Immunoprophylaxis against Klebsiella and Pseudomonas aeruginosa Infections


To determine if passive immunization could decrease the incidence or severity of Klebsiella and Pseudomonas aeruginosa infections, patients admitted to intensive care units of 16 Department of Veterans Affairs and Department of Defense hospitals were randomized to receive either 100 mg/kg intravenous hyperimmune globulin (IVIG), derived from donors immunized with a 24-valent Klebsiella capsular polysaccharide plus an 8-valent P. aeruginosa O-polysaccharide–toxin A conjugate vaccine, or an albumin placebo. The overall incidence and severity of vaccine-specific Klebsiella plus Pseudomonas infections were not significantly different between the groups receiving albumin and IVIG. There was some evidence that IVIG may decrease the incidence (2.7% albumin vs. 1.2% IVIG) and severity (1.0% vs. 0.3%) of vaccine-specific Klebsiella infections, but these reductions were not statistically significant. The trial was stopped because it was statistically unlikely that IVIG would be protective against Pseudomonas infections at the dosage being used. Patients receiving IVIG had more adverse reactions (14.4% vs. 9.2%).

Infections caused by Klebsiella species and Pseudomonas aeruginosa are associated with high numbers of cases of morbidity and mortality in hospitalized patients [1, 2]. Infection control and the prudent use of antibiotics are the foundation for prevention of these infections. Despite the best efforts, Klebsiella species and P. aeruginosa continue to be two of the most frequent causes of serious nosocomial infections and often acquire resistance to many antibiotics [3–5]. Consequently, there has been great interest in immunoprophylactic and immunotherapeutic agents to obviate or supplement conventional antimicrobial therapy and supportive care.

In developing immunologic approaches against Klebsiella species and P. aeruginosa, Cryz and colleagues [6–8] found that passive immunization with a hyperimmune globulin directed against the prevalent serotypes of Klebsiella species and P. aeruginosa and against exotoxin A had good functional activity in vitro and provided protection against most infections caused by these organisms in animal models. Plans were subsequently developed to validate these findings in humans, and this report summarizes the results of these studies.

Methods

Vaccines, immunoglobulin, and placebo. The 24-valent Klebsiella capsular polysaccharide (CPS) vaccine was prepared as described [6]. Each dose of vaccine contained 50 μg of CPS from the following serotypes: 2, 3, 5, 9, 10, 15–18, 21, 22, 25, 28, 30, 35, 43, 52, 53, 55, and 60–64. These vaccine serotypes represent >60% of the Klebsiella serotypes associated with bacteremic infections; they also cross-react with CPS of Enterobacter aerogenes. Each dose of the 8-valent P. aeruginosa O-polysaccharide–toxin A conjugate vaccine [7] contained 25 μg of O-polysaccharide of Pseudomonas IATS (International Antigen Typing Scheme)....
serotypes 1, 2/5, 3, 4, 6, 7, 10, and 16, representing 90% of bacteremic *P. aeruginosa* strains.

Hyperimmune globulin was prepared by immunization of donors free of human immunodeficiency virus, hepatitis B, and hepatitis C infections with *Klebsiella* and *P. aeruginosa* vaccines [8]. Donors mounting acceptable ELISA responses to the vaccines underwent plasmapheresis several times over the 6 months following immunization. The pooled plasma was then processed into an immune globulin for intravenous administration (IVIG) [8]. This IVIG is more efficacious than standard IVIG in treating lethal experimental *Klebsiella* and *P. aeruginosa* infections [8]. Subsequent studies in normal healthy volunteers and in intensive care unit (ICU) patients showed that the IVIG was well tolerated (unpublished data). Type-specific antibody levels in serum rose by 3- to 5-fold and did not return to baseline by 35 days in ICU patients or by 80 days in healthy volunteers, thus providing the rationale for a single infusion of IVIG at 100 mg/kg.

The albumin placebo was obtained from Alpha Therapeutics (Los Angeles) as a sterile stock solution and was diluted in physiological saline to a final concentration of 0.5% (wt/vol). The appearances of the two solutions were similar; the IVIG solution exhibited more foaming if vigorously shaken.

**Patient selection.** Patients entering surgical or medical ICUs (exclusive of coronary care and burn units) were eligible for inclusion. Patients were excluded for any of the following reasons: age <18 years old, expected survival <48 h, expected ICU stay <2 days, history of serum sickness or adverse reaction to gamma globulin, undergoing plasmapheresis, hypervitaminosis A, uncomplicated cardiac or peripheral vascular procedures during the current hospitalization, pregnancy, prior or current participation in this or another ongoing clinical trial, or inability to give consent.

