

Nosocomial Pneumonia, Including Ventilator-associated Pneumonia

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Patients with nosocomial pneumonia have evidence of immunosuppression. The most obvious defect in immunity is the loss of mechanical barriers with an endotracheal tube. Only a third of colonized patients on ventilators develop pneumonia, however, suggesting that altered immunity is more extensive. This subgroup of patients tends to get multiple synchronous and sequential infections. The exact mechanisms of this compromise of immunity remain to be fully elucidated. Both a temporary immunocompromised and a specifically predisposed subpopulation, however, can explain the clinical pattern. A temporary immunoparalysis clearly occurs and is associated with increased risk of infections. An underlying genetic predisposition may lead to a predisposed population. Genetic polymorphisms in pathogen recognition molecules increase the risk of nosocomial infections. Genetic variability in immune mediators increase severity of infections and mortality but have not been demonstrated as consistently to lead to infections. Adequate treatment of an initial infection is required for reversal of the temporary immunoparalysis, whereas specific immunomodulatory therapies can reverse the markers of immunoparalysis and may decrease the risk of infection.

Keywords: immunoparalysis; nosocomial infections; pneumonia; polymorphisms

Nosocomial pneumonia is usually considered as a category distinct from pneumonia in the immunocompromised host. Although components of the pathogenesis differ, patients with nosocomial pneumonia clearly suffer from a form of immunocompromise. Inclusion of nosocomial pneumonia in this symposium is entirely appropriate. Unfortunately, most of the information on nosocomial pneumonia is from studies of ventilator-associated pneumonia (VAP). Where applicable, data specific to nonintubated patients are included.

The most obvious compromise of normal host immunity in hospitalized patients is alteration of the mechanical components of lung defenses. For example, endotracheal intubation bypasses the entire upper respiratory tract mechanical barrier. Other aspects also are affected. Not only does the endotracheal tube compromise cough but also, even in nonintubated patients, use of sedatives, analgesics (or the pain itself), or anticholinergic agents can limit the effectiveness of cough. Many hospitalized patients are also kept in the supine position, further compromising mucociliary clearance and increasing aspiration risk. Hospitalized patients are frequently not in control of their own fluid balance, leading to decreased mucociliary clearance by dehydration or, conversely, compromise of alveolar macrophage chemotaxis and bacterial engulfment in patients with pulmonary edema.

Changing the microbiologic milieu is thought to be a major issue in hospitalized patients. The evidence that nosocomial pathogens are more virulent than community-acquired, however, is weak. Many people are exposed to microorganisms thought to be characteristic of severe nosocomial pneumonia, such as *Pseudomonas aeruginosa* in water supplies or *Aspergillus fumigatus* in soil, without ever developing infection. The critical issue in hospitalized patients is not necessarily exposure to more pathogenic microorganisms, but rather the iatrogenic change in normal flora with the nearly ubiquitous use of antibiotic therapy. Hospitalized patients rarely develop *P. aeruginosa* infection unless they have already received antibiotics.

Although loss of mechanical host defense and suppression of normal flora probably explain a major component of the increased risk of pneumonia in hospitalized patients, significant data also support compromise in other components of host defense.

CLINICAL EVIDENCE FOR ADDITIONAL IMMUNOCOMPROMISE IN VAP

Even in the seminal work on oropharyngeal and tracheal colonization by Johanson and coworkers (1), only approximately one third of the patients with gram-negative colonization subsequently developed VAP. Multiple subsequent studies have confirmed that, whereas tracheal colonization almost always occurs before development of VAP (2), many colonized patients never develop pneumonia. Clinical risk factors are associated with increased risk but rarely have immunologic parameters been included in the multivariate analysis (3). Clinical risk factors may only be statistical associations without pathogenic implications or surrogate markers for patients who have compromised immunity.

An underappreciated fact is that most nosocomial infections occur in a subgroup of critically ill patients. This subgroup can have multiple synchronous infections. This factor has always compromised the ability to diagnose VAP accurately, because with extensive diagnostic testing an average of more than two infections per episode of fever can be found in intubated patients suspected of VAP (4, 5). The association of sinusitis and VAP (4) may be explained by many of the mechanical and altered oropharyngeal flora noted previously, but infections at other sites are harder to explain by this mechanism. These data suggest that a more generalized immunocompromise is occurring in this subgroup.

A subgroup of patients in the intensive care unit also has multiple sequential infections. This group may or may not overlap with the one with multiple synchronous infections. Patients with intraabdominal infections can develop either recurrent intraabdominal infections or VAP or both (6). The mortality is greatest in the subgroup with both. Specifically in patients with pneumonia, recurrent VAP occurs in 15 to 30% of cases. For *Pseudomonas* VAP, the recurrence rates may be as high as 50% (7). Patients with recurrent VAP have a greater mortality than those with single episodes, even when caused by the same microorganism.

