# Adjunctive and Supportive Measures for Community-Acquired Pneumonia

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G.W. Waterer, R.G. Wunderink

## 38.1 Introduction

The widespread introduction of penicillin in the 1940s resulted in a substantial reduction in mortality from community-acquired pneumonia (CAP). However, despite significant advances in medical science, only a small improvement has occurred since, particularly in patients with bacteremic pneumococcal pneumonia [1, 2]. Even modern intensive care has only made a small difference to the mortality in patients with severe pneumonia [3, 4]. While the aging population, increased number of patients with severe co-morbid illnesses, and the human immunodeficiency virus (HIV) epidemic have certainly contributed to the persistently high mortality rate [2, 5, 6], apparently healthy, immunocompetent patients continue to die from CAP. Disturbingly, a recent British Thoracic Society study concluded that no available therapy could substantially reduce the mortality rate from severe CAP in young adults [7].

While some causative microorganisms, such as *Pseudomonas*, and some strains of common causative microorganisms appear to be more virulent, the majority of CAP patients who die are infected with organisms sensitive to commonly prescribed antibiotics. Even the recent emergence of high level penicillin-resistant strains of *S. pneumoniae* has not significantly increased the mortality of CAP. Given that most CAP patients die despite microbiological confirmation that they received appropriate antibiotic therapy, the introduction of new antibiotic classes is unlikely to reduce mortality further. For this reason, research has been directed into non-antibiotic therapeutic measures.

Generally, supportive measures for CAP can be separated into two categories – (1) immunomodulatory therapy for the systemic inflammatory response induced by pneumonia and (2) support for the gas exchange abnormalities unique to a pulmonary source of sepsis. Chapter 16 focuses on potential immunomodulatory therapies in patients with sepsis, including pneumonia. This chapter will focus on a few pneumonia-specific immunomodulatory therapies and other advances in the intensive care management of patients with severe CAP.

## 38.2 Pneumonia-Specific Immune Therapies

### 38.2.1 Corticosteroids

Although discussed in Chapter 16, a more detailed discussion of the recent controversy over high dose corticosteroids in patients with CAP is warranted.

The best evidence of benefit for corticosteroids comes from studies in specific, narrowly defined groups of CAP patients caused by less common agents. Randomized, controlled trials have shown corticosteroids reduce mortality in AIDS patients with *Pneumocystis carinii* pneumonia and significant hypoxia, if instituted at or prior to the onset of anti-pneumocystis therapy [8, 9]. Based on a small, retrospective study of 15 subjects, corticosteroids may also improve the outcome of severe *Varicella* pneumonia [10]. Anecdotally, corticosteroids are frequently used in the setting of severe fungal pneumonia, particularly due to *Histoplasmosis* [11, 12], and a small controlled trial of 55 patients supported their use in miliary tuberculosis [13].

Following the success of pre-antibiotic corticosteroids in children with meningitis [14], Marik and colleagues [15] studied the effect of a single dose of hydrocortisone (10 mg/kg) 30 min prior to antibiotic therapy in a small randomized placebo controlled trial of 30 adult patients with severe CAP (SCAP). Hydrocortisone had no detectable effect on tumor necrosis factor alpha (TNF) production in the following 12 h, mortality (only four deaths) or length of stay in the ICU. While not encouraging, the small number of subjects studied (14 received hydrocortisone), the use of only a single dose and the measurement of only a single pro-inflammatory cytokine for only 12 h does not qualify this study to be a definitive statement on the role of corticosteroids in CAP. An important finding of this study was that beta-lactam antibiotics did not result in a significant increase in serum TNF levels, as rapid antigen release due to bacterial lysis has been postulated as a potential cause of deterioration in patients with severe CAP [16].

Also supporting a possible role for corticosteroids in severe CAP, Montón and co-workers [17] studied the

effect of intravenous methylprednisolone on bronchoalveolar lavage fluid (BALF) and serum cytokines in 20 patients with severe nosocomial pneumonia or CAP. The 11 patients who received methylprednisolone had significantly lower serum and BALF TNF, interleukin (IL)-1β, IL-6 and C-reactive protein. There was also a non-significant trend to lower mortality in the steroid treated group (36 % vs. 67 %).

