39. ADJUNCTIVE AND SUPPORTIVE MEASURES FOR COMMUNITY-ACQUIRED PNEUMONIA

Grant W. Waterer and Richard G. Wunderink

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.

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. This chapter will review the immunomodulatory therapies that have been studied in animal and human subjects with pneumonia. Advances in the intensive care management of patients with severe CAP, such as differential lung ventilation and extracorporeal membrane oxygenation (ECMO) will also be discussed.

Therapies Directed at the Immune Response

Patients who succumb to CAP seem to fall into two broad groups. The first group can be loosely categorized as having an excessive immune response to infection, including those who develop septic shock, acute respiratory distress syndrome (ARDS) and multiorgan failure. The second group is patients who can be categorized as having an inadequate host response to infection, including the elderly, alcoholics, diabetics and patients with significant co-morbid illnesses, such as cardiac failure or cirrhosis. Any immunomodulation strategy is likely to have different effects on the two populations. Even when patients are overtly similar, marked vari-

J. Rello et al. (eds.), *Critical Care Infectious Diseases Textbook*
© Kluwer Academic Publishers 2001

ability in the clinical response to the same causative organism is seen. The cause(s) of this significant variability in response to CAP is multifactorial but may have a genetic basis [7], similar to bacterial meningitis [8].

Immune Suppression

CORTICOSTEROIDS

With their potent anti-inflammatory action and proven efficacy in a variety of autoimmune diseases, glucocorticoids are an obvious choice of agent to try in patients thought to have an excessive, and deleterious, immune response to CAP.

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 [9, 10]. Based on a small, retrospective study of 15 subjects, corticosteroids may also improve the outcome of severe *Varicella* pneumonia [11]. Anecdotally, corticosteroids are frequently used in the setting of severe fungal pneumonia, particularly due to *Histoplasmosis* [12, 13], and a small controlled trial of 55 patients supported their use in miliary tuberculosis [14].

Following the success of pre-antibiotic corticosteroids in children with meningitis [15], Marik and colleagues [16] studied the effect of a single dose of hydrocortisone (10 mg/kg) 30 minutes 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 (TNFα) production in the following 12 hours, 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 hours 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 TNFα levels, as rapid antigen release due to bacterial lysis has been postulated as a potential cause of deterioration in patients with severe CAP [17].

Also supporting a possible role for corticosteroids in severe CAP, Montón and co-workers [18] studied the effect of intravenous methylprednisolone on bronchoalveolar lavage fluid (BALF) and serum cytokines in 20 patients with severe nosocomial pneumonia or CAP. The eleven patients who received methylprednisolone had significantly lower serum and BALF TNFα, 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%). As higher TNFα [19–21] and IL-1β [10] concentrations in serum are known to correlate with greater mortality, this pilot study supports further research into the potential role of corticosteroids in severe CAP.

More damaging evidence for the potential role of corticosteroids as immunomodulatory agents in severe CAP are the unfavorable results from studies of septic shock. Pooled analysis of nine randomized, controlled trials showed no beneficial effect of corticosteroids in patients with septic shock [22]. Even more disturbing was a trend to greater mortality in patients receiving corticosteroids, particularly in those who developed secondary infections. The difficulty in balancing beneficial and detrimental effects is a common theme for all immunomodulatory therapy. Continuing research will hopefully define those subgroups most likely to benefit from corticosteroids, for example patients with refractory septic shock [23], or with specific pathogens, such as has already been demonstrated with *P. carinii* [9, 10].

ANTI-CYTOKINE THERAPIES

Anti-TNFα monoclonal antibodies [24–26], interleukin 1 receptor antagonist (IL1-Ra)

[27, 28], soluble TNFα receptors [29, 30], prostaglandin antagonists [31, 32], bradykinin antagonists [33] and platelet activating factor antagonists [34, 35] have all been assessed in patients with sepsis and septic shock. Pneumonia was the primary source of sepsis in a significant number of these trials. Despite promising initial studies, large, multicenter, phase III randomized controlled trials have failed to demonstrate any net beneficial effect from any of these agents [36].

