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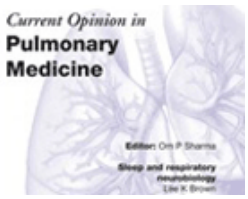
Severe Pneumonia in Intensive Care

Cause, Diagnosis, Treatment and Management: A Review of the Literature



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Abstract and Introduction

Abstract

Purpose of review Severe pneumonia is a common disease that intensive care physicians have to face. The review highlights recent findings about microbiology, diagnosis and treatment, including the management of critically ill patients with severe respiratory failure.

Recent findings Epidemiological and clinical risk factors strongly influence microbiological cause in patients with severe pneumonia. In addition to typical respiratory pathogens, less common microrganisms and multidrug-resistant (MDR) germs may cause severe lung infections. New molecular diagnostic techniques appear promising for early detection of microbes involved in severe pneumonia. Antimicrobials remain the mainstay of causative severe pneumonia treatment and the optimization of antibiotic therapy may be obtained by applying their pharmacodynamic/pharmacokinetic properties. Several new strategies have been implemented for the management of acute respiratory failure (ARF) due to severe pneumonia; however, their extensive clinical application is limited by the need for well trained physicians and adequate hospital centers.

Summary Despite advancements in antibiotic and life-supportive treatments, severe pneumonia remains a leading cause of intensive care unit (ICU) admission and death. Prompt and appropriate antimicrobial therapy is essential. The use of new nonconventional strategies for ARF management might be effective in more severe patients.

Introduction

Severe pneumonia in intensive care unit (ICU) patients represents a major concern for physicians because of the high mortality and morbidity rate attributable to these episodes.[1–3] During past decades many strategies have been implemented with the aim to optimize the outcome of patients with severe lung infections, and part of these efforts is focused upon the need to best define and predict illness severity.[4•] Additionally to some other available clinical scores, the last Infectious Diseases Society of America/American Thoracic Society(IDSA/ATS) guidelines have assessed major and minor criteria that seem to best define the severity of community-acquired pneumonia (CAP) and decide the need for ICU admission.[5,6•] It is note worthy that these scores were created for severe CAP (SCAP) and their application to the other severe pneumonia categories may be only extrapolated. Furthermore it might be difficult to discriminate whether a pneumonia is really community-acquired (CAP) or has been developing in a patient who was exposed to the healthcare environment [healthcare-associated pneumonia (HCAP)] or has been acquired in the hospital setting [hospital-acquired pneumonia (HAP)].[7,8•] Critically ill patients, already admitted to ICU, may subsequently develop severe pneumonia[9] [ventilator-associated pneumonia (VAP); nonventilator ICU-acquired pneumonia(NV-ICUAP)]. Both community-acquired or nosocomial pneumonia can progress to acute respiratory distress syndrome (ARDS) and acute lung injury(ALI), which are associated with a mortality rate of more than 50%.[10]

The aim of this study is to review the current knowledge about ICU patients affected by severe pneumonia, with regards to microbiological, diagnostic, therapeutic and management aspects.

Cause and Epidemiology

Causative agents of severe pneumonia may widely differ, mainly depending upon epidemiological and clinical factors (Table 1). Up to 10% of hospitalized patients with CAP need intensive therapies because of respiratory failure requiring mechanical ventilation and/or septic shock.[5,14] The frequency of microbiologically documented CAP is around 25%among in-patients, but the percentage of isolated pathogens in SCAP may be higher, due to the availability and extensive use of more reliable diagnostic tools in ICU.[15,16] In a recent cohort analysis, Restrepo *et al*.[1] observed *Streptococcus pneumoniae, Staphylococcus aureus* and *Pseudomanas aeruginosa* as the main pathogens isolated in patients admitted to ICU for severe pneumonia. *S. pneumoniae*, historically known as 'Captain of Men of Death',[17] harbors virulence factors that may induce an unbalanced systemic inflammatory response syndrome(SIRS) responsible for the disease severity, and this condition has been demonstrated to be associated with specific host genotypes.[18•] *Legionella pneumophila* is an agent well known to be responsible for SCAP and immune-mediated extrapulmonary involvement is often reported.[19] Mortality rate in *Pseudomanas* SCAP may be extremely high due to its capability to produce many virulence factors and protective biofilms.[20] *S. aureus* as causative agent of SCAP may be isolated from patients affected by influenza. Furthermore the rate of methicillin resistance

