ORIGINAL INVESTIGATION

Clinical and Epidemiologic Features of Group A Streptococcal Pneumonia in Ontario, Canada

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Background: Since the 1960s, group A streptococcus (GAS) has accounted for less than 1% of cases of community-acquired pneumonia. During the past 2 decades there has been a resurgence of invasive GAS infection, but no large study of GAS pneumonia has been performed.

Methods: To determine the clinical and epidemiologic features of GAS pneumonia, we conducted prospective, population-based surveillance of all invasive GAS infection in residents of Ontario from January 1, 1992, through December 31, 1999.

Results: Of 2079 cases of invasive GAS infection, 222 (11%) represented GAS pneumonia. The incidence of GAS pneumonia ranged from 0.16 per 100 000 in 1992 to 0.35 per 100 000 in 1999. Most cases were community acquired (81%). Forty-four percent of nursing home–acquired cases occurred during outbreaks. The case fatality rate was 38% for GAS pneumonia, compared with 12% for the entire cohort with invasive GAS infection and 26% for patients with necrotizing fasciitis. The presence of streptococcal toxic shock syndrome (odds ratio, 19; 95% confidence interval, 8.4-42; $P=.001$) and increasing age (odds ratio per decade, 1.45; 95% confidence interval, 1.2-1.7; $P<.001$) were associated with fatal outcome. Time to death was rapid, with a median of 2 days despite antimicrobial therapy and supportive measures.

Conclusions: Group A streptococcal pneumonia is a common form of invasive GAS disease but remains an uncommon cause of community-acquired pneumonia. Progression is rapid despite appropriate therapy. The incidence is similar to, and the case fatality rate higher than, that of necrotizing fasciitis.

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A complete list of the members of the Ontario Group A Streptococcal Study appears on page 471.

IN THE PREANTIBIOTIC era, group A streptococcal (GAS) pneumonia was a common clinical entity, accounting for 3% to 5% of community-acquired pneumonia. Most cases occurred after outbreaks of viral illness such as influenza or measles, local complications such as empyema were common, and the reported case fatality rate was as high as 50%.[1-3] Since the 1940s, the incidence of GAS pneumonia has declined dramatically. Numerous recent case series examining the etiologic agents of community-acquired pneumonia have failed to detect any contribution from GAS.[4-13] No large outbreaks have been reported, and only a few case reports[14-21] and case series[22] describe the modern presentation of GAS pneumonia.

During the past 15 years, the incidence of severe GAS infections has been rising.[23-28] The pattern of disease also changed with the recognition of streptococcal toxic shock syndrome (STSS) in 1987.[29,30] Whether these changes have led to a resurgence of GAS pneumonia or to a change in the clinical or epidemiologic features of this illness has not been addressed. We describe the clinical and epidemiologic features of 222 patients with invasive GAS pneumonia identified through population-based surveillance in Ontario between 1992 and 1999.

METHODS

POPULATION-BASED SURVEILLANCE

A detailed description of the methodology of our population-based surveillance system has been published.[23] In brief, from January 1, 1992, to December 31, 1999, all cases of invasive GAS infections occurring in Ontario (population, 11.2 million in 1996) were identified. Invasive infection was defined as illness associated with the isolation of GAS from any normally sterile site. All 155 clinical microbiology laboratories in Ontario telephoned the central office when GAS was identified from a sterile site. Annual audits were conducted; in each year, fewer than 10% of cases of invasive GAS

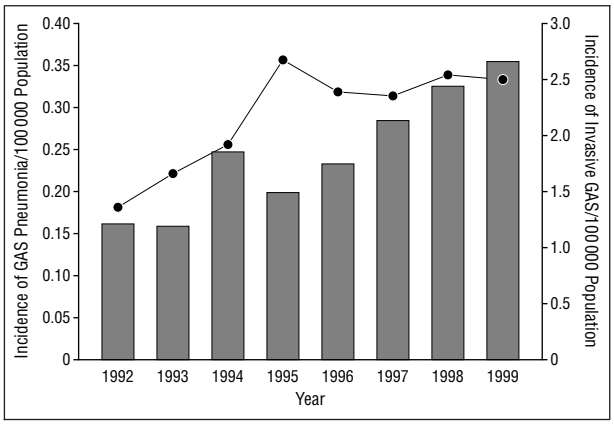

Figure 1. Annual incidence of all group A streptococcal (GAS) pneumonia (bars), compared with incidence of all invasive group A streptococcal infection (line, second axis), in Ontario, Canada, 1992 through 1999.

