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Epidemiology of Nosocomial Invasive Pneumococcal Disease in Toronto, Canada, 1995-2007

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Abstract (Revised)

Background: *Streptococcus pneumoniae* (SP) is an increasingly recognized cause of nosocomial infection. We describe the epidemiology of nosocomial, sterile site SP infections (NSP) in Toronto, Canada.

Methods: Population-based surveillance of all sterile site isolates of SP in Toronto/Peel region was performed from 1995-2007. Infection was defined as nosocomial if the first culture was obtained >3 days after admission and if there was no evidence of infection at admission. Cases were also considered nosocomial if infection was acquired during a prior recent hospitalization or procedure.

Results: SP was isolated from a sterile site in 4619 hospitalized patients. NSP occurred in 307 cases (6.6%). Primary sources of infection included lung (58%), bloodstream (34%) and CSF (3%). NSP incidence was 0.7/10,000 admissions. The median time to positive culture was 8 days; 86% occurred in <30 days. Compared to community acquired invasive SP infections (CASP), patients with NSP were older (median 70 vs. 57 years, P<0.001), more likely to have diabetes (P=0.001), cancer (P=<0.0001), chronic lung (P=0.003) or cardiac disease (P<0.001). NSP mortality was higher than CASP (46% vs. 17%, P<0.001). Increased NSP mortality was associated with older age (P<0.001), lung disease (P=0.048) or ≥1 chronic medical condition (P=0.02). NSP were caused by serotypes included in the 23-valent and the 7-valent SP vaccines (SPV) in 82% and 51% of cases. Among patients for whom SPV status was available, 52/228 (23%) received SPV prior to their illness. Before 2002, 3/11 patients who had received a fluoroquinolone (FQ) in the prior 3 months developed a FQ resistant (FQR) NSP, while after 2002, 0/22 patients developed a FQR NSP (P=0.03).

Conclusions: NSP have a high mortality rate. Patients who develop NSP are older and more likely to have a chronic disease. Most NSP are caused by vaccine covered serotypes. Efforts to increase SPV usage may reduce NSP. Since the introduction of "respiratory FQs", prior FQ use is no longer associated with developing FQR NSP.

Introduction

Streptococcus pneumoniae (SP) is a common cause of community acquired pneumonia, meningitis and bacteremia. SP has been described as an agent of nosocomial infection in several retrospective studies, primarily single hospital series and 1 population based study from Finland. Nosocomial SP infections have generally been associated with higher mortality rates than community acquired SP infections. Differences between studies are likely due to variations in patient population, SP microbiology, sterile site culture rates and timing, and pneumococcal vaccination rates.

Polysaccharide SP vaccine is recommended by the Canadian National Advisory Committee on Immunization for all individuals ≥ 65 years of age and younger patients with certain comorbid conditions.

The objectives of this study were to perform population-based surveillance of invasive pneumococcal disease in Toronto, Canada, and analyze for trends in incidence, seasonal variation, associated medical conditions, antibiotic resistance and serotype patterns.

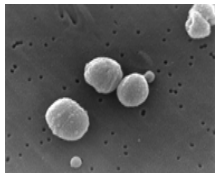

Figure 1. *S. pneumoniae* (photo: Janice Carr, CDC)

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Methods

• Population-based surveillance of invasive pneumococcal disease was performed by the Toronto Invasive Bacterial Diseases Network (TIBDN) from January 1, 1995 to December 31, 2007 in residents of metropolitan Toronto and the regional municipality of Peel (population 3.9M in 2007).

•TIBDN: a collaborative network of all hospitals, microbiology laboratories, infection control practitioners and public health units serving the defined population: 25 hospitals, 19 laboratories and 85 long-term care facilities participate in this surveillance program.

•Invasive pneumococcal disease: infection associated with isolation of SP from a normally sterile site (most commonly blood or cerebrospinal fluid).

• Isolates were confirmed to be SP in the TIBDN central microbiology laboratory at Mount Sinai Hospital.

• Serotyping and broth microdilution susceptibility testing were performed and interpreted using CLSI standards.

•Using a standard data collection form, patient demographics, comorbid conditions, details regarding hospitalization and mortality, recent antibiotic usage and prior pneumococcal vaccination were extracted through chart review and, where possible, by contacting patients, their caregivers and their general practitioners.

•Cases were defined as nosocomial if the first culture was obtained >3 days after admission and if there was no evidence of infection incubating at admission. Cases were also considered nosocomial if the infection was acquired during a recent prior hospitalization or in-hospital procedure.

Figure 2. TIBDN population area

•Data was analyzed using SAS for Windows, version 9.1 (SAS Institute, Cary, NC).