among severe community-acquired lung infections is growing continuously.[21] Among 128 patients with *S. aureus* CAP studied by Taneja *et al*.,[22] 79% were admitted to ICU and 24 died. Forty-three patients had initial cultures positive for methicillin-resistant strains.[22] Among viruses, adenovirus, respiratory syncytial virus, seasonal influenza and parainfluenza are mainly detected in respiratory samples, often as mixed bacterial infections. Swine origin influenza A (H1N1 2009) developed in 214 different countries causing 18 000 deaths and involved middle-age (20–40 years) patients, whereas obesity and pregnancy appeared to be important risk factors for severe respiratory complication occurrence (ALI/ARDS).[23•] Other pulmonary pathogens among bacteria (*Mycobacterium* spp.),viruses (herpesviruses), fungi (*Aspergillus* spp., *Pneumocystisjiroveci*, especially in patients with human immunodeficiency virus, *Cryptococcus neoformans* and endemic mycoses) and parasites may cause respiratory insufficiency in immunosuppressed patients.[24]

Table 1. Most common causes of severe pneumonia

SCAP[5] (mainly drug-susceptible strains)	**Severe HCAP/HAP/'late onset' VAP[11–13] (mainly multidrug-resistant strains)**
•*Streptococcus pneumoniae*	•*Pseudomonas aeruginosa*
• *Haemophilus influenzae*	•*Acinetobacter* spp.
• *Staphylococcus aureus*	•*Enterobacteriaceae* (*Klebsiella pneumoniae*; *Escherichia coli*; *Enterobacter* spp.)
• *Legionella* spp.	•*Staphylococcus aureus*
• Gram-negative bacilli	
• Virus and fungi (mainly in immmunosuppressed population)	

HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; SCAP, severe community-acquired pneumonia; SP, severe pneumonia; VAP, ventilator-associated pneumonia.

The real bacterial epidemiology of HCAP is still a challenge: about half of these pneumonia cases are culture-negative.[25•] However, those episodes severe enough to need intensive therapies are better documented microbiologically and they are usually caused by multidrug-resistant (MDR) pathogens.[26] A quarter of patients with HCAP die, due to the severity of the disease.[27,28] Among 190 severe pneumonia cases (ARDS rate 37%) retrospectively analyzed by Schreiber *et al*.,[29••] the most commonly isolated pathogens in episodes classified as HCAP were methicillin-resistant *S. aureus* (MRSA)and *P. aeruginosa. S. pneumoniae* and methicillin susceptible *S. aureus* were the most frequently isolated pathogens in those classified as SCAP. Six leading MDR bacterial species have been identified as causative agents of HAP/VAP: *S. aureus*, *P. aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Acinetobacter baumannii*, *Enterobacter* spp. The high frequency of drug resistance and the co-existence of several comorbidities are responsible for high mortality rates, despite ICU admission.[11,30] Recently Esperatti *et al*.[31••] observed in a large prospective cohort of ICU-acquired pneumonia that the causative agents (mainly *P. aeruginosa* and *S. aureus*) inpatients not mechanically ventilated were similar to those causing VAP, with similar mortality rate(42 vs. 36%; $P = 0.4$).