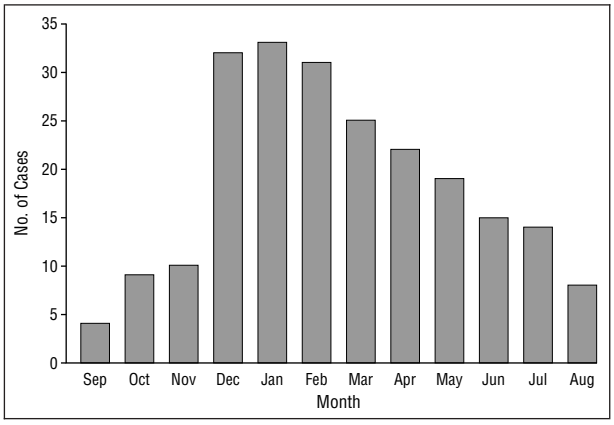

Figure 2. Seasonal variation in group A streptococcal pneumonia in Ontario, Canada, 1992 through 1999. Bars show the number of cases in each month during the 8-year period.

identified by audit were missed by regular reporting. Missed cases were subsequently added to the database. Clinical and microbiologic data were obtained from patients, attending physicians, and infection control practitioners. The study was approved by the Human Subjects Review Committee of the University of Toronto, Ontario.

DEFINITION OF PNEUMONIA

Cases were defined as pneumonia if the patient received a clinical diagnosis of pneumonia from the treating physician, supported by either radiographic or postmortem evidence of pulmonary infection, and if a blood, pleural fluid, or premortem or postmortem lung tissue culture yielded GAS.

OTHER DEFINITIONS

Patients were considered to have STSS if the case met the consensus definition of hypotension (systolic blood pressure ≤90 mm Hg) in combination with 2 or more of the following: acute renal failure, coagulation abnormalities, liver abnormalities, acute respiratory distress syndrome, generalized rash, and necrotizing fasciitis.[31] Patients who were dead on arrival to the hospital or who died within 48 hours of onset of illness and before the above information could be collected were also considered to have had STSS. Cases were considered to be nosocomial if the disease was not present or incubating at the time of admission.[32]

LABORATORY METHODS

Isolates were confirmed as GAS by standard techniques. Typing on the basis of M precipitation was performed at the National Centre for Streptococcus, Edmonton, Alberta.[33-35] Pulsed field gel electrophoresis (PFGE) was performed by standard methods.[36]

STATISTICAL ANALYSIS

Data were entered and analyzed in SAS Statistical Software Version 6.12 (SAS Institute Inc, Cary, NC). Differences in group proportions were assessed by the χ^2, likelihood ratio χ^2, or Fisher exact tests. Logistic regression was used for multivariate analysis of factors associated with case fatality. Variables considered in univariate analysis were age, sex, presence of underlying illness, presence of concomitant soft-tissue infection, and M serotype. Variables considered for inclusion into multivariable analysis were those potentially associated with case fatality ($P<.10$) in univariate analysis.

RESULTS

DEMOGRAPHICS

From 1992 to 1999, 2079 cases of invasive GAS infection were identified in Ontario. Of these, 222 (11%) met the case definition for pneumonia. This was similar to the proportion of cases classified as necrotizing fasciitis in the same cohort (224 [11%]). Twenty-three patients (10%) had a soft-tissue focus of infection in addition to pneumonia; 2 of these had necrotizing fasciitis.

The annual incidence of GAS pneumonia rose from 0.16 per 100 000 per year in 1992 to 0.35 per 100 000 in 1999, paralleling an increase in the incidence of all invasive GAS infections (**Figure 1**). Group A streptococcal pneumonia occurred predominantly during the winter, with a striking nadir in infections in August-September of each year (**Figure 2**).

Of the 222 patients, 128 were male and 94 female. The median age was 56 years (range, 1 day to 100 years). Significant chronic illness was identified in 61% of patients (**Table**). Three patients had GAS pneumonia complicating primary varicella. Most cases were community acquired (179 [81%]). Four of these cases (2%) occurred subsequent to other nonpharyngeal, culture-confirmed GAS infections in the same household. One patient's spouse had been admitted 3 days previously with GAS bacteremia, another patient's spouse had been admitted the previous day with epiglottitis due to GAS, a third patient's child had been treated for GAS vulvitis 1 week before the patient's presentation, and one 3-week-old infant's mother had had GAS endometritis. Paired isolates were available for comparison in 3 of the 4 cases: each pair were of the same M and T serotype and had indistinguishable PFGE patterns.