When initial enthusiasm and promising phase I and II trials did not translate into successful phase III trials, the complexity of the system of pro- and anti-inflammatory agents became more apparent than had been appreciated previously [36]. While investigators often felt that individual patients clearly benefited from intervention, the observation of no net benefit in large studies implies that some patients had a detrimental effect from the intervention. Until our ability to clearly define the patients most likely to benefit, this experience is likely to be repeated with other anti-sepsis drugs.

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 [37], with a corresponding decrease in the consolidated area of lung. Acetylsalicylic acid had a similar effect, reducing the shunt fraction from 38% to 23% [37]. The mechanism is unclear but may be due to reversal of prostaglandin inhibition of the hypoxia-induced pulmonary vasoconstriction.

In a small study of 10 subjects with pneumonia requiring mechanical ventilation, Hanley *et al.* [38] 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 [39], 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 [40]. 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 of ASA.

Immune Stimulation

IMMUNOGLOBULIN ENHANCEMENT

Before the advent of antibiotic therapy, passive immunization with serum was used with some success in patients with pneumonia [41]. 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 have been tried as an adjunct to antibiotics with some success in mice [42] and guinea pigs [43], and pseudomonas specific vaccines have enhanced antibiotic response in guinea pigs [44]. Anti-Pseudomonal antibodies appeared safe in human subjects with evidence of increased opsonophagocytic activity in a small phase I study of 20 subjects [45], 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 [46, 47]. 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.

NEUTROPHIL ENHANCEMENT

The neutrophil, or polymorphonuclear leukocyte (PMN), is a key cell in the host defense against microbial pathogens, particularly against bacteria and fungi. This includes the major pathogen in CAP, *S. pneumoniae* [48–54]. Both alcohol and diabetes, known risk factors for CAP [54, 55], have been shown to impair PMN function [56, 57]. A logical hypothesis following from this is that improving PMN function may improve the outcome of CAP.

Granulocyte colony stimulating factor (G-CSF) is one of a family of glycoproteins that control hematopoiesis [58]. G-CSF has significant effects on PMN function, increasing the response to chemotaxins, enhancing phagocytosis, increasing the respiratory burst, delaying neutrophil apoptosis and increasing bactericidal and fungicidal activity [58–60]. G-CSF also accelerates the development of PMNs leading to an increased rate of release from the bone marrow [59]. One further potential benefit of G-CSF is the enhancement of antibiotic uptake by phagocytic cells [61]. Due to these properties, G-CSF it is an attractive candidate for study in patients with pneumonia.

Since PMNs have been implicated in the development of multiorgan dysfunction, including ARDS [62, 63], the potential for harm from G-CSF therapy in some patients also exists. PMNs newly released from the bone marrow appear to preferentially sequester in the lung microvasculature [64], raising concern about an increased risk of ARDS. The effect of G-CSF in an individual CAP patient may also depend on the pathogen.

Animal pneumonia models demonstrate both potentials of GCSF treatment. Karzai and colleagues [65] used an endobronchial instillation model to demonstrate that G-CSF had a beneficial effect in *S. aureus* infected rats while *E. coli* infected rats had increased pulmonary injury and mortality with GCSF treatment. A significantly greater drop in peripheral PMN counts in *E. coli* infected rats was consistent with neutrophil mediated lung injury secondary to adherence to endothelium and subsequent degranulation, to which the lung is particularly susceptible [66, 67]. The dose of *E. coli* given was five-fold greater than the dose of *S. aureus*, raising the possibility that the *E. coli* arm actually produced a model of acute lung injury rather than pneumonia [68]. In other non-neutropenic animal models of pneumonia, G-CSF administration improved survival for both Gram-negative [69] and Gram-positive pathogens [70].

