Novalung and 4/4 conventional. However, of the deaths, all had uncorrectable underlying disease such as metastatic malignancy, non-specific interstitial pneumonitis or severe chronic obstructive pulmonary disease. These comorbidities or their severity were not known at the time of referral to our service. Although these are small numbers and it is difficult to make meaningful comparisons, the mortality in the published literature for patients with severe respiratory failure is 40-60% in large series.

Although some of our approach is based on the available evidence, the pathway in its entirety is not. However, there are relatively few trials examining specific therapies and even fewer comparing the relative merits of one form of support over another. Furthermore, given the complex nature of the patients and the wide range of comorbidities and aetiologies of the respiratory failure, each patient presenting with severe respiratory failure really needs tailored management to optimise the benefit and minimise the risks of therapy. This in turn may allow improvement in survival. Over time our approach will be further refined as more evidence becomes available. In particular techniques such as EIT have the potential to improve our ability to predict patients who will respond to recruitment or prone positioning. We also need to understand how the initial supportive therapy interacts with medium- and long-term outcomes for survivors. The evidence from patients managed...
with either ECMO or LPV is that there is a medium- and long-term improvement in respiratory function with persisting neuromuscular weakness and psychological problems lasting out to at least five years. Clearly long-term observational studies are required to assess any sustained difference in outcome between patients managed with different rescue therapies and this in turn needs to be considered when selecting supportive therapy during the acute illness.

**The Severe Respiratory Failure Service for England**

The National Specialist Commissioning Service in the UK held a tender process over 2011 to establish a number of severe respiratory centres for England. The results of that process were announced in December 2011 with five centres being commissioned to provide management for patients with severe respiratory failure – Glenfield Hospital in Leicester, Wythenshawe Hospital in Manchester, Papworth Hospital in Cambridge, the Royal Brompton Hospital and Guy’s and St Thomas’ Hospitals in London (Figure 2). This aims to give the UK a flexible and distributed tertiary capacity for patients with severe respiratory failure with the provision of ECMO and retrieval services included.

What is the rationale for this approach? Firstly the decision to have a small number of centres with higher volumes is based on the available evidence, where there has been an association between improved outcomes and volume of patients in a diverse range of fields – cardiology, oncology, cardiac surgery and indeed in the outcomes from mechanical ventilation. Secondly, a key component, the ability to provide ECMO, is particularly resource intensive. In part it requires significant capital to set up and maintain a programme, but mainly it is very heavily dependent upon having appropriate numbers of trained staff – nursing, perfusion, medical, physiotherapy and dietetics as well as the need for on-site back-up services including vascular and cardiothoracic surgery. Hence it is difficult to set up and maintain ECMO without a substantial investment in staffing and education in order to manage patients and potential complications.

The referral process for the network is straightforward. All regions in England have a nominated centre to which they refer. The referral criteria are patients with severe respiratory failure that is believed to be reversible, with a Murray score of 3 or more, with seven days or less of a plateau pressure greater than 30 cm H$_2$O and a FiO$_2$ of greater than 0.8. Early referral is essential for the successful use of rescue therapy as the evidence indicates that the time of mechanical ventilation prior to rescue therapy is a key predictor of mortality. This is thought to relate to the progression of ventilator-induced lung injury. Patients accepted into the service will be retrieved by the accepting centre either by using a conventional approach or using mobile ECMO. It is the centre’s responsibility to find a bed in the event that they have insufficient resources.

Retrieval of patients with severe respiratory failure is well established internationally with retrieval services in Australia, the US and Europe routinely transporting and managing patients on ECMO. Depending on the country involved these are either institution-dependent or centrally organised.

The UK has for many years had an excellent, though regional, specialist primary retrieval network able to respond to trauma, search and rescue and major incidents. Inter-ICU transfers have been performed in the UK on an ad-hoc basis, often utilising trainees with an on-demand ambulance organised by the referring hospital. In the case of severe respiratory failure referrals all retrievals are performed by a consultant or senior trainee with significant experience in the management of patients with severe respiratory failure and have to meet national standards of governance and audit. Such a system has been demonstrated to be safe for patients. CESAR demonstrated a 2.2% transport-related mortality. In our own series of cases we have successfully undertaken inter-hospital transport for 56 patients with severe respiratory failure over the last 18 months and had suffered no transport-related mortality.

**Horizon scanning**

There are a number of research and technological advances that will be impacting the management of severe respiratory failure in the next few years. Firstly, two major HFOV studies (OSCAR and OSCILLATE) will report their findings. Secondly, there are a number of new extracorporeal CO$_2$ removal devices that will be available, including A-LungTM, Novalung ActiveTM and HaemotecTM. Although each offers different technical solutions, all use a veno-venous approach to provide CO$_2$ clearance with a relatively low blood flow. At present there is little robust data to demonstrate that this technology improves patient outcomes, although there are case series and registry data sets demonstrating physiological improvements. It is intuitively appealing that these devices may well assist in the management of hypercapnic respiratory failure and may provide some benefit in the management of ventilated patients with severe respiratory failure.

**Declaration of interests**

The authors have no personal financial interests to disclose.

**References**


Original articles

Nicholas Barrett Consultant in Critical Care nicholas.barrett@gstt.nhs.uk
Luigi Camporota Consultant in Critical Care luigi.camporota@gstt.nhs.uk
Chris Langrish Consultant in Critical Care chris.langrish@gstt.nhs.uk
Guy Glover Consultant in Critical Care guy.glover@gstt.nhs.uk
Richard Beale Consultant in Critical Care richard.beale@gstt.nhs.uk
Department of Adult Critical Care, Guy’s and St Thomas’ NHS Foundation Trust, King’s Health Partners