**Study design.** Patients were randomly assigned to receive either IVIG or a similar-appearing albumin control preparation. The treatment assignment was double-blind and stratified according to medical center and body weight, using simple randomization. This method was used instead of permuted blocks because of the large sample size. All patients received a daily parenteral multivitamin preparation, in accordance with Department of Army guidelines that patients assigned to placebo receive some beneficial medication. The study drug was administered by intravenous infusion over 60–120 min. Patients were monitored during the administration of study drug and for 30 min afterward. The infusion was slowed if the patient sustained an adverse event possibly related to the infusion and was stopped if an adverse event persisted or recurred.

Baseline patient evaluations included clinical status, hematologic studies, and cultures of blood and other sites as clinically indicated. All patients were followed while hospitalized for the development of infection or other complication for a maximum of 6 weeks. Whenever an infection was suspected, culture samples were taken at the discretion of the attending physician.

Patients who developed infection received intravenous fluids, antibiotics, and other therapies as determined by their physician. Recommended antibiotic therapy of suspected gram-negative infection included either an extended-spectrum penicillin or a cephalosporin, with or without an aminoglycoside. Following the availability of susceptibility patterns, it was recommended that the earliest generation β-lactam be used at maximum dosing and the aminoglycoside be discontinued (with the possible exception of treatment for *P. aeruginosa*).

**End points.** The primary end points of the study were the occurrence of any *Klebsiella* or *P. aeruginosa* infection caused by the *Klebsiella* or *P. aeruginosa* serotypes present in the vaccine (i.e., vaccine-specific infection) and the severity of the most severe vaccine-specific infection at the time of diagnosis. The determination of the presence of specific infection was made by a central laboratory without knowledge of treatment assignment. The severity of infection was classified as local, systemic, infection with organ failure, or death from infection (see Appendix). To be classified as an infection for study purposes, culture documentation was required.

Secondary end points included mortality, time to onset of the first vaccine-specific infection, the incidence and severity of non-vaccine *Klebsiella* or *P. aeruginosa* infections, the incidence of adverse reactions, and vaccine-specific antibody concentration levels in infected versus uninfected patients.

**Serum sampling.** Blood samples were obtained from all patients before and 1 h after completion of the infusion of study drug or placebo. Serum samples were analyzed for antibody levels by the Swiss Serum & Vaccine Institute without knowledge of the treatment assignment. Sera from patients with a vaccine-specific infection and sera from a 25% random sample of patients without vaccine-specific infections were analyzed. Antibody concentrations were determined for all 8 *P. aeruginosa* vaccine serotypes and exotoxin A and for 6 of the 24 most prevalent *Klebsiella* serotypes.

**Statistical analyses.** According to the original study protocol, patients without vaccine-specific *Klebsiella* or *P. aeruginosa* serotypes at the time of randomization (i.e., "prophylactic" patients) and those with *Klebsiella* or *P. aeruginosa* infections at the time of randomization (i.e., "therapeutic" patients) were analyzed separately. The classification of patients into these 2 groups was done centrally by the coordinating center based on strict criteria before the study outcome was known.

Sample size was calculated to detect a 30% reduction in the incidence of vaccine-specific infection with IVIG at the 5% level of significance and with 80% power. The target sample size for a hypothesized 3.5% infection rate in the control group was 13,000 patients without *Klebsiella* or *P. aeruginosa* infection at the time of enrollment (prophylactic patients).

The comparability of the 2 treatment groups at baseline was assessed by the χ² test or Fisher’s exact test for discrete variables and the t test or Wilcoxon rank sum test for continuous variables. Time to death and time to infection were analyzed by life table methods; differences in cumulative incidences between the 2 treatment groups were assessed by the log-rank statistic. Antibody concentration data were analyzed by geometric mean titers (base 10 logs).