Nosocomial acquisition occurred in 16 cases (7%). Three of these patients were known to have had indirect contact with a patient with a culture-confirmed GAS infection. One patient developed GAS pneumonia 6 days after being in the same open intensive care unit (ICU) as a patient with GAS necrotizing fasciitis (GAS isolates

from 3 family members of the patient with necrotizing fasciitis, 1 ICU nurse, and another ICU patient with pneumonia and bacteremia were serotype M3, T3 and indistinguishable by PFGE). A second patient developed GAS pneumonia 3 days after being admitted to the same ICU bed as a patient with bacteremic GAS cellulitis who had died hours before; both isolates were M6, T6 and identical by PFGE. A third patient developed pneumonia 2 days after being admitted to a room with a patient with a GAS surgical site infection; both isolates were M5, T5 and identical by PFGE.

Nursing home acquisition occurred in 27 cases (12%), of which 12 (44%) occurred in the context of a defined GAS outbreak in the long-term care facility. Four of these occurred during one outbreak of GAS pneumonia complicating influenza A. The remaining 8 occurred as part of 7 different outbreaks, 1 of which occurred during an influenza A outbreak. In 6 of the 7 outbreaks, there were at least 2 bacteremic illnesses due to GAS, but most cases were associated with soft-tissue foci rather than pneumonia.

Chronic Underlying Conditions in Patients With GAS Pneumonia

Underlying Condition	No. (%) of Cases*
None	80 (39)
Chronic lung disease	42 (21)
Cardiac disease	35 (17)
Cancer	32 (16)
Alcohol abuse	19 (9)
Diabetes mellitus	17 (8)
Intravenous drug use	11 (5)
Renal impairment	10 (5)
Cirrhosis	8 (4)
HIV infection	3 (1)
Systemic lupus erythematosus	3 (1)
Organ transplant recipient	2 (1)

Abbreviations: GAS, group A streptococcus; HIV, human immunodeficiency virus.

*Data on chronic underlying conditions were available for 204 patients (92%). Column total exceeds 204 because of patients with multiple underlying conditions.

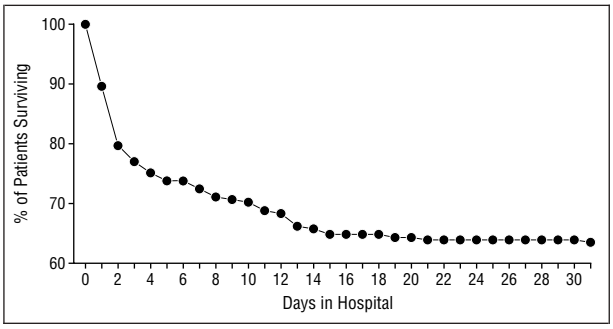

Figure 3. Cumulative in-hospital mortality in patients with fatal group A streptococcal pneumonia. The median time to death was 2 days.

MICROBIOLOGY

Blood cultures were positive in 178 patients (80%). Five of these patients also had *Streptococcus pyogenes* isolated from cultures of pleural fluid. Of the 44 patients in whom blood cultures were negative or not done, *S pyogenes* was isolated from pleural fluid in 37 and cultures of autopsy lung tissue in 7. Overall, GAS was isolated from pleural fluid in 44 patients, sputum and/or bronchoscopy specimens in 46, postmortem lung tissue in 15, and aspirates of pulmonary abscesses in 2; a total of 93 patients (42%) had 1 or more positive cultures from the respiratory tract.

Isolates were available for 196 patients (88%). The predominant M types were M1 (74 [38%]) followed by M3 (21 [11%]), M12 (15 [8%]), and M6 (10 [5%]). No other M type accounted for more than 5% of isolates. Among patients with invasive GAS infection in whom M typing was performed, isolates associated with pneumonia were more likely than others to be of M1 (74/196 [38%] vs 414/1539 [27%] [$P=.002$]) or M3 (21/196 [11%] vs 89/1539 [6%] [$P=.01$]) serotypes, and less likely to be M28 (6/196 [3%] vs 143/1539 [9%] [$P=.002$]).