The time course of VAP also suggests compromised immunity. The daily hazard rate for first episodes of VAP was high

(Received in original form August 2, 2005; accepted in final form September 9, 2005)

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Proc Am Thorac Soc Vol 2, pp 440-444, 2005

DOI: 10.1513/pats.200508-083JS

Internet address: www.atsjournals.org

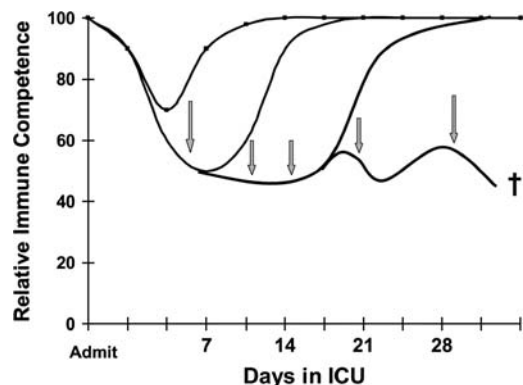


Figure 1. Temporary immunoparalysis causing multiple infections. Relative immune responsiveness is restored unless intercurrent infections or other immunosuppressive events (arrows), such as red blood cell transfusion or malnutrition, intervene. Recurrent infections occur in this population until either recovery of immune responsiveness or death.

for the first several days (3.3% per day at Day 5), and then decreases to 1.3% per day after Day 15 (8). The early onset (within 5–7 d) cases are not associated with any attributable mortality (7). Although still debatable, some degree of excess mortality occurs in patients with late-onset VAP. The fact that different diagnostic strategies or antibiotic treatment are associated with a mortality difference in VAP is fairly convincing (7). If a patient remains ventilated for more than several weeks, however, the rate of VAP plateaus, such that patients in chronic ventilator facilities have a much lower rate of VAP and those that do occur are rarely fatal.

This clinical evidence suggests that patients on ventilation suffer from greater immune compromise than just the alterations in mechanical host defense. Although multiple explanations are likely, the patterns suggest at least two possibilities. The first is that a temporary, acquired immunocompromise occurs and that, if patients survive this period of immunoparalysis, the risk of VAP (and other infections) decreases (Figure 1). The second possibility is that a particularly susceptible population is present. This population experiences most ICU infections and may increase the risk for others because of cross infection. This subgroup ultimately cannot survive the recurrent infections and the plateau in incidence and mortality of VAP occurs when this group dies (Figure 2). The available literature supporting both concepts is reviewed.

IMMUNOPARALYSIS

The initial efforts at immunomodulation of severe sepsis and septic shock were driven by the assumption that the adverse outcomes were related to an overly exuberant inflammatory response. An important component of this concept was the idea that compartmentalization of inflammation was important (9); inflammation at the site of infection is critical to control of infection, whereas systemic spillover or escape of inflammation led to septic shock and uninfected organ failure. The logical outcome was definition of the systemic inflammatory response syndrome to select patients appropriate for immunomodulatory trials more consistently (10).

The consistent failure of these generally antiinflammatory therapies resulted in a reexamination of this fundamental concept. Increasing attention was directed to the role of the corresponding compensatory antiinflammatory response syndrome (11). Several studies demonstrated an initial salvage of patients

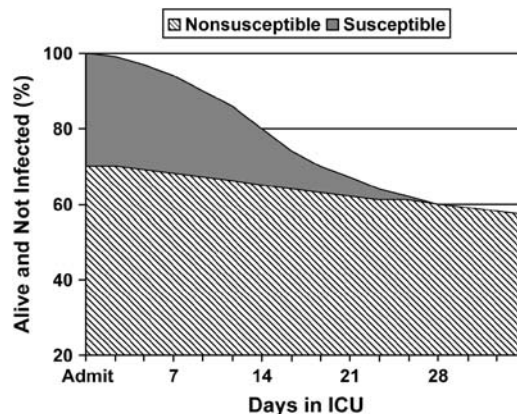


Figure 2. Susceptible subgroup causing multiple infections. Recurrent infections occur in a susceptible subgroup, usually resulting in death, whereas rare and isolated infections occur in the nonsusceptible subgroup.

with sepsis, especially those in shock, in the first few days with the antiinflammatory therapy, followed by an increased mortality in the subsequent days to weeks, ultimately resulting in equivalent 28-d mortalities (12). An interpretation of this pattern is that antiinflammatory therapy lowered mortality in the subgroup of patients with an excessive proinflammatory response, while increasing mortality in the subgroup with a normal or decreased inflammatory response.