Results

- Invasive pneumococcal disease: 5383 individual patients, 4619 admitted to hospital

Nosocomial invasive SP infection (NSP):

- 307 cases (6.6% of hospitalized cases)
- Incidence: 0.7/10 000 admissions
- Mortality vs. invasive community acquired SP infection: 46.3% vs. 17.0% (*P*<0.001)
- Median time to positive culture: 8 days
- 86% of cases occurred in first 30 days of admission
- Primary source of infection: respiratory (58%), bloodstream (34%) , CSF (3%)

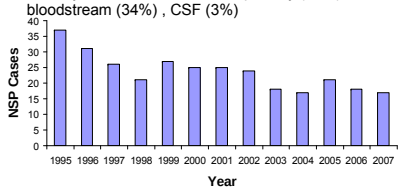

Figure 3. Number of nosocomial SP cases: 1995-2007

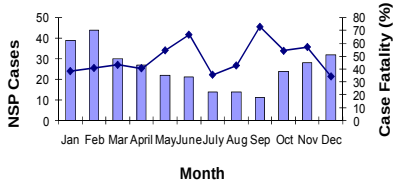

Figure 4. Number of nosocomial SP cases by month

•No significant decline in case fatality rate by year

•December-May : n=195, mortality=41.2% > *P*=0.017
June-November: n=112, mortality=55.4%

Table 1: *Comparison of characteristics between patients with nosocomial SP and community acquired SP infection*

Characteristic	NSP Infection (n=307)*	CASP Infection (n=5076)*	*P*-value	RR (95% CI)
Any chronic illness	265 (86.3)	2896 (57.0)	<0.0001	4.28 [3.10-5.92]
Diabetes mellitus	66 (21.6)	694 (14.5)	0.001	1.57 [1.21-2.04]
Cardiac disease	99 (32.4)	962 (20.1)	<0.0001	1.82 [1.45-2.29]
Pulmonary disease	71 (23.2)	798 (16.7)	0.003	1.47 [1.14-1.90]
Renal disease	33 (10.5)	231 (4.7)	<0.0001	2.21 [1.57-3.10]
Liver disease	32 (10.2)	257 (5.4)	0.0001	1.89 [1.33-2.67]
Cancer	118 (38.6)	715 (14.9)	<0.0001	3.22 [2.59-4.00]
Organ transplant recipient	10 (3.6)	64 (2.1)	0.09	1.66 [0.92-3.02]
HIV	10 (3.3)	218 (4.6)	0.27	0.72 [0.40-1.33]
Alcohol abuse	33 (10.5)	534 (10.1)	0.847	0.97 [0.68-1.37]
Current smoker	36 (19.5)	841 (26.3)	0.039	0.69 [0.48-0.98]
IV drug use	4 (1.44)	136 (4.39)	0.019	0.34 [0.12-0.90]
Age			<0.0001	
<18	20 (6.5)	1133 (21.1)		1
18-64	93 (30.3)	2030 (37.8)		2.53 [1.57-4.07]
>64	194 (63.2)	2202 (41.0)		4.67 [2.96-7.37]

Table 2: *Risk factors for nosocomial invasive SP infection mortality*

Characteristic	Died (n=145)*	Survived (n=162)*	Univariate Analysis *P*-value	Multivariate Analysis OR [95% CI]
Any chronic illness	129 (91.5)	136 (82.4)	0.02	
Diabetes Mellitus	32 (22.9)	34 (22.7)	0.86	
Cardiac disease	50 (35.5)	49 (29.7)	0.30	
Pulmonary disease	40 (28.4)	31 (18.8)	0.048	
Renal disease	12 (8.6)	21 (11.6)	0.40	
Liver disease	14 (10.1)	18 (11.0)	0.80	
Cancer	60 (42.6)	58 (35.6)	0.23	
Organ transplant recipient	3 (2.3)	7 (4.9)	0.42	
HIV	3 (2.2)	7 (4.5)	0.31	
Alcohol abuse	16 (11.6)	17 (10.4)	0.73	
Current smoker	15 (18.8)	21 (20.0)	0.83	
IV drug use	1 (0.8)	2 (1.4)	0.95	
Male	80 (56.3)	94 (57.0)	0.91	
Age			<0.001	1.34 [1.19-1.55]

*Number in parentheses represents percentage of cases with data available

- 50.9% of serotyped nosocomial invasive SP (NSP) cases were serotypes covered by 7-valent conjugate SP vaccine
- 82.4% of serotyped NSP cases were serotypes covered by 23-valent poylsaccharide SP vaccine
- Among patients with known SP vaccination status, 52/228 (23%) had received vaccination prior to developing a NSP infection
- 92.2% of NSP cases had an Canadian National Advisory Committee on Immunization indication for SP vaccination

Table 3: NSP *antiobiotic resistance rates*

Antibiotic	Resistant Isolates (%)[1]	Case Fatality (%)
Penicillin	13 (4.6)	6 (46.2)
Penicillin Int.[2]	27 (9.6)	8 (29.6)
Erythromycin	40 (14.3)	12 (30.0)
Fluoroquinolone	10 (3.9)	5 (50.0)
Clindamycin	21 (7.5)	5 (23.8)
Tetracycline	22 (9.7)	7 (31.8)
Vancomycin	0	0

[1] Percentage of isolates with susceptibility data available
[2] Penicillin intermediate susceptibility (0.12 ≤ MIC ≤ 1µg/mL)

- Erythromycin resistance was associated with reduced nosocomial invasive SP (NSP) infection mortality (P=0.049)
- Before 2002, 3/11 patients who had received a fluoroquinolone (FQ) in the prior 3 months developed a FQ resistant (FQR) NSP infection, while after 2002, 0/22 patients developed a FQR infection (P=0.03).

Conclusions: Nosocomial invasive SP (NSP) infections have a high mortality rate. Patients who develop NSP infections are older and more likely to have a chronic disease. Most NSP infections are caused by vaccine covered serotypes. Efforts to increase SP vaccination usage may reduce NSP infection rates. Since the introduction of "respiratory fluoroquinolones (FQ)", prior FQ use is no longer associated with developing a FQ resistant NSP infection.