Initial studies of G-CSF in non-neutropenic human patients with pneumonia were encouraging [71]. In the most extensive trial published to date, Nelson *et al.* [72] conducted a prospective, multicenter, randomized, placebo controlled trial of G-CSF 300μg/day (for up to 10 days) in 756 CAP patients, 380 of whom received active drug. G-CSF appeared to be safe in this population, with even a trend to less ARDS and disseminated intravascular coagulation (DIC), although the numbers of each complication was small. Overall, no significant benefit was demonstrated, although a trend to better outcome in patients with multilobar pneumonia was found. The similar

trend was found in a recently completed multicenter trial [72b].

The likelihood is that G-CSF will not benefit all patients. GCSF does not appear to improve outcome in severe pneumonia with septic shock. Further research into both pathogen specific responses and specific patient subgroups, such as the elderly, diabetics and alcoholics, is needed before final conclusions on the role of G-CSF in pneumonia can be made. One important consideration will be the cost-benefit ratio, which has been questioned for G-CSF as therapy for neutropenia in patients receiving chemotherapy [73]. G-CSF clearly reduces the duration of neutropenia but no reduction in mortality or morbidity has been demonstrated in clinical trials in these patients.

MACROPHAGE ENHANCEMENT

Legionella pneumophila is consistently identified as a leading cause of CAP, particularly in patients with severe CAP [49, 50, 74–77]. Unlike pneumococcal pneumonia, the immune response to Legionella infection is predominantly of a TH1 type [78] and bacterial killing is predominantly by macrophages [79]. Skerrett and Martin studied the effect of interferon gamma (IFNγ), a potent stimulator of macrophage function [80, 81], given as an intratracheal bolus in rats with experimental *L. pneumophila* pneumonia [82]. 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 IFNg by aerosol is particularly appealing as it not only avoids the systemic side effects, but also has a much greater effect on intrapulmonary macrophage function than systemic administration [83]. Aerosolized IFNγ has also been shown to be safe in patients with drug resistant tuberculosis [84], and may have a role in treatment of this condition. Further studies of nebulized IFNγ, especially in patients with pulmonary Legionellosis, are awaited.

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.

Improving Oxygenation

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 [85]. 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.

DIFFERENTIAL LUNG VENTILATION

Differentially ventilating each lung by means of a dual lumen endotracheal tube may also be ben-

eficial [86, 87]. 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 [88]. The point at which differential ventilation is worth commencing is not clear, but Carlon and colleagues [86] suggest optimal benefit occurs when there is a 200 ml or greater difference in distribution of tidal volume between each lung.

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 [89] 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 [90]. Modification of the neonatal ECMO technique has also been effective in some pediatric patients with respiratory failure [91], including those with pneumonia from both bacterial [92] and viral [93] pathogens. As would be expected, as the duration of ECMO required increases, the prognosis decreases [92].

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 [94], 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* [95, 96], pneumococcal [97] and *Varicella* pneumonia [98] have all been reported.

The clearest indication for ECMO in adults may be the recently described Hantavirus Pulmonary Syndrome (HPS). With no effective antiviral therapy, care is entirely supportive. In a small series of three cases the dramatic but time-limited cardiovascular and pulmonary hemorrhagic manifestations of HPS appeared to be well supported by ECMO [99].

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 remains to be determined by prospective studies.

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 perfleurocarbon doubled survival compared to antibiotics alone [100].

Nitric oxide (NO) inhalation has also been studied as adjunctive therapy of ARDS, as well as some other forms of severe pulmonary hypertension. While there are no studies specifically addressing human patients with pneumonia, in dogs with *Eschericia coli* pneumonia, inhaled NO had a minimal effect on oxygenation and no effect on sepsis induced pulmonary hypertension [101].

Since NO is one of the effector molecules released by macrophages to kill bacteria [102],

inhaled NO has a potential antibacterial effect. Hoehn and colleagues studied the bacteriostatic effect of NO on bacterial cultures from neonates [103]. 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 [104].

