Pneumonia Outbreak Associated with Group A Streptococcus Species at a Military Training Facility

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Background. Although group A streptococci (GAS) infections are a major cause of morbidity and mortality, outbreaks of associated pneumonia are rare. We report an outbreak of GAS pneumonia that occurred at a US military training camp.

Methods. Standard epidemiologic and laboratory procedures were used to characterize the outbreak and causative organism(s). A case-control study and determination of the prevalence of GAS infection among camp personnel were also performed.

Results. A total of 162 of 4500 Marine Corps personnel were hospitalized for respiratory symptoms during the period of 1 November and 20 December 2002, and 127 (78%) had radiographically confirmed pneumonia. The attack rate was 1.6 cases per 100 person-months. Thirty-four (27%) of 127 patients with pneumonitis had definite or probable GAS pneumonia; an additional 22 (17.3%) were coinfected with GAS and another pathogen. Pathogens, in addition to GAS, included Chlamydia pneumoniae (27 patients), Mycoplasma pneumoniae (19), adenovirus (5), and Streptococcus pneumoniae (2). A survey revealed that the pharyngeal carriage rate of GAS among camp personnel was 16%. Molecular characterization of the GAS isolates found emm type 3, multilocus sequence type 15. The epidemic ended after administration of additional prophylaxis with a single dose of intramuscular benzathine penicillin (1.2 million U) or azithromycin (1 g orally). Because the number of days from the last penicillin injection was correlated with a positive throat culture result and the occurrence of pneumonia, the dosing interval of benzathine penicillin was shortened from every 28–35 days to every 21 days.

Conclusions. This is the largest outbreak of GAS pneumonia reported in >30 years. This outbreak emphasizes the potential for GAS to cause epidemics of severe infection and demonstrates the need for surveillance and consideration of appropriate antibiotic prophylaxis among particularly high-risk populations.

Although GAS has long been recognized as a major pathogen, the magnitude of disease it caused in the military remained underappreciated until World War II. During that conflict, ≈1 million US Navy personnel were infected with GAS [1–3]. Despite the high incidence of GAS infection in the military [4–8], GAS has rarely caused outbreaks of pneumonia [9]; the last reported outbreak occurred in 1964–1966 [10].

The Commission on Streptococcal and Staphylococcal Diseases of the Armed Forces Epidemiological Board initially advocated the use of intramuscular repository benzathine penicillin (BPG) for mass prophylaxis against this organism [11–14]. Since the 1950s, BPG has been used at military training camps; some facilities administer only 1 injection, whereas others administer additional doses to minimize carriage rates and prevent epidemic disease [15–20]. At the Marine Corps Recruit Depot (MCRD) and Naval Training Centers in San Diego, California, GAS carriage rates have been historically high; consequently, 2 injections of BPG during the...
13-week training period have been required. A 1986–1987 outbreak of rheumatic fever occurred at the Naval Training Centers in San Diego after BPG administration had been briefly discontinued [5]. We report a large outbreak of GAS pneumonia in a recruit training population that occurred despite antibiotic prophylaxis.

METHODS

Setting and subjects. This outbreak occurred among MCRD recruits. At arrival, each recruit receives influenza, *Streptococcus pneumoniae* (polyvalent pneumovax 23; Merck), and meningococcal (Menomune quadriivalent polysaccharide vaccine; Avantis Pasteur) vaccinations. GAS prophylaxis at MCRD involves year-round administration of BPG (Monarch Pharmaceuticals) at the beginning of the training period plus an additional dose 28–35 days later. Recruits with self-identified penicillin allergies received self-administered erythromycin (250 mg po b.i.d.) for the first 30 days of training.

Data collection. A cluster of lower respiratory infections was noted at MCRD in November 2002. After recognition of this cluster, all MCRD recruits who presented with a radiographically confirmed infiltrate were admitted to Naval Medical Center San Diego. Patients were treated as inpatients for graphically confirmed infiltrate were admitted to Naval Medical this cluster, all MCRD recruits who presented with a radiographic confirmation of pneumonitis were admitted to and throat samples were obtained for GAS culture surveillance studies.

