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Immunological perspectives in prevention and treatment of nosocomial pneumonia

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Abstract. The high mortality associated with current therapeutic approaches to nosocomial pneumonia has motivated consideration of newer immunologic approaches to prevention or therapy of this infection. Serotype specific vaccines, hyperimmune immunoglobulins, and monoclonal antibodies have been developed for certain problematic pathogens. *Pseudomonas aeruginosa* has been the major focus of this approach, and trials of hyperimmune anti-*Ps. aeruginosa* globulins for treatment of pneumonia are underway. Broad-spectrum, anti-lipopolysaccharide antibody preparations have also been employed for prophylaxis of nosocomial pneumonia, but to date these trials have not been successful. Finally, anti-cytokine antibody therapy to reduce infection-initiated inflammatory lung damage is under consideration.

Key words: Nosocomial pneumonia – Vaccines – Immunoglobulins – Monoclonal antibodies – Cytokines

It is not surprising that an illness, such as nosocomial pneumonia, with high mortality would motivate investigations into new therapeutic approaches. Recent technological advances in antibody therapy, as well as increased understanding of the immune mediators of infectious pathology, have provided new incentive to explore immunologic approaches to the problem of nosocomial pneumonia.

This paper will discuss general issues regarding immunotherapy (Table 1) and specific immune strategies that have been employed or might be employed in the near future. It must also be kept in mind that considerable overlap occurs when considering various immunologic approaches to pneumonia (Fig. 1). And finally, a number of immunologic properties are unique to lung tissue which again may influence immunotherapeutic strategies (Table 2).

Table 1. Immunologic approach to nosocomial pneumonia: issues to consider

- Spectrum: narrow vs broad
- Prevention vs treatment
- Active vs passive immunization
- Non-microbiological approaches (e.g. anti-cytokine)

General issues of immunotherapy

Spectrum of immunotherapy

The spectrum of immunotherapy is one of several general issues regarding immunotherapy which should be considered. The classical approach to immunization is to raise an antibody in the host which reacts specifically against a specific microorganism. For nosocomial pneumonia, the logical target organisms would be aerobic Gram-negative bacilli, including *Klebsiella* spp., *Escherichia coli*,

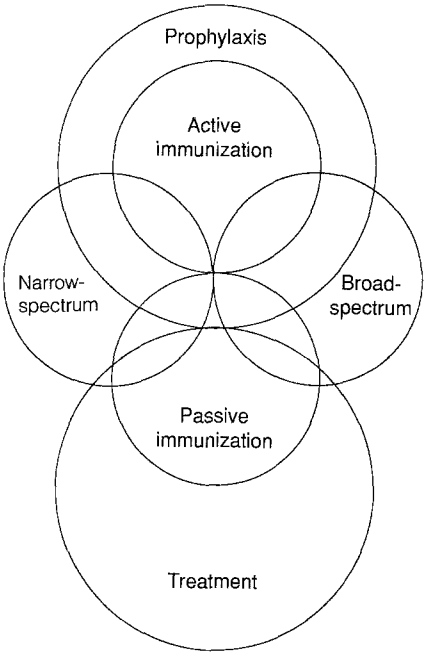

Fig. 1. Overlapping immunologic approaches to nosocomial pneumonia

Table 2. Lung-specific issues for immunologic approach to nosocomial pneumonia

- Divergent local vs systemic antibody formation (i.e. response and type)
- Lack of IgM and complement in non-inflamed airways
- Unique bronchoalveolar white cell distribution
- Divergent local vs systemic immune cell functions
- Local cytokine status
- Bronchoalveolar epithelial interaction with pathogens

Pseudomonas aeruginosa, *Serratia marcescens*, *Proteus* spp., etc. In fact, serotype specific antibodies remain the most potent form of anti-gram-negative antibody [1, 2]. At least theoretically, another advantage of such narrow spectrum (organism-specific) antibody therapy is that only limited microflora would be affected in the host.

Unfortunately, there are two major disadvantages to type-specific, narrow spectrum antibody therapy. First is the wide array of O-side chain serotypes among Gram-negative bacilli. Literally hundreds of vaccines or monoclonal antibodies would be necessary to allow for selection of an appropriate specific antibody for a given infection. Also, prophylaxis using a serotype specific preparation would require a mixture of hundreds of antibodies (or vaccine antigens) to ensure coverage for most potential pathogens. The other disadvantage of the type-specific approach is that rapid, and serotype specific diagnosis would be necessary to allow early treatment with the correct type-specific antibody. While in some cases this is possible, in many other instances, the exact etiology, let alone the serotype of the nosocomial pneumonia is uncertain. These drawbacks have engendered development of broad-spectrum antibody preparations for Gram-negative bacillary infections. Experience with such preparations in nosocomial pneumonia, however, is limited.