Aerosolized prostacyclin has also been shown by Walmrath *et al.* to improve oxygenation by reducing shunt and pulmonary hypertension in patients with pneumonia [105]. 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.

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.

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 [106]. However, retained secretions are also one of the causes of failure of NIV. An important strategy to avoid this complication is to avoid continuous application 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 [107]. Therefore its therapeutic use should be limited. One of the few studies in 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.

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 [108], are encouraging but need further study. Guafenesin 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 bromohexine, rhDNase and polymixin B, there is no data to support their use in patients with pneumonia.

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*. The development of pathogen specific therapies, such as INFγ for *L pneumophila*, based on an improved understanding of host-pathogen interactions, are 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.

The past 20 years has seen an explosion in our knowledge of human immunology and we are only now beginning to explore the therapeutic possibilities this has made available. The next 10 years promises to finally provide a significant advance in the therapy of pneumonia, the first substantial gain since penicillin.

References

1. Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors and prognosis. Rev Infect Dis 7:133, 1985.
2. Watankunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital, 1992–1996. Arch Intern Med 157:1965, 1997.
3. Hook EW, Horton CA, Schaberg DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. JAMA 249:1055, 1983.
4. Franklin C, Henrickson K, Weil MH. Reduced mortality of pneumococcal bacteremia after early intensive care. J Intensive Care Med 6:302, 1991.
5. Torres JM, Cardenas O, Vasquez A, Schlossberg D. *Streptococcus pneumoniae* bacteremia in a community hospital. Chest 113:387, 1998.
6. Plouffe JF, Breiman RF, Facklam RR, Franklin County Pneumonia Study Group. Bacteremia with *Streptococcus pneumoniae*. Implications for therapy and prevention. JAMA 275:194, 1996.
7. Waterer GW, Quasney MW, Zhang Q, Jones CB, Wunderink RG. The impact of the TNFb + 250 gene polymorphism on the severity of community-acquired pneumonia. Chest 116:265S Abstract, 1999.
8. Westendorp RGJ, Langermans JAM, Huizinga TWJ, Elouali AH, Verweij CL, Boomsma DI, *et al*. Genetic influence on cytokine production and fatal meningococcal disease. Lancet 349:170, 1997.
9. Gagnon S, Ahmad M, Boota ND, *et al*. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 323:1444, 1990.
10. Bozette SA, Sattler FR, Chiu J, *et al*. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 323:1451, 1990.
11. Mer M, Richards GA. Corticosteroids in life-threatening varicella pneumonia. Chest 114:426, 1998.
12. Goldman M, Johnson PC, Sarosi GA. Fungal pneumonias. The endemic mycoses. Clin Chest Med 20:507, 1990.
13. Bradsher RW. Histoplasmosis and blastomycosis. Clin Infect Dis 22:S102, 1996.