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Case definitions. All patients with pneumonia had respiratory symptoms and radiographic confirmation of an infiltrate/opacification by a staff radiologist. Cases of GAS pneumonia were categorized as definite or probable. A definite case required a positive result of a GAS culture of blood or pleural fluid samples and/or the development of toxic shock syndrome. A probable case of GAS pneumonia was defined as a sputum or throat culture positive for GAS, an ASO titer of >250 Todd units or anti-DNAse B titer of >250, or an increase in the ASO or anti-DNAse B titer of ≥0.2 log units between acute- and convalescent-phase specimens, with no other identified cause of infection [10, 21].

A confirmed case of *M. pneumoniae* pneumonia was defined by IgG seroconversion, and a probable case was defined by isolated positive IgM without a positive IgG [25, 26]. A confirmed case of *C. pneumoniae* pneumonia was defined as a 4-fold increase in the IgG titer over a 3–4-week period or an IgM titer of ≥16, and a possible case was defined as an isolated IgG titer of ≥512 without a corresponding positive IgM [27].

Treatment. Inpatient treatment was standardized. Patients initially received intravenous ceftriaxone (2 g q.d.) plus levofloxacin (500 mg q.d.) or azithromycin (500 mg q.d.). Hypotensive patients and those with either toxic shock syndrome or concurrent soft-tissue infection were also given clindamycin (900 mg iv q8h); patients with toxic shock syndrome also received a 5-day course of intravenous immunoglobulin (150 mg/
kg q.d.). When patients improved and were discharged, oral amoxicillin was given to those with definite or probable GAS infection; other patients received oral levofloxacin.

**Data analysis.** The data were entered into an Excel database (Microsoft). Comparisons among groups were made with Fisher’s exact test for dichotomous variables or the Wilcoxon rank sum test for continuous variables with use of SPSS software, version 9.0 (SPSS). Correlations between variables were determined using the correlation test, and statistical significance was defined as a *P* value of <.05.

**RESULTS**

**Course of the epidemic.** During the period of 1 November through 20 December 2002, a total of 162 of 4500 camp personnel were admitted for a respiratory illness, 127 (78.4%) of whom had radiographically confirmed pneumonia (figure 1). The attack rate of pneumonia during this outbreak was 1.6 cases per 100 person-months. The baseline rate of pneumonia resulting in hospitalization during the winter months had been 0.2 cases per 100 person-months in previous years.

The initial active surveillance (*n* = 493) on 10 December 2002 revealed a 15% prevalence of GAS on pharyngeal cultures. In addition, a high rate of allergy to penicillin (30%) and poor compliance with (self-administered) oral erythromycin therapy (<20%) were noted. The entire recruit and staff population (4500 persons) was screened on 15 December, and the prevalence of GAS noted by throat culture was 16%. Each subject received a 1.2-mU dose of BPG or, for patients who were allergic to penicillin, directly observed weekly oral doses of azithromycin (1 g). The outbreak of pneumonia immediately ended (figure 1). An algorithm was introduced that reduced the rate of self-reported penicillin allergy from 30% to 10%.

Individuals with a positive GAS culture result were more likely to have a sore throat than were those with a negative culture result (OR, 1.3; *P* = .01). Evaluation of the MCRD staff revealed that the persons who had worked most closely with the recruits (i.e., drill instructors) had the highest prevalence of GAS, as determined by throat culture (OR, 2.9; *P* < .001). The number of days since receipt of the last penicillin shot was highly correlated with a positive throat culture result (*P* < .001) (figure 2). The risk of pneumonia was also found to correlate with the timing of the 1.2-mU injections of BPG; the number of hospital admissions peaked at the end of the BPG dosing interval (figure 3). The BPG dosing schedule was subsequently switched to every 21 days (for a total of 3 injections) instead of 2 injections at days 0 and 28–35 of training.