Subsequent development of assays to monitor immune status confirmed that a temporary immunoparalysis does occur in critically ill patients, especially those admitted with sepsis. Noninfectious inflammatory disorders, such as pancreatitis or cardiopulmonary bypass, have demonstrated a similar effect (3). Most studies use two classes of assay to define immunocompromise: circulating mediator levels or cell-surface marker expression. The latter are probably more reliable because their expression is governed by a large number of mediators and may reflect the balance between proinflammatory and antiinflammatory responses.

Measurement of HLA-DR expression on peripheral monocytes seems to be a good marker of global immune function, correlating with cytokine production in response to bacterial antigens, lymphocyte proliferation in response to recall antigens, or new antigen presentation. Low levels of HLA-DR expression have been found in patients who subsequently developed nosocomial infections (3, 13–15). In one of the few studies to include measurement of immune function in a multiple logistic regression, low HLA-DR levels were an independent predictor of septic complications (3).

The pattern of HLA-DR expression correlates well with the concept of a temporary immune dysfunction predisposing to nosocomial pneumonia. In patients with inflammatory disorders, such as sepsis, trauma, or pancreatitis, HLA-DR expression routinely decreases in the first few days after admission to the intensive care unit. Levels in survivors and nonsurvivors do not differ significantly at this early point (16–18). Persistence of low (< 40%) HLA-DR expression on monocytes at 5 to 7 d after septic shock is associated, however, with an ultimately fatal outcome (15). In survivors, HLA-DR levels normalize within the first week. Subsequent nosocomial infections seem to blunt the recovery of HLA-DR expression (19), setting up a vicious cycle of one nosocomial infection leading to increased risk for new infections.

Endotoxin Tolerance

Ex vivo experiments have also documented reversible endotoxin tolerance in critically ill patients (20–23). Trauma patients whose peripheral mononuclear cells demonstrated a blunted cytokine release on exposure endotoxin tolerance had more clinical infections than those without (21). Recovery of a normal cytokine response to endotoxin was associated with survival (20), although a less exaggerated response in the first 2 to 4 hours after trauma may lead to less complicated recovery (22).

Endotoxin tolerance alone may not explain the immune hyporesponsiveness because some components of innate immune response are actually augmented (23, 24). Defective *ex vivo* cytokine release on endotoxin exposure was most prominent in patients with documented gram-negative infections (20). This finding is not explained by decreased expression of toll-like receptor-4 (TLR4), because human studies demonstrate that cell-surface TLR4 receptor expression was upregulated in patients with endotoxin tolerance, whereas TLR2 and CD-14 expression were unchanged (25). This type of immunosuppression may be selective rather than global, leaving the patient susceptible to similar pathogens but still protected from others.

Mediator Levels

Measurement of mediator levels also provides evidence for compromised immune function in patients who develop nosocomial pneumonia. Interpretation of these studies is complicated by variability in assays, timing of sampling, variety of causative microorganisms and site of infection, coexisting conditions, and therapeutic interventions. The major focus of these studies has not been on risk of subsequent nosocomial infection, although many have looked at subsequent survival, which should be influenced by nosocomial infections.

Increased levels of IL-10 seem to correlate best with immune suppression in hospitalized patients. Serum IL-10 levels or the ratio of IL-10 to tumor necrosis factor seem to correlate with outcome of infected patients (26). IL-10 levels correlated with survival in septic shock, whereas tumor necrosis factor and transforming growth factor- β did not (27). Serum cytokine levels do not necessarily predict mortality better than clinical models, such as severity of illness or organ failure scores (16).

Decreased expression of HLA-DR correlates with IL-10 levels but not transforming growth factor- β , another important antiinflammatory cytokine (17, 18, 27). Endocytosis of HLA-DR when healthy-donor monocytes are exposed to serum from patients with sepsis is substantially blocked by anti-IL-10 antibodies (18). Because IL-10 is a potent suppressor of multiple proinflammatory cytokines (28), this relationship is not surprising.

Correlation of HLA-DR expression with serum IL-10 levels has not always been demonstrated (13), although levels of cortisol, another antiinflammatory mediator, seem to downregulate HLA-DR on a transcriptional basis. The most likely explanation for lack of correlation is that cytokine levels result in a temporary suppression of immune response (29, 30), whereas HLA-DR expression reflects the net effect of multiple mediators acting in concert. Another explanation is that local levels are important. In a study specifically focused on VAP (14), serum levels of IL-10 did not explain the risk of VAP in a trauma population. Persistent suppression of HLA-DR expression on alveolar macrophages, however, predicted development of VAP and correlated with bronchoalveolar lavage (BAL) IL-10 levels.

Lymphocytopenia

Sepsis-induced lymphocytopenia seems to correlate with immunocompromise and with mortality (31, 32). This lymphocytopenia seems to be induced by increased apoptosis signals (32–35).

Adoptive transfer of apoptotic splenic cells seems to induce immunosuppression in a murine model, whereas necrotic cells increase immune response (36). Use of an inhibitor of apoptosis also seemed to restore immunity (37).