14. Tognian S, Jiayu Y, Liye Z, Weiwu D, Zhaoying S. Chemotherapy and its combination with corticosteroids in acute miliary tuberculosis in adolescents and adults: analysis of 55 cases. Chin Med J 94:309, 1981.
15. Lebel MH, Freij BJ. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo controlled trials. N Engl J Med 319:964, 1988.
16. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. Chest 104:389, 1993.
17. Klugman K. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 3:171, 1990.
18. Torres A, Ewig S, El-Ebiary M, Filella X, Xaubet A. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Resp J 14:218, 1999.
19. Casey LC. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. Ann Intern Med 119:771, 1993.
20. Puren AJ, Feldman C, Savage N, Becker PJ, Smith C. Patterns of cytokine expression in community-acquired pneumonia. Chest 107:1342, 1995.
21. van Dissel JT. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet 351:950, 1998.
22. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MAD, *et al.* Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med 12:1439, 1995.
23. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert E, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26:645, 1998.
24. Reinhart K, Wiegand-Lönhart C, Grimminger F, *et al.* Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multi-center, randomized, placebo-controlled, dose-ranging study. Crit Care Med 24:733, 1996.
25. Abraham E, Wunderink R, Silverman H, *et al.* Efficacy and safety of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis syndrome: a randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. JAMA 273:934, 1995.
26. Cohen J, Carlet J, INTERSEPT: an international, multi-center, placebo-controled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. Crit Care Med 24:1431, 1996.
27. Opal SM, Fisher CJ, Dhainault JF. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med 25:1115, 1997.
28. Fisher CJ, Dhainault JF, Opal SM, *et al.* Recombinant human interleukin-1 receptor antagonist in the treatment of patients with sepsis syndrome. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 271:1836, 1994.
29. Fisher CJJ, Agosti JM, Opal SM, *et al.* Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. N Engl J Med 334:1697, 1997.
30. Abraham E, Glauser MP, Butler T, *et al.* p55 tumor necrosis factor receptor fusion protein in the treatment of patients with severe sepsis and septic shock. Ro 45-2081 Study Group. JAMA 277:1531, 1997.
31. Haupt MJ, Jastremski MS, Clemmer TP, Metz CA, Goris GB. Effect of ibuprofen in patients with severe sepsis: a randomized, double-blind, multicenter study. Crit Care Med 19:1339, 1991.
32. Bernard GR, Reines HD, Halushka PV. The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 336:912, 1997.
33. Fein AM, Bernard GR, Criner GJ, *et al.* Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127): results of a randomized, double-blind, placebo-controlled trial. JAMA 277:482, 1997.
34. Dhainault JF, Tenaillon A, Le Tulzo Y, *et al.* Platelet-activating factor receptor antagonist BN 52021 in the treatment of severe sepsis: a randomized, double blind, placebo-controlled, multicenter clinical trial. Crit Care Med 22:1720, 1994.
35. Dhainault JF, Tenaillon A, Hemmer M, *et al.* Confirming phase III clinical trial to study the efficacy of a P.A.F. antagonist, BN 52021, in reducing mortality of patients with severe gram-negative sepsis. Am J Respir Crit Care Med 151:A47, 1995.
36. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS)