Treatment differences for the primary end point (vaccine-specific infection) were monitored by the method of Lan and Wittes based on conditional power [9]. All analyses were performed by the method of intention to treat. The incidence of vaccine-specific infection was tested at the 5% level of significance (two-sided), and all other end points were tested at the 1% level to provide some control for multiplicity, based on one fixed sample size test at the end of the trial. All reported *P* values are two-sided. The progress of the study was monitored annually by an independent Data Monitoring Board.
Table 1. *Klebsiella* (K) and *Pseudomonas* (P) infections.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Albumin</th>
<th>IVIG</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>667 (100.0)</td>
<td>725 (100.0)</td>
<td>.86</td>
</tr>
<tr>
<td>Total</td>
<td>185 (27.7)</td>
<td>198 (27.3)</td>
<td>.77</td>
</tr>
<tr>
<td>KP (total)</td>
<td>64 (9.6)</td>
<td>73 (10.1)</td>
<td>.77</td>
</tr>
<tr>
<td>KP serotype</td>
<td>44 (6.6)</td>
<td>44 (6.1)</td>
<td>.79</td>
</tr>
<tr>
<td>K serotype</td>
<td>18 (2.7)</td>
<td>9 (1.2)</td>
<td>.05</td>
</tr>
<tr>
<td>P serotype</td>
<td>29 (4.3)</td>
<td>39 (5.3)</td>
<td>.39</td>
</tr>
<tr>
<td>Non-KP (total)</td>
<td>147 (22.0)</td>
<td>161 (22.2)</td>
<td>.94</td>
</tr>
<tr>
<td>Other gram-negative</td>
<td>39 (5.8)</td>
<td>49 (6.7)</td>
<td>.49</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>79 (11.8)</td>
<td>68 (9.4)</td>
<td>.14</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients that had ≥1 infection of type specified. Total KP nos. include all KP serotypes (vaccine plus nonvaccine). IVIG, intravenous immune globulin.

* Fisher’s exact test.

Results

Study population. Between September 1990 and March 1992, 4479 patients were screened and 1495 (33%) were randomized in 10 Department of Veterans Affairs and 6 Department of Defense medical centers. The two major reasons for patient exclusion were an expected ICU stay of <24 h and lack of consent. One hundred three randomized patients (46 albumin, 57 IVIG) were subsequently found to have had *Klebsiella* or *P. aeruginosa* infection at study entry (therapeutic patients) and were excluded from analysis of prophylactic efficacy, according to the original study protocol. Among the remaining 1392 prophylactic patients, 667 had been randomly assigned to albumin and 725 to IVIG. This apparently large imbalance resulted from early termination of the trial and does not affect the validity of the study results.

In comparison of baseline parameters, of the >60 factors examined, 3 (infection, lung failure, heart failure) were different between the 2 groups at the 5% level of significance (data not shown). All 3 were more frequent in those assigned to receive IVIG.

Mortality. The 6-week survival status was known for all study patients. Overall, mortality in the 2 treatment groups was not significantly different (17.8% for IVIG vs. 16.5% for albumin, *P* = .52). There were no differences in proportions of cause-specific deaths or deaths associated with vaccine-specific infection (data not shown).

Incidence and severity of infection. Overall, ~28% of patients in each treatment group had at least one infection of any type during the 6-week period of follow-up (table 1). The incidence of all *Klebsiella* and *P. aeruginosa* infections was 10%. The percentage of patients with at least one *Klebsiella* or *P. aeruginosa* vaccine-specific infection was 6.6% in the albumin group and 6.1% in the IVIG group (*P* = .79).

The incidence of vaccine-specific *Klebsiella* infections was reduced by >50% in patients receiving IVIG (*P* = .05), but the difference was not significant at the preassigned 1% level.

In contrast, patients receiving IVIG had a higher incidence of vaccine-specific *P. aeruginosa* infections (*P* = .39). The time to initial *Klebsiella*-specific infection was earlier in the albumin group (*P* = .05, figure 1A), while the higher incidence of *Pseudomonas*-specific infection in the IVIG group resulted from late infection (*P* = .37, figure 1B). Patients receiving IVIG did not demonstrate an increased rate of infection due to bacteria other than *Klebsiella* species or *P. aeruginosa* (table 1).

When the severity of infection was examined, there were no significant differences between the 2 treatment groups for all vaccine-specific infections (table 2). For *Klebsiella*, however, there were fewer severe vaccine-specific infections and no cases of bacteremia in the group receiving IVIG (*P* = .05); the differences were not significant at the 1% level.

Adverse drug reactions. More patients in the IVIG group had one or more drug reactions (14.4%) than did those receiving albumin (9.2%, *P* = .01). Severe reactions occurred more

![Figure 1](https://academic.oup.com/jid/article-abstract/174/3/537/902690/figure1)
frequently in the IVIG group (2.0%) than in the albumin group (0.5%, \( P = .01 \)). The most frequent reaction was fever, occurring in 5.5% of those receiving albumin and 6.8% of those receiving IVIG (\( P = .37 \)). The most frequent severe reaction was hypertension, which occurred in 4 patients receiving IVIG.

The occurrence of reactions did not seem to correlate with a specific underlying disease or concomitant use of a specific class of drugs. Most reactions occurred 30–60 min after initiation of the infusion. Examination of study solutions associated with reactions revealed no microbial contamination, pyrogens, or vasoactive substances.