Immunotherapy for prevention versus treatment

If it was clear that prophylactic use of vaccines or antibody preparations was effective in preventing nosocomial pneumonia, it would be most ethical to use them in this fashion. However, proving preventive efficacy for a specific type of Gram-negative pneumonia has been difficult due to the relative infrequency of specific etiologic agents in a given hospital. For example, if one is prophylaxing for *Ps. aeruginosa*, and this pathogen only accounts for 10% of all ICU pneumonias, and pneumonia only occurs in 15% of all patients admitted, and the rate of incidence reduction expected is 50%, one can then calculate that a sizable study would be needed in order to prove efficacy. On the other hand, if the incidence of *Ps. aeruginosa* in a given setting rose to 50% or 70% (epidemic), feasibility would be improved for a type-specific prophylaxis study. Past reports suggest that this epidemic situation might occur [3]. This "problem pathogen" approach justifies continued consideration of prophylaxis with certain narrow-spectrum antibody preparations [4]. Using a broad-spectrum antibody preparation for prophylaxis might make even more sense, but to date the clinical experience with such preparations has been mixed (see Section "Immunologic approaches").

In contrast to prophylactic strategies, immunologic treatment strategies greatly limit patient exposure to these products. Since certain vaccines and monoclonal antibodies may be associated with side effects, these are relevant considerations. However, timing of immune therapy is critical, and for some cases of acute hemorrhagic Gram-negative pneumonia, it may be impossible to begin immune therapy early enough to affect outcome.

Active versus passive immunization

Active vaccination offers an inexpensive and convenient form of immunization. Unfortunately, the time needed to raise an immune response usually exceeds 7 – 10 days. Acutely hospitalized patients in the intensive care unit are at risk for, or may develop nosocomial pneumonia well within this time period. Thus, a more rapid means for raising desired antibody titers has been sought. A number of antibody preparations are under investigation which can be used in high doses by intravenous infusion. These include hyperimmune (high titer) immunoglobulin preparations and monoclonal antibodies. In most cases, the titers achieved far exceed those to be expected from active vaccination. These preparations are likely to be more expensive than vaccines, however, and the antibody response is of considerably shorter duration than that resulting from active vaccination.

Type of immune approach

While use of antibodies against micro-organisms is the classic approach to immunologic therapy, several newer approaches with relevance to nosocomial pneumonia are emerging. The evidence that cytokines, such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), are important mediators of pathology during bacterial infection, raises the possibility that antibodies or other substances which neutralize these cytokines might be useful in treating nosocomial bacterial pneumonia, as discussed below. In addition, recombinant DNA produced proteins which augment select components of the host defense system have been developed (e.g. granulocyte colony stimulating factor, gamma interferon). Use of these "pro-host" cytokines for nosocomial pneumonia is at least a rational concept.

Finally, in considering immunologic approaches to nosocomial pneumonia, it must be recognized that the lung is an organ which is immunologically unique and, in some instances, distinct from the systemic immune system. A review of this unique respiratory immune system is beyond the scope of this discussion but is summarized in Table 2, and more extensively treated in reviews by Reynolds [5], Toews [6] and Wood [7].

Immunologic approaches to prevention and treatment

Serotype-specific approach to immunotherapy

The objective of a serotype-specific immunologic approach to nosocomial pneumonia is to identify a pathogen which is particularly difficult to treat and to develop specific vaccines or antibody preparations which

confer added protection beyond antibiotics alone. *Ps. aeruginosa* is such a problem pathogen in the intensive care unit setting [4]. Early trials utilized a lipopolysaccharide (LPS)-based vaccine which incorporated antigens from the seven most common clinical serotypes. In one controlled trial, active immunization of 48 patients in a surgical ICU resulted in a reduced frequency of *Ps. aeruginosa* respiratory infections and deaths as compared to 51 non vaccinated controls [8] (Table 3). Overall mortalities in the unit were not affected, however. More recently, a hyperimmune intravenous immunoglobulin (IGIV) preparation has been developed, which contains antibody titers against common *Ps. aeruginosa* serotypes which are fivefold higher than titers in normal commercial IGIV preparations [9]. A pilot trial in Germany suggested that this preparation might improve survival from nosocomial *Ps. aeruginosa pneumonia* [10]. Animal experiments have also suggested that treatment efficacy of pneumonia might be improved over that achieved with antibiotics alone [11]. Currently, a double blind, placebo controlled multicenter clinical trial is underway in the United States to determine whether this preparation will reduce mortality or morbidity from nosocomial *Ps. aeruginosa* pneumonia. While the trial is not complete, an interim analysis suggested that morbidity (days on ventilator, days in intensive care unit) may be reduced for patients receiving this preparation.