Recently, Confalonieri and colleagues compared intravenous hydrocortisone (200 mg bolus followed by 10 mg/h for 7 days) with placebo in 46 patients with severe CAP admitted to the ICU [18]. The trial was stopped early after an interim analysis showed a significant mortality benefit in the steroid group (0 % vs 30 %, $p = 0.009$). However, the mortality difference was driven by deaths after day 8 and a high incidence of "delayed septic shock". The marked incidence of this scenario has not been seen in any other SCAP study. Significant differences in the percent of patients who received noninvasive ventilation rather than intubation and mechanical ventilation also compromise the data regarding a beneficial effect of steroids on gas exchange. Noninvasive ventilation has been shown by the same group to decrease mortality compared to invasive ventilation [19]. The statistical design of the study led to an early closure of the study, limiting the ability to exclude the possibility that other factors explain the mortality difference. The complete absence of any mortality in the corticosteroid group has also raised significant concerns about potential bias in patient selection and whether either the control or case cohort were truly representative of the general group of patients with severe CAP.

Despite the reservations, all three pilot studies suggested a trend toward benefit with steroids so further clinical studies clearly need to be conducted.

### 38.2.2 Prostaglandin Inhibitors

Prostaglandin antagonists are worth special comment as they have been studied in animal and human patients with pneumonia. Ibuprofen reduced the intrapulmonary shunt fraction from 29 % to 21 % in dogs with lobar pneumonia [20], with a corresponding decrease in the consolidated area of lung. Acetylsalicylic acid had a similar effect, reducing the shunt fraction from 38 % to 23 % [20]. The mechanism is unclear but may be due to reversal of prostaglandin inhibition of the hypoxia-induced pulmonary vasoconstriction.

In a small study of ten subjects with pneumonia requiring mechanical ventilation, Hanley et al. [21] studied the effect of indomethacin (1 mg/kg oral or rectal) on arterial oxygenation. Five subjects had substantial improvement in oxygenation with a small improvement in three additional patients. Improvement tended to occur in the patients with the greatest degree of hypoxemia. As ibuprofen administration appears to be relatively safe, even in the setting of sepsis [22], further studies are warranted.

In contrast, Ferrer et al. found a 2 g infusion of acetylsalicylic acid (ASA) had no effect on arterial oxygenation in seven patients with severe unilateral pneumonia [23]. Although intrapulmonary shunting did reduce by a small amount (28 ± 17 % vs. 23.5 ± 13 %), the lack of clinically apparent benefit was discouraging. Several possible explanations were advanced to explain the discrepancy between this study and that of Hanley et al. Clearly, a difference in efficacy between ASA and indomethacin may be the cause. However, the subjects in the study by Hanley et al. were also more severely hypoxic, with a mean $Pa0_2/Fi0_2$ of 138 compared to 168. In any event, it would seem reasonable for future studies to use indomethacin in preference to ASA.

### 38.2.3 Immunoglobulin Enhancement

Before the advent of antibiotic therapy, passive immunization with serum was used with some success in patients with pneumonia [24]. Mortality was reduced by approximately 10 % in most age groups with a diminishing effect in patients over the age of 60. With the exception of patients with specific immunoglobulin deficiencies, this therapy has largely been abandoned due to the much greater efficacy of antibiotics in addition to the difficulty, and cost, of obtaining sufficient serum. The development of new antiviral drugs has also largely obviated the anecdotal use of hyper-immune serum in cytomegalovirus and varicella pneumonitis.

While the overall efficacy of pneumococcal immunization is unclear, especially in the elderly with some comorbid illnesses, several studies and a meta-analysis have suggested that even if pneumococcal pneumonia is not prevented, the incidence of invasive pneumococcal disease is decreased.