Diagnosis

Pretreatment blood and lower respiratory tract samples for culture should be collected in all patients with severe pneumonia.[32••] In a recent retrospective study involving 3116 consecutive patients with CAP, Falguera *et al*.[33] developed a prediction score, including six variables, for estimating the risk of bacteremia. The authors observed that patients with a score value of at least 2 showed a blood stream infection rate ranging between 16 and63%. Urinary antigen assays are available in order to detect *S. pneumoniae* and *L. pneumophila* infections.[5] Main advantages of their use rely on high diagnostic accuracy, immediate availability of the results and good performance under antibiotic therapy. Ameta-analysis showed that *Legionella* urinary antigen test has excellent specificity (0.99) but lower sensitivity (0.74); however, the authors observed poor quality and publication bias in the available studies.[34] A recent prospective study upon a cohort of 171 adult patients hospitalized with CAP (ICU admission, 8%) observed a sensitivity of71% and a specificity of 96% for pneumococcal urinary antigen test.[35•] In patients affected by severe pneumonia who did not still receive endotracheal intubation (ETI), the diagnostic reliability of deep cough-produced sputum and nasopharyngeal aspirates is uncertain.[36] The application of noninvasive ventilation (NIV) enables the performance of fiberoptic broncoscopy (FOB) with bronchoalveolar lavage (BAL) in hypoxemic patients with pneumonia, without increasing the work of breathing during FOB.[37,38•] In patients undergoing ETI, many authors discourage routine use of endoatracheal aspirate for microbiological sampling.[12] Protected specimen brushing (PSB) and FOBwith BAL

or miniBAL (performed without fiberoptic guide) are invasive procedures used for microbiological diagnosis of severe pneumonia in ICU patients. Data from the literature do not favor the use of bronchoscopic techniques over 'blind' ones, so the choice strictly depends upon institutional resources and expertise.[11] Gram stain of respiratory samples, available within a few hours, may help clinicians in narrowing or broadening the antimicrobial spectrum.[13] Current literature encourages the use of quantitative cultures for the bacterial diagnosis of pneumonia in intubated patients.[11,39] Early molecular detection methods, mainly using real-time polymerase chain reactions (PCRs),are under development.[40•] With regards to bacterial cause, multiplex amplification assays might include frequently involved microorganisms, and incases of hospital-acquired infections, possible resistance gene targets may be detected too.[41] A recent Swedish study from the Karolinska University Hospital has compared traditional diagnostic methods with PCR-based methods in a cohort of 124 patient with CAP (6%were treated in ICU).[42] The authors observed that by the implementation of this molecular technology a higher microbiological yield was achieved, with frequent mixed infection involving *S. pneumoniae* and respiratory viruses. Despite potentially enormous advantages of PCR-based diagnostic methods (rapidity, sensitivity, convenience),several limitations, such as the need of a quantitative cut-off in order to differentiate colonizing bacteria from infectious ones or to detect living viruses from prolonged harmless shedding, still limit their wide distribution in clinical practice. In addition increased costs should be considered.[43] Fungal antigen detection in BAL specimens might be useful in the management of immunocompromised patients with severe pneumonia, in which case aspergillosis, endemic mycosis and *Pneumocystis jiroveci* are suspected.[44,45•] However, also in this field, the use of real-time PCR assays are showing promising results, as recently reported by Torelli *et al*. in a cohort of high-risk patients (60%admitted to ICU).[46•] Inflammatory biomarkers, such as procalcitonin (PCT), are frequently used as a guide to define the length of antimicrobial therapy.[47] Nevertheless, in adjunction to novel molecular-based diagnostic methods, they may be helpful to identify highest-risk severe pneumonia patients and to decide on the most appropriate site of care.[48,49•]