The outbreak of pneumonia ended on 20 December 2002. One week later, the rate of pharyngeal carriage of GAS was 2.2%, compared with the rate of 16% noted on 15 December. Since this time, carriage rates have remained at <2%. In addition, passive surveillance revealed that pneumonia admission rates and clinical GAS pharyngitis rates were stable for 1 year after the outbreak period.

**Demographic data.** Recruits admitted with pneumonia (*n* = 127) had a median age of 19 years (range, 17–33 years). There were no significant differences in age, race, or other

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**Figure 1.** Diagram of an outbreak involving 127 cases of group A Streptococcus (GAS) pneumonia at a Marine Corps Recruit Depot in San Diego, California.
measured parameters between the total recruit population and the population of recruits with pneumonia.

**Laboratory findings and clinical features.** Definite or probable GAS was implicated in 44% of the hospital admissions for pneumonia. Thirty-four (27%) of 127 pneumonia cases were associated with GAS alone (7 were definite and 27 were probable cases) (table 1). Patients with probable GAS pneumonia included 16 persons with elevated ASO or anti-DNAse B titers, 5 with sputum or throat cultures positive for GAS, and 7 with both elevated ASO and/or anti-DNAse B titers and a positive culture result without a different etiologic agent identified. Of the 16 patients with an elevated ASO titer alone, the mean titer was 593 Todd units.

Twenty-two cases of pneumonia (17%) were determined to be coinfections with GAS and another pathogen. Twenty-eight patients (22%) were infected with a single non-GAS etiologic agent. There were 19 cases of *M. pneumoniae* infection (3 definite and 16 probable), 27 cases of *C. pneumoniae* infection (8 definite and 19 possible), 5 cases of adenovirus infection, 2 cases of *S. pneumoniae* infection, 1 case of *Haemophilus influenzae* infection, and 1 case of *Moraxella catarrhalis* infection. Overall, a probable microbiologic cause was established for 84 (66%) of the 127 cases of pneumonia.

Patients with definite or probable GAS pneumonia were demographically and clinically similar to patients with pneumonia due to other agents. Ninety-nine percent of patients with pneumonia had cough (median duration, 13 days). Fever and sore throat were noted in 58% of patients, pleuritic chest pain was noted in 47%, and dyspnea was noted in 43%. Patients with GAS pneumonia did not differ from patients with other types of pneumonia with regard to presenting symptoms. The median ASO titer was higher in the GAS pneumonia group (479 vs. 68 Todd units; \( P < .001 \)). The median WBC count at the time of hospital admission was higher in patients with GAS pneumonia (14,800 cells/mm\(^3\)) than in those with non-GAS pneumonia (12,600 cells/mm\(^3\); \( P = .15 \)). Two patients (5.9%) with GAS pneumonia had elevated creatinine levels (>2.0 mg/dL). The duration of hospitalization was greater in the GAS pneumonia group (\( P = .003 \)).

Two patients with GAS pneumonia developed streptococcal toxic shock syndrome and required intensive care management (one patient was hospitalized for 25 days, and the other was hospitalized for 34 days). Two patients with GAS pneumonia and 1 coinfecting patient had extrapulmonary infection, including lower extremity cellulitis and a GAS peritonsillar abscess. There were no deaths due to GAS pneumonia or to any pneumonia during this outbreak. A coincident fatal case of serogroup C meningococcemia occurred on 15 December 2002; premortem cultures and autopsy results did not reveal GAS.

**Radiographic features.** Of the 127 patients with pneumonia, 65 (51%) had multilobar involvement, 30 (24%) had a pleural effusion, and 5 (4%) had empyema; all cases of empyema occurred in association with definite GAS pneumonia. Of the 34 patients with GAS pneumonia, 20 (59%) had multilobar involvement. No one had intrathoracic adenopathy or cavitary lesions noted on a radiograph.