The use of specific anti-pseudomonal exotoxin antibodies has been tried as an adjunct to antibiotics with some success in mice [25] and guinea pigs [26], and *Pseudomonas* specific vaccines have enhanced antibiotic response in guinea pigs [27]. Anti-pseudomonal antibodies appeared safe in human subjects with evidence of increased opsonophagocytic activity in a small phase I study of 20 subjects [28], but further studies are required to determine whether they have any clinically relevant effect. In human sepsis studies, generic anti-endotoxin strategies have so far been disappointing [29, 30]. Although they have not specifically been studied in pneumonia, the primary site of sepsis in many of the patients in these studies was the lung, indicating a low likelihood of benefit.

### 38.2.4 Macrophage Enhancement

*Legionella pneumophila* is consistently identified as a leading cause of CAP, particularly in patients with severe CAP [31–34]. Unlike pneumococcal pneumonia, the immune response to *Legionella* infection is predominantly of a TH1 type [35] and bacterial killing is predominantly by macrophages [36]. Skerrett and Martin studied the effect of interferon gamma (IFNγ), a potent stimulator of macrophage function [37, 38], given as an intratracheal bolus in rats with experimental *L. pneumophila* pneumonia [39]. Intratracheal IFNγ markedly reduced the replication of *L. pneumophila* in corticosteroid treated rats, but had no detectable effect in immunocompetent rats or when given intraperitoneally.

The ability to give IFNγ by aerosol is particularly appealing since not only are systemic side effects avoided, but also a much greater effect on intrapulmonary macrophage function is seen compared to systemic administration [40]. Aerosolized IFNγ has also been shown to be safe in patients with drug resistant tuberculosis [41], and may have a role in treatment of this condition. Further studies of nebulized IFNγ, especially in patients with pulmonary legionellosis, are awaited.

### 38.2.5 Drotrecogin Alpha (Activated Protein C)

After many unsuccessful trials of non-antibiotic agents designed to disrupt or ameliorate the pro-inflammatory process driving septic shock and associated organ failure, activated protein C (drotrecogin alpha activated) was the first successful agent to reduce mortality in a large randomized, double blind, placebo controlled trial [42]. While 28-day mortality was clearly better in sub-groups of patients who received drotrecogin alpha activated [42], the subgroup with community-acquired pneumonia drove most of the benefit of the drug [43], with the greatest reduction in mortality seen with *Streptococcus pneumoniae* infection (RR=0.56; 95% CI 0.35–0.88). The availability of rapid urinary antigen detection for *S. pneumoniae* allows this association to enter clinical decision-making (several references for urinary antigen). Drotrecogin alpha activated appeared to have a greater effect in single organ failure than waiting for multiple (≥ two) organ failure but clearly has its greatest benefit in patients who have the highest acuity of illness. Worsening thrombocytopenia, suggestive of early disseminated intravascular coagulation, appears to be another important indicator for patients likely to respond to drotrecogin alpha activated [44]. While different criteria for the administration of drotrecogin alpha activated have been established in different institutions around the world, the presence of pneumonia and shock should prompt physicians to consider its use as early as is possible.

## 38.3 Other Supportive Measures

The main additional supportive therapy unique to CAP is improved oxygenation and secretion clearance. The remainder of supportive care is not different than that of other critically ill patients with infection.

### 38.3.1 Positioning Therapy

CAP is one of the more common causes of severe hypoxic respiratory failure. A common method to improve oxygenation, the addition of positive end expiratory pressure, may actually make oxygenation worse in patients with severe asymmetrical lung disease like CAP. The PEEP will tend to overdistend the unaffected lung, increasing pulmonary vascular resistance on the local area. This overdistension may then direct greater blood flow to the pneumonic area, especially if hypoxic vasoconstriction has been blocked by some bacterial product.

With extensive unilateral pneumonia, positioning the ventilated patient in the lateral decubitus position with the affected lung up has been demonstrated to improve oxygenation [45]. Positioning increases perfusion to the dependent, non-involved lung, increases secretion clearance from the affected lung, and may allow addition of PEEP without increasing shunt because the dependent lung is now less compliant and less likely to become overdistended. The combination of positioning and prostaglandin inhibitors is usually adequate to temporarily improve oxygenation until hypoxic vasoconstriction is restored.