GENETIC PREDISPOSITION

An alternative explanation for compromised immunity in patients who develop nosocomial pneumonia is a fixed, rather than a temporary, defect in immunity. Clearly, patients with known types of congenital immune deficiency disorders occasionally are admitted to the hospital and their risk of nosocomial infections is expected to be increased. The number of patients with these disorders is small, however, and does not explain more than a small fraction of nosocomial pneumonias.

A more likely explanation for the increased risk of pneumonia in a subgroup of hospitalized patients is polymorphisms (gene mutations with a frequency of $> 1\%$ in the general population) in important components of the host response to infection. Dissecting the contribution of genetic factors to a complex disorder, such as nosocomial pneumonia, is very difficult. Accurate case definition, comorbid conditions, use of agents with immunomodulatory effects, and variable nongenetic risk for pneumonia suggest that multivariate analysis is required to separate gene-environment-treatment interactions. Because more than 200 mediators are involved in the pathogenesis of sepsis, the multitude of candidate genes suggests gene-gene interactions are also very likely. Susceptibility to pneumonia may be increased, whereas risk of death or complications may be decreased by the same polymorphism. Despite all these difficulties, increasing data suggest that genetic variations do affect the risk of or response to nosocomial infection.

Studies on the genetic risk for nosocomial infections have focused on two aspects of the normal host response: pattern recognition molecules and the inflammatory mediators themselves. Pattern recognition molecules are the most likely to increase susceptibility to nosocomial pneumonia. Endotoxin tolerance can clearly result from an abnormal TLR4 (38), and TLR4 polymorphisms are more common in patients with septic shock, especially gram-negative (39). The support for increased infections with gram-positive infections with TLR2 is less convincing. TLR5 signaling is initiated by flagellin and variant alleles are more common in patients with *Legionella* infections (40). Other components of the endotoxin recognition and signaling have less convincing evidence (41). Mannose-binding lectin has not been studied in nosocomial pneumonia but has been found to increase the risk of severe sepsis, invasive pneumococcal pneumonia, and meningitis (41).

Polymorphisms in genes for molecules, such as tumor necrosis factor, IL-6, lymphotoxin- α , plasminogen activation inhibitor-1, IL-1 receptor antagonist, and IL-10, have been associated with increased risk of septic shock and death once infection occurs (41, 42), but the evidence for increasing susceptibility to pneumonia is less clear. Interferon- γ polymorphisms associated with decreased function have been associated with an increased risk of infection in a trauma population (43). A polymorphism in the angiotensin-converting enzyme gene has been associated with an increased risk of adult respiratory distress syndrome and increased mortality (44). Mortality in adult respiratory distress syndrome is often associated with development of secondary infections. One possibility for the increased mortality associated with the angiotensin-converting enzyme polymorphism may be an increased risk of this complication, as suggested by studies of community-acquired pneumonia (41).

The multitude of polymorphisms in mediators involved in susceptibility to pneumonia and the difficulties in association

studies preclude definitive statements regarding the genetic risk for an immunocompromised state. Genetic predisposition is likely to play an important role, however, especially in the patient with recurrent infections. An interaction between genetic polymorphisms and the acquired immunoparalysis described previously is also possible.

TREATMENT AND PREVENTION

General principles for prevention of the immunocompromised state leading to nosocomial pneumonia include adequate source control of an initial infection. This may be a major problem with recurrent *Pseudomonas* VAP. Control of infectious sites by surgery restores HLA-DR expression (19), whereas other major noninfectious surgery suppresses expression once again. The better outcomes of a lower blood transfusion threshold (45) may reflect avoidance of the immunosuppressive effects of transfusion. Many of the abnormalities now ascribed to immunoparalysis were first thought to be part of malnutrition in the critically ill and inadequate nutrition may still play a role.

Several attempts at specific treatment of the immunosuppression of critical illness have been made. A small study of inhaled interferon- γ in patients with low HLA-DR expression decreased the VAP rate from 5/10 to 1/11 ($p < 0.05$) (46). Both inhaled and intravenous interferon- γ therapy effectively increased the HLA-DR expression, helping to clear sepsis (47). Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have been used to reverse the impaired immune response with equivocal results on clinical infection rates (48–50).

Until a clear benefit for one of these agents is demonstrated, measurement of HLA-DR expression, genotype, or other markers of immune depression in the critically ill remains a research tool.

CONCLUSIONS

Patients with nosocomial pneumonia clearly have evidence of immunosuppression. The exact mechanisms of this compromise of immunity remain to be fully elucidated. Both a temporary immunoparalysis and underlying genetic predisposition, however, are likely to play a role.

Conflict of Interest Statement: R.G.W. has received an investigator-initiated research grant from Eli Lilly and Company to examine genetic polymorphisms as risk factors for pneumonia.

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