MANAGEMENT AND OUTCOMES

Treatment included supportive care and intravenous antibiotics for most patients. Data on the timing of initial administration of an antibiotic effective against GAS was collected from 1994 onward: 132 (88%) of 150 patients for whom data were available received such an antibiotic within 12 hours of presentation. Data on initial antibiotic selection was available for 187 patients (84%). Cephalosporins were the most commonly used initial antibiotic (89 [48%]), followed by macrolides (39 [21%]) and penicillins (36 [19%]). Fourteen patients received intravenous immunoglobulin. Admission to an ICU was required for 99 (49%) of 204 patients and mechanical ventilation for 60 (29%). Twenty-five patients (11%) with pneumonia received a concomitant diagnosis of acute respiratory distress syndrome, compared with 29 (13%) of 224 patients with necrotizing fasciitis.

Local complications included empyema in 42 patients (19%) and pulmonary abscess in 3. The STSS occurred in 71 patients (32%), including 7 patients dead on arrival to the hospital and 17 who died within 48 hours of onset of illness and before a full assessment was completed. The STSS was significantly less common in the entire cohort of invasive GAS infection, occurring in 13% of patients overall ($P<.001$).

Among patients for whom outcomes data were available, the case fatality rate was 38% (85/222) compared with 12% (217/1748) for the remainder of the cohort of invasive GAS infection ($P<.001$) and 26% (58/221) of patients with necrotizing fasciitis ($P=.008$). The progression of fatal cases was rapid, with a median time to death of 2 days (**Figure 3**). In univariate analysis, increased case fatality rate was associated with the presence of STSS (odds ratio [OR], 5.3; 95% confidence interval [CI], 3.3-8.5; $P=.001$), older age (OR per decade, 1.4; 95% CI, 1.2-1.6, $P<.001$), underlying illness (OR, 2.8; 95% CI, 1.5-5.5; $P=.001$), and male sex (OR, 1.8; 95% CI, 1.0-3.3; $P=.04$), but not with M serotype, the presence of bacteremia, or concomitant soft-tissue infection. In multivariate analysis, only the presence of STSS (OR, 19; 95% CI, 8.4-42; $P=.001$) and increasing age (OR

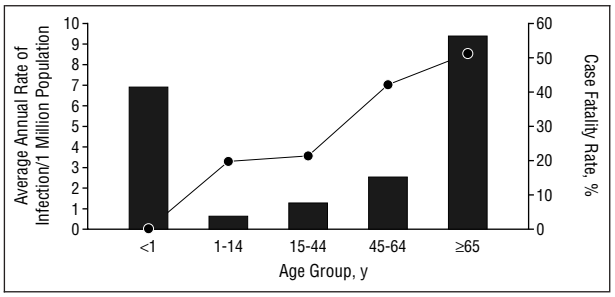

Figure 4. Age-specific incidence and case fatality rate associated with group A streptococcal pneumonia. The bars show the average annual incidence of group A streptococcal pneumonia in different age groups during the 8 years of the study. The line shows the case fatality rate in the same age group.

per decade, 1.45; 95% CI, 1.2-1.7; $P<.001$) were associated with a higher case fatality rate. Although the case fatality rate increased significantly with age (**Figure 4**), significant mortality also occurred in young adults. The case fatality rate in previously healthy patients aged 1 to 64 years was 18% (9/49).

COMMENT

The features of GAS pneumonia were well characterized in the preantibiotic era, when it represented a common cause of community-acquired pneumonia.[1,2] Dramatic changes have since been seen in the incidence and nature of invasive GAS infections.[23,29,30,37] As a result, it is no longer clear whether previous descriptions reflect the current clinical and epidemiologic features of GAS pneumonia. Recent descriptions of the clinical features of GAS pneumonia are primarily case reports describing severely ill patients with frequent complications. Reviewing case reports may give an inaccurate impression of the severity of GAS pneumonia and the frequency of complications, as these reports may describe particularly severe presentations. Our results, to our knowledge, represent the only large population-based study of GAS pneumonia since the description of STSS.