and multiple organ dysfunction syndrome (MODS). Ann Intern Med 125:680, 1996.
37. Light RB. Indomethacin and acetylsalicylic acid reduce intrapulmonary shunt in experimental pneumococcal pneumonia. Am Rev Respir Dis 134:520, 1986.
38. Hanley PJ, Roberts D, Dobson K, *et al.* Effect of indomethacin on arterial oxygenation in critically ill patients with severe pneumonia. Lancet 1:351, 1987.
39. Bernard GR, Reines HD, Halushka RV, Higgins SB, Metz CA, Swindell BB, *et al.* Prostacyclin and thromboxane A_2 formation is increased in human sepsis syndrome. Am Rev Respir Dis 144:1095, 1991.
40. Ferrer M, Torres A, Bauer R, Hernández C, Roca J, Rodriguez-Roisin R. Effect of acetylsalicylic acid on pulmonary gas exchange in patients with severe pneumonia: a pilot study. Chest 111:1094, 1997.
41. Dowling HF, Lepper MH. The effect of antibiotics (penicillin, aureomycin, and terramycin) on the fatality rate and incidence of complications in pneumococcic pneumonia. A comparison with other methods of therapy. Am J Med Sci 222:396, 1951.
42. Kohzuki T, Eguchi Y, Kato M, Irie K, Ohtsuka H, Higuchi A, *et al.* Protective activity of anti-exotoxin A monoclonal antibody against mice infected with toxin-producing *Pseudomonas aeruginosa*. J Infect Dis 167:119, 1993.
43. Hector RF, Collins MS, Pennington JE. Treatment of experimental *Pseudomonas aeruginosa* pneumonia with a human IgM monocolonal antibody. J Infect Dis 160:483, 1989.
44. Pennington JE, Hickey WF, Blackwood LL, *et al.* Active immunization with lipopolysaccharide *Pseudomonas* antigen for chronic Pseudomonas bronchopneumonia in guinea pigs. J Clin Invest 68:1140, 1981.
45. Saravolatz LD, Markowitz N, Collins MS, Bogdanoff D, Pennington JE. Saftey, pharmokinetics, and functional activity of human anti-*Pseudomonas aeruginosa* monoclonal antibodies in septic and nonseptic patients. J Infect Dis 167:784, 1991.
46. Greenman RL, Schein RMH, Martin MA, *et al.* A controlled trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 266:1097, 1991.
47. Ziegler EJ, Fisher CJ, Sprung CL, *et al.* Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double blind, placebo-controlled trial. N Engl J Med 324:429, 1991.
48. Bates JH, Campbell GD, Barron AL, McCracken GA, Morgan PN, Moses EB, *et al.* Microbial etiology of acute pneumonia in hospitalized patients. Chest 101:1005, 1992.
49. Blanquer J, Blanquer R, Borrás R, Nauffal D, Morales P, Menéndez R, *et al.* Aetiology of community acquired pneumonia in Valencia, Spain: a multicentre prospective study. Thorax 46:508, 1991.
50. Macfarlane JT, Finch RG, Ward MJ, Macrae AD. Hospital study of adult community-acquired pneumonia. Lancet 2:255, 1982.
51. Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis 11:586, 1989.
52. Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease. Risk factors for morbidity and mortality. Arch Intern Med 154:2417, 1994.
53. Moldawer LL. Biology of proinflammatory cytokines and their antagonists. Crit Care Med 22:S3, 1994.
54. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med 333:1618, 1995.
55. Musher DM. Infections caused by *Streptococcus pneumonia*: clinical spectrum, pathogenesis, immunity and treatment. Clin Infect Dis 14:801, 1992.
56. Repine JE, Clawson CC, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetes. J Infect Dis 142:869, 1980.
57. Brayton RG, Stokes PE, Schwartz MS, Louria DB. Effect of alcohol and various diseases on leucocyte mobilization, phagocytosis and intracellular bacterial killing. N Engl J Med 282:123, 1970.
58. Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): The first 10 years. Blood 88:1907, 1996.
59. Dale DC, Liles WC, Summer WR, Nelson S. Granulocyte colony-stimulating factor-role and relationships in infectious diseases. J Infect Dis 172:1061, 1995.
60. Roilides E, Walsh TJ, Pizzo PA, Rubin M. Granulocyte colony-stimulating factor enhances the phagocytic and bactericidal activity of normal and defective human neutrophils. J Infect Dis 163:579, 1991.
61. McKenna PJ, Nelson S, Anderson J. Filgastrim