**Evaluation of the GAS outbreak strain.** All GAS isolates recovered from patients with GAS pneumonia were susceptible to all 15 antibiotics tested, including penicillin, clindamycin, erythromycin, and azithromycin. All clinical GAS pneumonia—

![Figure 2. Prevalence of group A Streptococcus (GAS) species on pharyngeal cultures in relationship to timing of penicillin prophylaxis](image-url)
Figure 3. The relationship between cases of pneumonia and the timing of antibiotic prophylaxis

associated isolates were identified as emm type 3 by emm gene sequencing and as sequence type 15 by MLST. Among the isolates recovered from patients with positive screening pharyngeal culture results, 27 of 30 were also emm type 3, sequence type 15. The 3 non-emm type 3 strains identified among patients with positive pharyngeal culture results included 2 emm type 6 strain (sequence type 37) and 1 emm type 28 strain (sequence type 52). All emm type 3/sequence type 15 isolates tested positive for all 3 pyrogenic exotoxin genes that encode SpeA, SpeB, and SpeC superantigens.

**DISCUSSION**

This is the largest reported outbreak of GAS pneumonia in nearly half a century [10]. Military trainees are at particular risk for streptococcal infection because of their crowded living conditions [5, 6, 10, 12]. These outbreaks highlight the continued need for adequate prophylaxis against GAS infection among particularly high-risk groups.

GAS is an uncommon cause of pneumonia in the era of antibiotics, accounting for <1% of community cases [28, 29]. An estimated 9600 cases of invasive GAS disease (3.5 cases per 100,000 persons) are reported annually in the United States, and the rate has been stable since the 1980s; ~12% of cases of disease are pneumonia [30, 31]. Although military camps are at risk for epidemics of respiratory diseases, including influenza and infections with *Mycoplasma* species, pneumococcus, meningococci, and adenovirus [32–37], the outbreak of GAS pneumonia was somewhat surprising, given the paucity of invasive GAS infections over the past 15 years and given the ongoing prophylaxis program.

The outbreak at our military training facility correlated with a high prevalence (16% of 4500 persons) of GAS noted on throat cultures. Increased time from last dose of prophylaxis with BPG or erythromycin was associated with higher rates of GAS on pharyngeal cultures and higher pneumonia rates. Given these data and on the basis of work by Bass et al. [38], who

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. (%) of patients, by pneumonia classification</th>
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<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>GAS</td>
<td>34 (26.8)</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>19 (15)(^b)</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>27 (21.3)(^c)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>5 (3.9)</td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2 (1.6)</td>
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<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>84 (66.1)(^d)</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>43 (33.9)</td>
</tr>
</tbody>
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**NOTE.** GAS, group A Streptococcus species.

\(^a\) Patients with probable cases include 16 patients with elevated anti-streptolysin O (ASO) or anti-DNAse B titers, 5 with sputum or throat cultures positive for GAS, and 7 with both elevated ASO titer and/or anti-DNAse B titers and positive culture results. By definition, no other etiologic agent was identified in this group.

\(^b\) Nine probable cases and 1 definite case of *M. pneumoniae* pneumonia occurred with concurrent evidence of an elevated ASO titer and/or throat or sputum culture positive for GAS.

\(^c\) Three cases of possible *C. pneumoniae* pneumonia occurred among patients with definite GAS infection. In addition, 8 possible cases and 1 definite case *C. pneumoniae* infection occurred with concurrent evidence of an elevated ASO titer and/or throat or sputum culture positive for GAS.

\(^d\) Some patients had dual infections.
showed that serum penicillin levels decrease after 1–2 weeks, we decreased the time interval of administration of penicillin prophylaxis from every 28–35 days to every 21 days. Previously described epidemics also occurred in situations involving inadequate prophylaxis [5, 16]. We developed a screening process to “confirm” self-reported penicillin allergy and administered directly observed weekly doses of azithromycin instead of self-administered erythromycin to assure compliance [39]. The outbreak of GAS pneumonia ended after these interventions. Both penicillin and azithromycin have been shown to prevent acute respiratory disease beyond the elimination of GAS [39, 40]. These regimens have potential complications, including increased risk of penicillin allergy and anaphylaxis, as well as an increased prevalence of azithromycin-resistant streptococci. GAS isolates have remained susceptible to penicillin and macrolides at the MCRD, but increasing macrolide resistance has been noted in some areas in the United States, and it is more pronounced overseas [41].