Treatment

Patients affected by severe pneumonia need to be treated urgently and appropriately, given the importance of rapid pathogens' clearance in reducing infection-driven systemic inflammatory activation and preventing multiorgan dysfunction.[3,11,50] Current guidelines for the treatment of severe pneumonia in ICU may help physicians in daily clinical practice (Table 2). IDSA/ATS recommendations[5] for the management of SCAP in ICU highlight the importance of a combination therapy including a β-lactam and either azithroomycin or a respiratory fluoroquinolone; however, in the case of suspicion of *Psudomonas* or MRSA involvement, the antibacterial scheme should cover also these pathogens. In addition to the activity against a typical pathogens, macrolides have been advocated by some authors as an adjunctive tool in severe pneumonia because of their presumed immunomodulatory properties. A recent multicenter prospective cohort study,[51•] conducted in 27 ICUs of 9countries, showed that patients with SCAP showed a lower ICU mortality rate when treated with macrolides compared to fluoroquinolones (hazard ratio 0.48; $P = 0.03$). The empirical antimicrobial regimen for HCAP, HAP and VAP proposed by current guidelines[11–13] is a triple drug scheme including MRSA and nonfermentative Gram-negative rods coverage. In a recent study conducted in four academic ICUs,[52••] better compliance to international recommendations with regards to HCAP/HAP/VAP empirical treatment was associated with increased mortality. Nonadherence to guidelines mainly included nonuse of combination therapy for Gram-negative infections. However, the lack of randomization, the differences of baseline clinical conditions and the higher frequency of *Pseudomonas* pneumonia in the compliant group raise many concerns about the clinical reliability of these results.[53] The optimal treatment of severe pneumonia in critically ill patients includes the evaluation of numerous variables that may influence final microbiological and clinical outcome. Antimicrobials with good pulmonary distribution (such as linezolid) should be preferred, or alternative additional administration strategies might be added (aerosolized antibiotics); isolated microorganisms' minimal inhibitory concentrations (MICs) have to be carefully considered and antibiotics' bactericidal properties may be optimized by applying their pharmacodynamic/pharmacokinetic properties (time-dependent/concentration-dependent molecules).[54] In addition, pathophysiological changes occurring during severe infections (increased cardiac output; leaky capillaries/altered protein binding; end-organ dysfunctions) modify drug clearance (Cl) and volume of distribution (Vd) according to their hydrophilic or lipophilic nature.[55] Given their low pulmonary penetration, high aminoglycoside doses (i.e. amikacin 25 mg/kg) are needed in order to reach effective peak concentrations in critically ill patients, especially those ones with severe pneumonia.[56] A recent systematic review[57••] has confirmed the pharmacodynamic/pharmacokinetic advantages of prolonged/continuous infusion of β-lactams; however, antibiotics' therapuetical drug monitoring (TDM) still represents the best tool to ensure optimal drugs exposure in critically ill patients. Despite the optimal duration of severe pneumonia being unclear, surrogate biomarkers, like procalcitonin, may be useful to guide antibiotic therapy duration.[58] Some preclinical and clinical studies[59,60] suggest the use of steroids as an adjunctive tool in critically ill patients with pneumonia; however, evidence from current literature does not recommend their extensive use in severe pneumonia.[61] Subgroups of patients (i.e. those with pulmonary immune reconstitution inflammatory syndrome and with severe pneumonia evolving into ALI/ARDS despite adequate treatment) may benefit from their anti-inflammatory properties.[62•] In light of its immunomodulatory properties, the use of drotrecogin alfa activated (DAA) inpatients with severe pneumonia developing septic shock has been proposed in the past.[63] However, given the negative results of a multinational placebo-controlled trial of DAA in septic shock (PROWESS SHOCK), requested by the

European Medicines Agency and not yet published, the molecule has been recently withdrawn from the market [http://www.emea.europa.eu]. Other adjunctive therapies are under investigation, but results are still unconvincing (prostaglandin inhibitors, anticoagulant agents, surfactant, immunoglobulin, statins, γ-interferon).[64]

Table 2. Empirical antibiotic approach for the treatment of severe pneumonia

CAP[5,32••]	HCAP/HAP/VAP[11–13]
Absence of risk factors for *P. aeruginosa* and MRSA Non-antipseudomonal cephalosporin III (cefotaxime, ceftriaxone) *Plus* Macrolide (azithromycin) or respiratory fluoroquinolone (moxifloxacin, levofloxacin) Presence of risk factors for *P. aeruginosa* and MRSA Antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) *plus* Ciprofloxacin or (macrolide plus aminoglycoside) *plus* Linezolid or vancomycin	Antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) *plus* Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, tobramicyn) *plus* Linezolid or vancomycin Early-onset VAP/HAP without risk factors for MDR pathogens Aminopenicillin plus β-lactamase-inhibitor (amoxicillin–clavulanic acid; ampicillin–sulbactam) *or* Non-antipseudomonal cephalosporin II/III (cefuroxime, cefotaxime, ceftriaxone) *or* Respiratory fluoroquinolone (moxifloxacin, levofloxacin) *or* Ertapenem

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; SP, severe pneumonia; VAP, ventilator-associated pneumonia. In settings where the prevalence of multidrug-resistant Gram-negative pathogens is particularly high, empirical colistin may be preferred to aminoglycosides or antipseudomonal fluoroquinolones in the management of nosocomial pneumonia.