None of the adverse reactions was associated with patient mortality, and all were readily treatable by stopping the infusion and giving supportive therapy. Mortality was not greater in patients with adverse reactions to either IVIG or albumin compared with those with no reactions. Most reactions were mild, although some (e.g., chills) were disconcerting to patients.

**Serum antibody levels.** Pre- and postinfusion serum antibody levels against *Klebsiella* and *P. aeruginosa* serotypes are shown in table 3. As expected, postinfusion levels were ~2-fold higher for both *Klebsiella* and *P. aeruginosa* serotypes than preinfusion levels for patients receiving IVIG. The postinfusion levels in patients who later became infected were similar to those in uninfected patients. Antibody levels in infected patients were not lower at the time of infection compared with their postinfusion levels. Patients with the highest levels of antibodies seemed to be less likely to have an infection, but the numbers analyzed were too small to be statistically significant (data not shown). Although the levels of functionally active antibodies to *Pseudomonas* exotoxin A increased 4-fold in patients receiving IVIG (data not shown), these increased levels were not associated with any reduction in the incidence or severity of *Pseudomonas* infections, contrasting with previous observations on the importance of exotoxin A as an important virulence determinant for *P. aeruginosa* [10, 11].

**Discussion**

Despite the development of newer antibiotics, antimicrobial resistance continues to be an important problem, resulting in increased patient morbidity and mortality and increased health care costs [5, 12]. *Klebsiella* species and *P. aeruginosa* are two of the most important causes of hospital-acquired infections [1–4]. Factors that influence the incidence and severity of infections with these two gram-negative organisms include the increased use of antibiotics, length of hospitalization, and presence of underlying disease. Both pathogens are also frequently resistant to multiple antibiotics, and acquired antibiotic resistance can develop during therapy for *P. aeruginosa* infections [13, 14].

Host defenses against these two bacteria, as with most organisms, depend in great measure on serotype-specific immunity. Hence, it is a reasonable hypothesis that passive administration of antibodies directed against these pathogens would provide protection. In the present study, the setting to evaluate this hypothesis was the ICU, where *Klebsiella* and *P. aeruginosa* infections are frequent. Fully 28% of our study population developed some microbial infection over the 6 weeks of observation, with 10% developing *Klebsiella* or *Pseudomonas* infections (or both). The results of this study appear to support the hypothesis in the case of *Klebsiella* but not *Pseudomonas* infections. Although the numbers were small and the results not statistically significant at the 1% level, use of the hyperimmune IVIG was associated with a reduction in both the overall incidence and severity of infection caused by *Klebsiella pneumoniae* serotypes that were included in the vaccine. The major effect of the immunoglobulin was, as expected, on the severity of infection.

In our study, 100 mg/kg IVIG led to a doubling of antibody levels, which may have been sufficient for protection against *Klebsiella* but not *Pseudomonas* infections. The rationale for having selected that dose was 3-fold: This dose conferred good protection in animals, lower cost, and a low colloidal load. Despite some protection against *Klebsiella* infections, the absence of any protection against *Pseudomonas* infections led the Data Monitoring Board to conclude that no significant protection against *P. aeruginosa* could be reasonably expected by additional study. Therefore, the study was stopped after the first analysis of the data, and a new study using 300 mg/kg IVIG was initiated to determine whether the increased concentrations of antibody in blood would provide protection against infections caused by *P. aeruginosa* as well as *Klebsiella* species.

The incidence of adverse drug reactions associated with IVIG in this study was higher than previously reported [15–22]. The differences may relate to closer monitoring of ICU
patients (e.g., a study nurse continuously monitored patients during the infusion, obtaining blood pressures every 15 min). The high reaction rates were not limited to a particular study site, nor was there any clustering of reactions correlating with a particular period of time or product lot. The time of onset of some reactions (i.e., ~1 h after the start of the infusion) is compatible with an aggregated complex or foreign-body-type reaction; however, no foreign substances or aggregated materials were associated with the study drugs in patients with reactions. Of particular note was the increased incidence of changes in blood pressure in this study. Our patients may have been generally more ill and their vascular status may have been more unstable than those of previously studied patients. We could not establish any direct links to the use of particular drugs (e.g., antihypertensive agents, calcium-blocking drugs) or the presence of specific underlying disease (e.g., heart disease). Whether premedicating patients with acetaminophen, antihistamines, or both would reduce adverse reaction rates is the subject of a future study.