GAS pneumonia may be preceded by infection with viral or bacterial pathogens. Early in the 20th Century, GAS was often a second invader, following influenza, measles, pertussis, varicella, or M. pneumoniae infection [9, 42–48]. Like many of these respiratory pathogens, GAS occurs predominantly during the winter [31, 49]. Although we detected few other pathogens in our patients with defined GAS pneumonia, we did find a significant number of cases of pneumonia coincident with the GAS pneumonia outbreak; the pathogens identified included Mycoplasma species, Chlamydia species, adenovirus, and the pneumococcus. Patients from whom multiple pathogens were isolated did not have a more complicated course; the most-clinically severe cases occurred in patients from whom GAS was isolated from the blood or pleural space.

GAS pneumonia has been noted to cause a severe interstitial or confluent bronchopneumonia, with a predilection toward pleural effusions and empyema, particularly on the left side [9, 10, 29, 43]. Bacteremia is present in 10%–15% of patients and is more common in older patients [45]. Case-fatality rates before the introduction of penicillin in the 1940s were ~50%, but deaths have been much less common in the antibiotic era [42]. Older age, toxic shock syndrome, and pneumonia are predictors of death in persons with invasive GAS disease; those aged <30 years have an extremely low risk of death (P < .001) [30]. In our outbreak of pneumonia, none of 34 patients with GAS pneumonia died, although 2 patients spent several weeks in the intensive care unit.

Despite attempts to create precise definitions for the cause of pneumonia in this outbreak, our case definitions had limitations. The use of sputum and/or throat cultures for diagnosis of GAS pneumonia may lead to an overestimation of the number of cases of GAS pneumonia, because positive results may occur in patients with GAS pharyngitis or pharyngeal carriage alone. Our use of ASO titers for the diagnosis of probable GAS pneumonia may also be questioned [50], but in an ongoing GAS pneumonia outbreak, we feel that this was justified for patients who did not have any other identifiable pathogen isolated. Most patients with GAS pneumonia had high ASO titers (>500 Todd units) and/or increasing titers. Finally, diagnosis of M. pneumoniae and C. pneumoniae infections by serologic testing alone may be problematic [25–27]. Despite these limitations, GAS was clearly the predominant pathogen identified, and administration of BPG was associated with the end of the outbreak, lending support to the hypothesis that GAS was the primary etiologic agent.

The microbiologic analysis of the GAS revealed emm type 3. This epidemic strain has been frequently found in invasive disease, specifically bronchopneumonia [30, 51, 52]. The presence of pyrogenic exotoxins is associated with severe sequelae, such as streptococcal toxic shock syndrome [53–55]. Although this outbreak was not associated with necrotizing fasciitis, rheumatic fever, or poststreptococcal glomerulonephritis, evidence of shock was seen in 2 patients. The presence of all 3 superantigen gene sequences in the clone circulating during our epidemic may account for the unusual presentation and virulence.

We report a large outbreak of GAS pneumonia at a US military training camp. This outbreak confirms the need for ongoing GAS surveillance and appropriate use of antibiotic prophylaxis among particularly high-risk populations.

Acknowledgments
We would like to express our gratitude to the many clinicians who cared for the patients in this report and the laboratory personnel who identified the microbiologic agents of this outbreak. We especially thank Dwight Johnson for determining ASO titers and emm sequencing at the World Health Organization Collaborating Center at the University of Minnesota (Minneapolis). We also thank Judy Christensen for design of the figures in this report.

Potential conflicts of interest. All authors: no conflicts.

References