(rhuG-CSF) enhances ciprofloxacin uptake and bactericidal activity of human neutrophis *in vitro*. Am J Respir Crit Care Med 153:A535, 1996.
62. Fujishima S, Aikawa N. Neutrophil-mediated tissue injury and its modulation. Intensive Care Med 21:277, 1995.
63. Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 320:365, 1989.
64. Sato Y, van Eeden SF, English D, Hogg JC. Bacteremic pneumococcal pneumonia: bone marrow release and pulmonary sequestration of neutrophils. Crit Care Med 26:501, 1998.
65. Karzai W, von Specht BU, Parent C, Haberstroh J, Wollersen K, Natanson C, *et al.* G-CSF during *Escherichia coli* versus *Staphylococcus aureus* pneumonia in rats has fundamentally different and opposite effects. Am J Respir Crit Care Med 159:1377, 1999.
66. Bersten A, Sibbald WJ. Acute lung injury in septic shock. Crit Care Clin 5:49, 1991.
67. Repine JE, Bechler CJ. Neutrophils and adult respiratory distress syndrome: two interlocking perspectives in 1991. Am Rev Respir Dis 144:251, 1991.
68. Nelson S. A question of balance. Am J Respir Crit Care Med 159:1365, 1999.
69. Smith WS, Sumnicht GE, Sharpe RW, Samuelson D, Millard FE. Granulocyte colony-stimulating factor versus placebo in addition to penicillin G in a randomized blinded study of gram-negative pneumonia sepsis: analysis of survial and multisystem organ failure. Blood 86:1301, 1995.
70. Preheim LC, Snitily MU, Gentry MJ. Effects of granulocyte colony-stimulating factor in cirrhotic rats with pneumococcal pneumonia. J Infect Dis 174:225, 1996.
71. de Boisblanc BP, Summer WR, Mason C, Shellito J, Logan E, Bear M, *et al.* Phase 1 trial of granulocyte-colony stimulating factor in severe community acquired pneumonia. Am J Respir Crit Care Med A204, 1998.
72. Nelson S, Belknap SM, Carlson RW, Dale D, BeBoisblanc B, Farkas S, *et al.* A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. J Infect Dis 178:1075, 1998.
72b. Nelson S, Heyder AM, Stone J, *et al.* A randonited controlled trial of filgastrim for the treatment of hospitalized patients with multilobar pueumonia, J Infect Dis 182:970, 2000.
73. Urban T, Lebeau B. Colony-stimulating factor therapy and febrile neutropenia induced by chemotherapy: need for economical studies. Eur Resp J 13:1228, 1999.
74. Klimek JJ, Ajemian E, Tontecchio S, Gracewski J, Klemas B, Jiminez L. Community-acquired bacterial pneumonia requiring admission to hospital. Am J Infect Control 11:79, 1983.
75. Aubertin J, Dabis F, Fleurett J, Bornstein N, Salamon R, Brottier E, *et al.* Prevalence of legionellosis among adults: a study of community-acquired pneumonia in France. Infection 15:328, 1987.
76. Fang GD, Fine MJ, Orloff J, Arisumi D, Yu VL, Kapoor W, *et al.* New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine 69:307, 1990.
77. Lieberman D, Schlaeffer F, Boldur I, Horowitz S, Friedman MG, Leiononen M, *et al.* Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 51:179, 1996.
78. Tateda K, Matsumoto T, Ishii Y, Furuya N, Ohno A, Miyazaki S, *et al.* Serum cytokines in patients with Legionella pneumonia: relative predominance of Th1-type cytokines. Clin Diag Lab Immunol 5, 1998.
79. Friedman H, Yamamoto Y, Newton C, Klein T. Immunologic response and pathophysiology to *Legionella* infection. Semin Resp Infect 13:100, 1998.
80. Murray HW. Interferon-gamma, the activated macrophage, and host defense against microbial challenge. Ann Intern Med 108:608, 1989.
81. Nathan CF, Prendergast TJ, Wiebe ME, Stanley ER, Platzer E, Remold HG, *et al.* In vivo and in vitro activation of alveolar macrophages by recombinant interferon-γ. J Exp Med 160:600, 1984.
82. Skerrett SJ, Martin TR. Intratracheal interferon-γ augments pulmonary defenses in experimental legionellosis. Crit Care Med 149:50, 1994.
83. Jaffe R, Buhl R, Mastrangeli A, Holroyd KJ, Saltini C, Czerski D, *et al.* Organ specific cytokine therapy. J Clin Invest 88:297, 1991.
84. Condos R, Rom WN, Schluger NW. Treatment of multidrug-resistant pulmonary tuberculosis with interferon-gamma via aerosol. Lancet 349:1513, 1997.
85. Remolina C, Khan AU, Santiago TV, *et al.* Posi-