Management

Optimizing severe pneumonia management may consist not only of the discovery of new therapies but also of the effective application of well known beneficial interventions, grouped in clinical 'bundles'. Five key elements have been proposed by Rello[65] with the aim to obtain the best early treatment of patients with severe pneumonia: 'risk assessment' (including pulse oxymetry and point-of-care lactates), 'early fluid resuscitation', 'prompt oxygenation', 'immediate combined antibiotic therapy' and 'evaluation for ICU admission'. When severe pneumonia is complicated by severe sepsis and septic shock, adherence to a resuscitation interventions bundle within the first 6h (measure of serum lactates, control of hypotension, early antibiotic administration after performing cultures) and 24 h (low-dose steroids administration, glucose control, maintenance of inspiratory plateau pressure<30cmH_2O for mechanically ventilated patients) is associated with improved outcome.[66•,67•]

A major challenge that physicians attending to patients with severe pneumonia have to face is the management of acute respiratory failure (ARF) requiring mechanical ventilation. Sequential supportive interventions aimed to manage severe ARF in patients with pneumonia are summarized in Fig. 1. NIV, delivered through a facial mask or a helmet, represents a possible first-line intensive treatment for ARF, both in hypoxemic and hypercapnic patients.[68] Although the main reason for choosing NIV in patients with severe pneumonia and ARF is to avoid the complications associated with invasive mechanical ventilation, clinicians have to carefully consider those elements that may predict NIV failure, thus preventing dangerous delays in performing ETI.[69•,70]