Prevention of infections caused by nosocomial pathogens such as *K. pneumoniae* and *P. aeruginosa* would represent an important advance that has not been achievable by other means. The success of this approach depends on having an IVIG with a sufficient breadth of antibacterial activity, a favorable pharmacokinetic profile, a large margin of safety, and a high degree of cost-effectiveness. In this study, we targeted *P. aeruginosa* and *Klebsiella* species, including *K. pneumoniae*, *K. oxytoca*, *K. rhinoscleromatis*, and *K. ozonae*. In addition to reactions against the 24 capsular polysaccharides in the *Klebsiella* vaccine, there are cross-reactions with 10 more capsular polysaccharides of *Klebsiella* and with *E. aerogenes*. Efforts to broaden the range of antibacterial activity for this product are currently underway. A 12-valent O-polysaccharide–toxin A conjugate vaccine for *Escherichia coli* has been developed and administered safely to >200 vaccinees [23]. Others are developing vaccines directed against gram-positive pathogens such as *Staphylococcus aureus* [24]. Thus, it may be possible to develop a more broadly based IVIG, which might then be a cost-effective preventive measure in lowering the incidence and severity of common nosocomial infections. Ideally, a profile could be developed to identify and target patients at high risk for these infections to maximize the cost-effectiveness of the intervention.

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References


Appendix: Definitions of Infection

Uninfected. This was the definition for a patient with no clinical illness and no culture positive other than for normal flora.

Colonized. Colonized patients were those with no clinical findings but a positive culture.

Localized infection. This definition was applied to a patient with a positive culture who had either localized clinical findings or fewer than five systemic findings (defined below). Localized findings included the following at the site of involvement: purulent exudate, Gram’s stain revealing neutrophils and bacteria compatible with an isolate (>1 organism/×500 field), erythema, warmth, tenderness, and swelling.

Systemic infection. This definition fit a patient with bacteremia or a localized infection who had at least five of the following systemic or constitutional findings within a 48-h period: (1) fever (rectal temperature >38.9°C) or hypothermia (rectal temperature <35.5°C), (2) tachypnea (>28 breaths/min) or hypopcapnia (PaCO2 <32 mm Hg), (3) tachycardia (heart rate >100 beats/min), (4) hypotension (supine position, cuff or arterial catheter pressure in the upper arm <90 mm Hg, systolic), (5) abnormal white blood cell count (<3500 or ≥15,000/mm3), (6) thrombocytopenia (<100,000 platelets/mm3), (7) surgical or invasive procedure(s) performed during the preceding 48 h or the presence of an obvious primary septic site, (8) altered sensorium due to the acute septic event and defined as a new onset of confusion manifested by disorientation to location in space and time or impaired ability to perform calculations (i.e., serial 7s) that were not attributed to medication or cerebral anatomic lesions, (9) new onset of hypoxemia (PaO2/FiO2 <250).

Infection with organ failure. A patient with systemic sepsis who had at least one end organ with failure, as defined below, that was not due to direct anatomic but metabolic effects of the infection was considered to have an
infection with organ failure. Renal failure required a serum creatinine ≥2.5 times the baseline value. Pulmonary failure required respiratory support with a ventilator for >48 h related to an acute infectious process other than pneumonia. Liver failure required at least two of the following: alanine transaminase ≥2 times normal, bilirubin ≥2.5 times the baseline value, or a prothrombin or partial thromboplastin time 2 s longer than normal. Cardiac failure required the use of medications to support the circulation. Cerebral insufficiency required obtundation (unresponsive or responsive only to painful stimulation or loud noises in the ear) not due to cerebrovascular accident, medications, or other nonseptic etiology.

Death from infection. This was defined as the absence of life in infected patients (by standard criteria) that was not, in the judgment of the responsible investigator, attributable to progression of preexisting disease(s).

Bacteremia. Blood cultures were considered evidence of bacteremia if they yielded growth of a pathogen from almost all blood cultures in a series (at least two sets) obtained from different venipuncture sites and the isolated microbe was judged likely not to be a contaminant. In the case of Klebsiella or P. aeruginosa, any blood culture yielding such an organism (even one) was considered evidence of bacteremia.

Septic shock. Patients with positive cultures (blood or other site) were considered to be in septic shock if after adequate fluid challenge they fulfilled one of two criteria: (1) systolic blood pressure <90 mm Hg or 50 mm Hg less than a previously defined pressure in a hypertensive patient and decreased organ perfusion as evidenced by an altered mental status or oliguria (<0.5 mL/kg/h) or (2) requirement of vasopressors to maintain an adequate blood pressure or level of perfusion. This definition excludes patients in hemorrhagic shock, cardiogenic shock from myocardial infarction, or shock from other obvious nonseptic causes.