The primary limitation of the study is the lack of objective clinical criteria to distinguish GAS pneumonia from GAS bacteremia complicated by adult respiratory distress syndrome. Nevertheless, there is sufficient evidence that most cases reflect true GAS pneumonia. Overall, 11% of patients in our cohort of invasive GAS disease presented with pneumonia, similar to the proportion of cases of pneumonia in other reports.[31] Direct pulmonary involvement was demonstrated by culture in 42% of patients. Perhaps more important, since the definition of pneumonia is that used in clinical practice, the clinical and epidemiologic conclusions drawn from these data remain valid despite the possible misclassification of pulmonary disease.

The incidence of invasive GAS pneumonia during the period of our study ranged from 0.16 to 0.35 per 100 000 population, with a trend toward increasing frequency. Data from the Centers for Disease Control and Prevention's Active Bacterial Core Surveillance reports suggest that similar frequencies of invasive GAS disease and pneumonia occur in the United States. Active bacterial core surveillance from 1997 to 1999 reported an overall incidence of invasive GAS of 3.5 per 100 000 population, with 11% representing pneumonia.[38] Although GAS pneumonia is rare compared with the common causes of community-acquired pneumonia, such as *Streptococcus pneumoniae*, it occurs with a frequency similar to that of other well-recognized causes of severe community-acquired pneumonia, such as *Staphylococcus aureus* or *Klebsiella pneumoniae*. In a population-based study by Marston et al,[39] 0.3% of cases in which a definite etiologic agent was identified were caused by GAS, compared with 0.4% caused by *S aureus*.

In the past, GAS pneumonia appeared to occur in clusters after outbreaks of viral illness[1-3] or in military recruits with high rates of pharyngeal colonization with GAS.[40,41] More recently, small outbreaks of invasive streptococcal infections, including GAS pneumonia, have also been described in chronic care facilities and within families.[42-44] Despite this, our study suggests that most cases occur sporadically in the community. No geographic clustering of community-acquired cases was seen. In contrast, a high proportion of patients with institutionally acquired GAS pneumonia had had contact with other patients with invasive GAS disease. Of the nursing home–acquired cases, 44% occurred in the setting of GAS outbreaks within the facility, and 2 of 7 nursing home outbreaks occurred in association with influenza. Among the hospital-acquired cases, 3 (19%) of 16 had indirect exposure to another case of invasive GAS infection.

These results emphasize the importance of transmission of GAS in institutional settings. The Centers for Disease Control and Prevention has recently released recommendations that all cases of surgical site and postpartum GAS infection be investigated[45]; our data suggest that these recommendations should be extended to include cases of institutionally acquired GAS pneumonia. Even a single case of GAS pneumonia occurring in the nosocomial or nursing-home setting should prompt a search for evidence of GAS transmission and secondary cases.

Transmission of GAS occurs in households, but related cases of invasive GAS disease are infrequent; it is not clear that prophylaxis would be beneficial for close contacts of such patients. Recommendations on household contact prophylaxis have been published.[45]

Our report confirms the impression established by case reports that GAS pneumonia is a severe illness of sudden onset frequently associated with local and systemic complications, particularly empyema (19%), STSS (32%), and death (38%). The high case fatality rate and the rapid progression from diagnosis to death were particularly striking features. The case fatality rate of 38% is consistent with the 30% to 60% mortality found in bacteremic GAS pneumonia in other studies[16,17,19,45] and is considerably higher than the case fatality rate of necrotizing fasciitis in our cohort of invasive GAS infection (26%) and the case fatality rate for community-acquired bacteremic pneumococcal pneumonia (12% to 20% in recent studies).[46-49]

The high mortality and rapid progression occurred despite early appropriate antibiotic therapy and the use of advanced supportive measures, suggesting that inter-

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ventions directed at the underlying pathogenesis of STSS will be required to improve outcomes. Recent interest in this area has centered on the use of intravenous immune globulin.[50-52] However, support for the clinical utility of intravenous immune globulin consists only of case reports and one comparative observational trial and remains controversial.[50,53] In our data, too few patients received intravenous immune globulin to draw any conclusions as to its efficacy.

CONCLUSIONS

Group A streptococcal pneumonia is a rapidly fatal illness that can affect all age groups, even in the absence of underlying medical conditions. Although rare, it occurs more frequently and has a higher case fatality rate than GAS necrotizing fasciitis. New therapies instituted early in the disease process will be required before improvements in outcome will be seen.

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James E. Dalen, MD, MPH
Editor