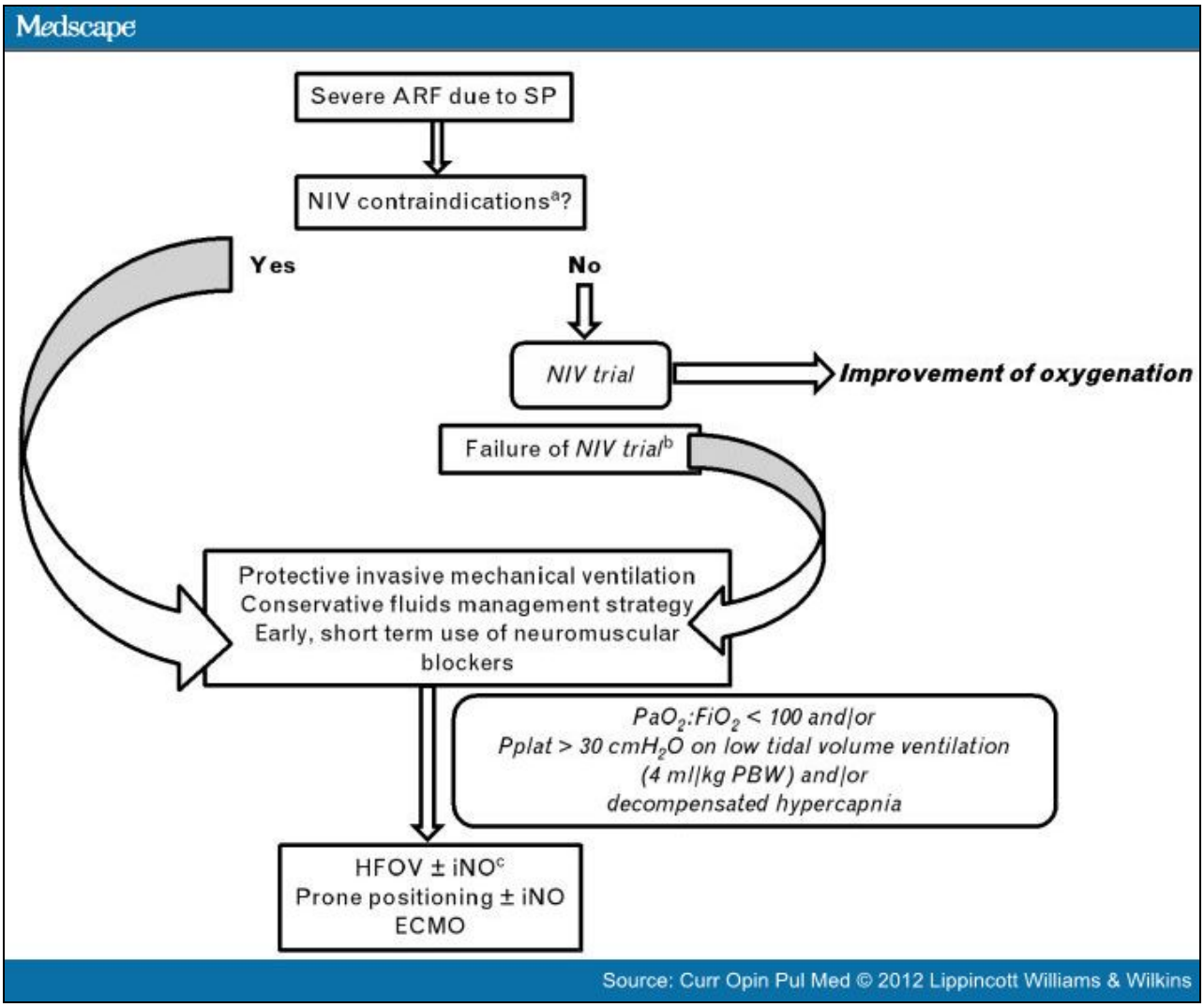

Figure 1. Supportive strategies for the management of acute respiratory failure due to severe pneumonia. [a]Severe central neurological disturbances, unstable hemodynamic conditions, organ dysfunction other than neurological, inability to protect the airway or clear respiratory secretions, severe gastrointestinal bleeding, inability to fit the interface, undrained pneumothorax. [b]Failure to maintain PaO_2 : FiO_2 ratio above 100, neurological impairment, persistence of dyspnea and tachypnea, hemodynamic instability and intolerance of the interface. [c]Considered in patients with high recruitment potential. ARF, acute respiratory failure; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; NIV, noninvasive ventilation; PBW, predicted body weight; SP, severe pneumonia.

Patients with severe pneumonia and severe ARF evolving into ALI/ARDS [acute onset, bilateral infiltrates on chest X-ray, pO_2/FiO_2 ratio ≤ 200 mmHg (≤ 300 mmHg for ALI) and absence of clinical evidence of left atrium hypertension] commonly need nvasive ventilation.[71] In these patients, a lung protective ventilation strategy with a tidal volume of 4–8 ml/kg of ideal body weight (IBW) and a plateau pressure (P_{plat}) of 30cmH_2O or less is required in order not to perpetuate lung injury.[10,72] Currently, the optimal positive end-expiratory pressure (PEEP) value has not been clearly established. However, a recent meta-analysis of studies comparing different PEEP values for the management of ALI/ARDS (50% of patients were affected by severe pneumonia) observed that higher PEEP (around 15cmH_2O) values were associated with improved survival rate (P = 0.03).[73] Additionally, conservative fluid strategies and early use of short term neuromuscular blocking agents are being associated with improved outcome.[74,75•]

Patients whose gas exchanges are not adequately maintained are candidates for nonconventional ventilatory supportive strategies.

One of these interventions is represented by the prone position in patients with ARDS. The principal pathophysiological mechanisms that would improve oxygenation during prone positioning include redistribution of ventilation and perfusion matching, alveolar recruitment and avoidance of heart compression upon the lungs.[76•] In a recent meta-analysis of

randomized controlled trials (RCTs) upon prone positioning in ALI and ARDS patients, Sud *et al*.[77•] observed that, in patients with a PaO_2/FiO_2 below 100, the use of this ventilator-supportive strategy was associated with reduced mortality.