### 38.3.2 Differential Lung Ventilation

Differentially ventilating each lung by means of a dual lumen endotracheal tube may also be beneficial [46, 47]. This allows the use of higher levels of PEEP in the affected, less compliant, lung and lower levels of PEEP in the normal lung, thus reducing the risk of barotrauma. A study by Ranieri et al. showing a correlation between the level of PEEP and pro-inflammatory cytokine production further supports this approach to protect the 'normal' lung [48]. The point at which differential ventilation is worth commencing is not clear, but Carlon and colleagues [46] suggest optimal benefit occurs when there is a 200 ml or greater difference in distribution of tidal volume between each lung.

### 38.3.3 Extracorporeal Membrane Oxygenation

ECMO, a modification of cardiopulmonary bypass, was designed to provide oxygenation in patients with severe respiratory failure. Although available since the 1970s, initial poor results from a National Institutes of Health sponsored prospective, multicenter randomized trial [49] limited the use of ECMO to research centers. However, a significant reduction in complications has led to resurgence in interest in ECMO as a means of providing oxygenation when all other means have failed.

The role of ECMO has most extensively been studied in neonates. In newborn infants with respiratory failure unresponsive to other therapy it has proven highly effective, having an overall survival of 80 % in over 10,000 neonates where nearly 100 % mortality would be expected [50]. Modification of the neonatal ECMO technique has also been effective in some pediatric patients with respiratory failure [51], including those with pneumonia from both bacterial [52] and viral [53] pathogens. As would be expected, as the duration of ECMO required increases, the prognosis decreases [52].

In the NIH-sponsored ECMO trial, adults with viral pneumonia did particularly poorly. In a retrospective review of 100 adults with severe acute respiratory failure supported with ECMO by Kolla and colleagues [54], a 53 % survival rate was found in the 49 patients with a primary diagnosis of pneumonia. Although this mortality seems high, patients selected for ECMO had an expected mortality in excess of 90 %. Predictors of poor response to ECMO were increasing age, days of ventilation prior to commencement of ECMO and the degree of respiratory failure as measured by the $Pa0_2/Fi0_2$ ratio. Cases of successful intervention in adults with severe *Legionella* [55, 56], pneumococcal [57] and *Varicella* pneumonia [58] have all been reported.

The clearest indication for ECMO in adults may be the Hantavirus pulmonary syndrome (HPS). With no effective antiviral therapy, care is entirely supportive. In a small series, the dramatic but time-limited cardiovascular and pulmonary hemorrhagic manifestations of HPS appeared to be well supported by ECMO [59].

ECMO would appear to have a role in some patients with severe respiratory failure secondary to pneumonia. The timing, duration and patient selection for what is an expensive, labor intensive therapy remain to be determined by prospective studies.

### 38.3.4 Other Therapies

Liquid ventilation with volatile hydrocarbons has been studied in the management of ARDS. Little data is currently published on its use specifically in human subjects with pneumonia. In rats given lethal doses of pneumococci, partial liquid ventilation in combination with perfluorocarbon doubled survival compared to antibiotics alone [60].

Nitric oxide (NO) inhalation has also been studied as adjunctive therapy of ARDS, as well as some other forms of severe pulmonary hypertension. While no studies specifically address human patients with pneumonia, in dogs with *Escherichia coli* pneumonia, inhaled NO had a minimal effect on oxygenation and no effect on sepsis induced pulmonary hypertension [61].

Since NO is one of the effector molecules released by macrophages to kill bacteria [62], inhaled NO has a potential antibacterial effect. Hoehn and colleagues studied the bacteriostatic effect of NO on bacterial cultures from neonates [63]. At 120 ppm (greater than the usual dose range of 40 – 80 ppm) NO inhibited the growth group B Streptococcus, *Staphylococcus epidermidis* and *E. coli* but not *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Further studies will be required to determine whether inhaled NO has any real bacteriostatic effect in vivo, particularly as it may have deleterious effects on the function of neutrophils [64].