tional hypoxemia in unilateral lung disease. N Engl J Med 304:523, 1981.
86. Carlon GC, Ray CR, Klein R, *et al.* Criteria for selective positive end-expiratory pressure and independent synchronized ventilation of each lung. Chest 74:501, 1978.
87. Hillman KM, Barber JD. Asynchronous independent lung ventilation (AILV). Crit Care Med 8:390, 1980.
88. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:77, 1999.
89. Zapol WM, Snider MT, Hill JD. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 242:2193, 1979.
90. ECMO Registry of the Extracorporeal Life Support Organization (ELSO). ECMO Quarterly Report (January) 1997.
91. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF, *et al.* The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Crit Care Med 24:323, 1996.
92. Masiakos PT, Islam S, Doody DP, Schnitzer JJ, Ryan DP. Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure. Arch Surg 134:375, 1999.
93. Meyer TA, Warner BW. Extracorporeal life support for the treatment of viral pneumonia: collective experience from the ELSO registry. J Pediatr Surg 32:232, 1997.
94. Kolla S, Awad SS, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH. Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544, 1997.
95. Ichiba S, Jenkins DR, Peek GJ, Brennan KJ, Killer HM, Sosnowski A, *et al.* Severe acute respiratory failure due to legionella pneumonia treated with extracorporeal membrane oxygenation. Clin Infect Dis 28:686, 1999.
96. Nakajima H, Kutsuwada T, Ohdaira T, Saito A, Satoh K, Igarashi K, *et al.* Extracorporeal membrane oxygenation for acute respiratory failure induced by *Legionella pneumophile.* Nihon Kyobu Shikkan Gakkai Zasshi 35:1363, 1997.
97. Codispoti M, Sanger K, Mankad PS. Successful extracorporeal membrane oxygenation (ECMO) support for fulminant community-acquired pneumococcal pneumonia. Thorax 50:1317, 1995.
98. Lee WA, Kolla S, Schreiner RJ, Hirschl RB, Bartlett RH. Prolonged extracorporeal life support for varicella pneumonia. Crit Care Med 25:997, 1997.
99. Crowley MR, Katz RW, Kessler R, Simpson SQ, Levy H, Hallin GW, *et al.* Successful treatment of adults with severe Hantavirus pulmonary syndrome with extracorporeal membrane oxygenation. Crit Care Med 26:409, 1998.
100. Dickson EW, Heard SO, Chu B, Fraire A, Brueggemann AB, Doern GV. Partial liquid ventilation with perfluorocarbon in the treatment of rats with lethal pneumococcal pneumonia. Anesthesiology 88:218, 1998.
101. Quezado ZM, Natanson C, Karzai W, Danner RL, Koev CA, Fitz Y, *et al.* Cardiopulmonary effects of inhaled nitric oxide in normal dogs and during *E. coli* pneumonia and sepsis. J Appl Physiol 84:107, 1998.
102. Anggard E. Nitric oxide: mediator, murderer, and medicine. Lancet 343:1199, 1994.
103. Hoehn T, Huebner J, Paboura E, Krause M, Leititis JU. Effect of therapeutic concentrations of nitric oxide on bacterial growth *in vitro.* Crit Care Med 26:1857, 1998.
104. Chollet-Martin S, Gatecel C, Kermarrec N, Gougerot-Pocidalo M, Payen DM. Alveolar neutrophil functions and cytokine levels in patients with the adult respiratory distress syndrome during nitric oxide inhalation. Am J Respir Crit Care Med 153:985, 1996.
105. Walmrath D, Schneider T, Pilch J, Schermuly R, Grimminger F, Seeger W. Effects of aeroslized prostacyclin in severe pneumonia. Am J Respir Crit Care Med 151:724, 1995.
106. Confalonieri M, Potena A, Carbone G, Della Porta R, Tolley EA, Meduri GU. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 160:1585, 1999.
107. Joshi N, Localio AR, Hamory BH. A predictive risk index for nosocomial pneumonia in the intensive care unit. Am J Med 93:135, 1992.
108. Olivier KN, Bennett WD, Hohneker KW, Zeman KL, Edwards LJ, Boucher RC, *et al.* Acute safety and effects on mucociliary clearance of aerosolized uridine 5′-triphospate +/− amiloride in normal human adults. Am J Respir Crit Care Med 154:217, 1996.