High-frequency oscillatory ventilation (HFOV)is a ventilator mode which provides a small tidal volume by oscillating a bias gas flow in the airway. The delivery of a small tidal volume at a high respiratory frequency (generally 3–15 Hz; 3–6 Hz in adults) and high mean airway pressure (mPaw) may result in improved alveolar recruitment with less risk of over distension. Primary determinants of oxygenation are the fixed mPaw and the fraction of inspired oxygen, whereas the pressure amplitude of oscillation and the respiratory frequency are the main determinants of CO_2 elimination.[78•]

With the aim of reducing ventilation/perfusion mismatch, refractory hypoxemic ARDS patients may benefit from the use of inhaled vasodilators. Inhaled nitric oxide (iNO) has been shown to improve oxygenation in ARDS patients and, despite a lack of evidence to support its benefits with regards to mortality rate and duration of mechanical ventilation, its use may be a rescue intervention for the management of ARDS patients.[79,80]

For those patients with severe hypoxemia unresponsive to the above mentioned unconventional ventilatory strategies, extracorporeal membrane oxygenation (ECMO) may be considered.[81•] ECMO consists of extracting a large amount of venous blood from a central vein and returning it to venous or arterial circulation through an oxygenator and heat exchanger. Best documented data upon this topic come from the CESAR trial[82] in which 180 severe ARF patients (60% due to severe pneumonia) were randomized 1 : 1 to receive conventional treatment or to be considered for ECMO. Cases allocated to the ECMO group showed a significantly lower mortality rate compared with the control group (47 vs. 63%; $P = 0.03$). However, only75% of patients considered to receive ECMO actually received the treatment and, in addition, supportive interventions were not standardized in the comparative group. More recently, a well matched cohort study and an observational study[81•,83••] confirmed a lower mortality rate (23.7 and 32 vs. 52.5%; $P = 0.006$) in patients with H1N1 ARDS who were transferred to an ECMO center in comparison with non-ECMO referred controls. Given the possibility of severe complications (i.e. bleeding, thromboembolism) and the intrinsic difficulty of extracorporeal circulation techniques, treatment with ECMO needs well trained clinicians and adequate hospital centers. Hence, a network organization aimed at centralizing ARDS patients who may benefit from ECMO should be available in each country.

Conclusion

Severe pneumonia is still a common reason for ICU admission. Given the importance of early treatment of critically ill patients, a prompt recognition of those conditions that require ICU management is crucial. Causative agents are widely different, depending on epidemiological and individual risk factors. Rapid microbiological diagnosis is essential in order to avoid inappropriate empirical treatment and early clinical failures. The efficacy of antimicrobials may be optimized by the application of pharmacodynamic/pharmacokinetic rules. Few data are available to support the use of pharmacological interventions other than conventional antimicrobial treatments. Patients with severe pneumonia often develop severe ARF needing invasive or noninvasive mechanical ventilation. In addition to standard supportive ventilatory strategies, innovative measures, such as extracorporeal oxygenation, are now available and may represent the future of the treatment of a historical illness.

Sidebar

Key Points

- There are many factors that influence severe pneumonia cause. Microbiological infective type strictly depends upon the environment in which pneumonia is contracted and the immune condition of the patients.
- In ICU invasive diagnostic procedures are widely available. However, new molecular techniques are being implemented to make microbiological diagnosis not only faster but more accurate.
- Antimicrobial therapy is still the primary causative treatment of severe pneumonia, whereas the benefits of other pharmacological measures remain in dispute. Pharmacodynamic/pharmacokinetic principle application may optimize the clinical efficacy of drugs used to fight severe pneumonia.
- Patients affected by severe pneumonia need lifesupportive interventions, especially for respiratory function. Beyond traditional ventilatory support, unconventional strategies are becoming more available. However, particular expertise is required in order for their survival benefits to surpass the potential complications.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

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