More recently, human monoclonal antibodies against *Ps. aeruginosa* have been developed. These antibodies have been effective in animal models of pneumonia [12], and are well tolerated by humans [13]. Further investigation of their usefulness in treatment of nosocomial pneumonia is awaited.

Broad-spectrum approach to immunotherapy

A simplified approach to development of immunologic preparations for Gram-negative bacillary infections is to utilize a vaccine or antibody which reacts with an epitope which is commonly expressed on the cell wall of all Gram-negative bacilli. The core-glycolipid structure of LPS appears to be such an epitope. A variety of preparations have been and are currently under study which utilize this principle (recently reviewed by Baumgartner [14]) (Table 3).

In one controlled trial, a cross-protective anti-LPS immune plasma was used in 126 high-risk surgical patients as prophylaxis against nosocomial sepsis [15]. Many of these patients were intubated and at high risk of nosocomial pneumonia. While septic shock was reduced in the plasma recipients as compared to 136 control patients, there was no reduction in incidence of pneumonia. In a more recent trial, Cometta et al. have reported that prophylactic use of a different broad-spectrum anti-LPS antibody preparation (an IGIV) was also unsuccessful in reducing Gram-negative pneumonia in 108 surgical ICU patients, as compared to 112 placebo treated controls [16]. However, in the same trial, a group of 109 patients who received conventional IGIV did show reduced rates of nosocomial pneumonia ($p < 0.02$). The reason for this discrepancy is unclear.

Table 3. Clinical studies employing immunologic approaches for nosocomial pneumonia

Immunization	Reference	Design; outcome
Type specific immunization		
Pseudomonas vaccine	[8]	Controlled, prophylaxis; success
Pseudomonas immunoglobulin	[10]	Controlled, treatment; success
Broad spectrum immunization		
Antiendotoxin serum	[15]	Controlled, prophylaxis; failed
Immunoglobulin (regular and hyperimmune anti-endotoxin)	[16]	Controlled, prophylaxis; success

Finally, despite the availability of several reports utilizing broad-spectrum, anti-LPS antibody preparations for treatment of Gram-negative bacteremia (reviewed in [14]), there have been no clinical trials reported in which such preparations were employed specifically for treatment of nosocomial pneumonia.

Anti-cytokines strategies

A number of low molecular weight pro-inflammatory proteins are secreted by mononuclear leukocytes upon stimulation by infectious pathogens. These proteins, commonly called cytokines, appear to mediate much of the pathology associated with both Gram-negative as well as Gram-positive sepsis. One particularly potent cytokine, known as tumor necrosis factor (TNF), has recently been associated with adult respiratory distress syndrome (ARDS) in patients with sepsis. In one report, both mortality as well as incidence and severity of ARDS were associated with higher levels of TNF in the plasma of septic patients [17]. In another report, this trend was again noted, but statistical significance was not achieved [18]. In yet another report, local bronchoalveolar concentrations of TNF were elevated in five patients with ARDS [19]. Only one of these five patients had sepsis as the underlying etiology of ARDS, however. While ARDS does not equate with nosocomial pneumonia, they are often associated. Thus, the recent development of monoclonal antibodies which neutralize TNF [20], suggests the possibility that anti-TNF antibody therapy might play a role in nosocomial pneumonia when associated with ARDS. Clinical trials will be necessary to verify this hypothesis.

In addition to ARDS, elevated bronchoalveolar TNF concentrations have been documented in an animal model after intrabronchial challenge with *E. coli* LPS [21]. It was of interest that TNF was not detected in serum after intrabronchial challenge. Whether this local TNF is beneficial to local host defenses, or is mediating inflammatory lung damage is currently uncertain. Again, clinical trials will ultimately be needed to clarify whether neutralization of TNF in the lung compartment during Gram-negative pneumonia would be useful.

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