Aerosolized prostacyclin has also been shown by Walmrath et al. to improve oxygenation by reducing shunt and pulmonary hypertension in patients with pneumonia [65]. Twelve patients with severe pneumonia ($Pa0_2/Fi0_2 < 150$), six of whom had interstitial lung disease (ILD), received varying doses of prostacyclin. Patients with ILD required substantially larger doses of prostacyclin to produce a clinical effect. Although its efficacy has not been compared to NO in patients with pneumonia, its greater cost is a significant disadvantage.

### 38.3.5 Clearance of Secretions

Significant accumulation of mucopurulent secretions can occur in CAP, particularly in patients on mechanical ventilation. Mucus impaction can lead to obstruction, ranging in severity from linear atelectasis to lobar collapse.

#### *38.3.5.1 Physical Removal*

Clearly the most effective secretion clearance is a spontaneous cough. However, the respiratory compromise often attendant to severe CAP may prevent an effective cough. Support with noninvasive ventilation (NIV) may benefit the patient by both improving respiratory mechanics while allowing the patient to spontaneously expectorate [66]. However, retained secretions is also one of the causes of failure of NIV. An important strategy to avoid this complication is to avoid continuous ap-

plication of NIV and actively encourage the patient to cough during periods off NIV.

In mechanically ventilated CAP patients, removal of secretions by regular suctioning is essential. The use of percussion or vibration in ventilated patients has been associated with worsening of gas exchange and the benefit in CAP patients in general is unclear.

The benefit of bronchoscopy for secretion removal is also poorly supported. Bronchoscopy for secretion removal has been associated with an increased risk of development of subsequent nosocomial pneumonia [67]. Therefore its therapeutic use should be limited. One of the few studies on this area has suggested that if lobar atelectasis is accompanied by an air bronchogram, bronchoscopy is unlikely to find a mucus plug or benefit the patient.

#### *38.3.5.2 Mucolytics*

Changing the rheologic properties of thick tenacious mucus is often attempted with little scientific support. Avoidance of dessication and inspissation of secretions does appear to be important. Adequate hydration may be the most effective therapy. Intubated CAP patients with significant secretions are poor candidates for heat and moisture exchangers and should usually have ventilation initiated with heated humidification.

The pharmacologic intervention most often ordered is *N*-acetylcysteine. Most support for this therapy is an extension of results in some cystic fibrosis patients. Whether the same benefit can be achieved in CAP patients is unclear as there is no published data of *N*-acetylcysteine use in this setting. The potential benefit is also partially offset by induction of bronchial irritation and bronchospasm in some patients. Preliminary data on agents with more physiologic support, such as UTP [68], are encouraging but need further study. Guaifenesin has limited data in non-pneumonia patients and is unlikely to have a major benefit in intubated CAP patients. Although a variety of other mucolytic agents are available, including bromhexine, rhDNase and polymyxin B, there is no data to support their use in patients with pneumonia.

## 38.4 Conclusion

CAP remains a significant health problem and patients continue to die despite receiving appropriate antibiotic therapy. Modification of the host immune response, both anti- and pro-inflammatory approaches, has yet to live up to the promise of improved outcome. Despite this, there is significant reason for optimism. Some immunomodulatory therapies clearly have efficacy in some patients. As our understanding of the immune response to pneumonia improves, our ability to tailor specific therapies for individual patients will also improve, hopefully avoiding the deleterious effects that have so far prevented the development of an effective immune based therapy. The possibility of delivering cytokines directly to the lung, such as with nebulized IFNγ, is a particularly promising way of achieving the desired pulmonary effect without systemic side effects.

Corticosteroids are currently unique in that they have a proven role in the therapy of pneumonia due to *P. carinii*. Recent research suggests there may be a much wider therapeutic indication for corticosteroids in severe CAP and further research is awaited.

Once respiratory failure has ensued, supportive measures such as patient positioning and differential lung ventilation can improve oxygenation at no additional risk in some patients, particularly those with severe unilateral pneumonia. In facilities where ECMO is available it may be beneficial in selected patients when all other means of providing respiratory support have failed. The role of inhaled NO and partial liquid ventilation is also currently unclear and awaiting further study.

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