Impact of Antibiotic Therapy on Outcome of Bacteremic Pneumococcal Pneumonia in Toronto, Canada

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Abstract

Background: Choice of antibiotic (AB) regimen may influence mortality in patients with severe pneumococcal infection. We examined the impact of treatment choices on mortality from pneumococcal bacteremia (PB) in adults in Ontario, Canada.
Methods: Population based surveillance for PB in residents of Toronto, Canada (pop=4M) is on-going. Since 2000, demographic and medical data collected from patients and MDs includes AB therapy. Eligible episodes of PB were those in adults (age>15y) for which treatment and susceptibility data were available.
Results: From 1/2000 to 12/2004, there were 1037 eligible episodes of PB. Median age of patients was 67y (range 16-108y); 549 (53%) were male, 778 (54%) had chronic underlying illness: most commonly cardiac disease (305, 29%), lung disease (242, 23%), diabetes mellitus (193, 19%), cancer (170, 16%). 32 isolates (3.1%) were resistant to penicillin, 114 (11%) to erythromycin, 11 (1.1%) to ceftriaxone, 11 (1.1%) to levofloxacin, and 4 (0.4%) to moxifloxacin. 316 (30%) patients were admitted to ICU; 213 (21%) required mechanical ventilation (MV). The 30d mortality rate was 22% (N=224). No patients received discordant AB therapy. Non-treatment factors associated with 30d mortality in multivariable analysis were: older age (OR/decade, 1.5, P<.001), chronic organ system disease (OR 1.6, P=.03), nursing home acquisition (OR 3.8, P<.001), ICU admission (OR 3.1, P<.001), requirement for MV (OR 3.2, P<.001), and infection with serotype 11A (OR 2.9, P=.03) or 19F (OR 2.9, P=.002). In adjusted analysis, an increasing number of ABs was associated with survival for regimens without fluoroquinolones (FQ) (OR 1.8 per drug, 95%CL 1.1, 2.88) but not with FQ (OR 0.9/drug, 95%CL 0.6, 1.2). Use of FQ containing regimens was associated with increased survival (OR 5.6, 95% CL 1.3, 25).
Conclusion: BP disease in adults is associated with high mortality. Regimens including a FQ were associated with significantly lower mortality; use >1 AB increased survival only for regimens not including FQ.

Background

There is emerging evidence that the choice of antibiotic regimen may influence outcomes and mortality in patients with community-acquired pneumococcal infection. However these are observational studies only with limited data on pneumococcal bacteremia and little data post introduction of fluoroquinolones for treatment. We examined the impact of treatment choices on mortality from pneumococcal bacteremia in adults in Ontario, Canada from 2000 to 2004

3.7M persons:
11% Canadian population

Methods

The Toronto Invasive Bacterial Diseases Network is a collaborative network of all hospitals and microbiology laboratories serving residents of metropolitan Toronto and Peel region (population 3.7 million). This network comprises 25 hospitals, 19 laboratories, 85 long term care facilities and 2 public health units who have been conducting population-based surveillance for invasive pneumococcal disease since January, 1995. Laboratories report all sterile site and respiratory cultures yielding *S. pneumoniae* to the central study office. Each case is assigned to a study nurse who obtains consent, information from patient, and data from chart and family physicians. Susceptibility testing to CLSI standards and serotyping are performed at the central study laboratory. Annual audits are performed to ensure reporting accuracy. Eligible episodes of pneumococcal bacteremia included in this analysis were those in adults (age>15y) for which treatment and susceptibility data were available. Factors associated with 30-day mortality were evaluated, using multivariable logistic regression (SAS version 9.1). Initial antibiotic therapy included any antibiotic administered on the first day of hospitalization.

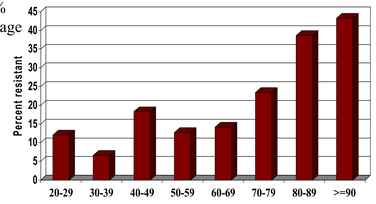
Results

Between January 2000 and December 2004, there were 1792 episodes of pneumococcal bacteremia reported to the study. Of these, 215 did not require hospitalization, 89 were acquired in an acute care facility and 307 were in children <16 years old. 62 (5.2%) of the remaining 1181 cases did not have isolates available for susceptibility testing and 58 (4.9%) had incomplete antibiotic data leaving 1037 evaluable cases.

Table 1. Patient characteristics included in univariate analysis

	Survived N=813	Died N=224	P-value
Age (median, range)	63 (16-108)	76 (21-98)	<0.0001
No (%) male	427 (54%)	124 (55%)	0.451
Any chronic underlying illness:	593 (73%)	187 (83%)	0.0012
Cardiac disease	205(25%)	100 (45%)	<0.0001
Lung disease	178 (22%)	64 (29%)	0.03
Diabetes	150 (18%)	43 (19%)	0.799
Cancer	119 (15%)	51 (23%)	0.003
Nursing home resident	73 (9%)	66 (29%)	<.0001
Vaccinated against pneumococcal disease	171 (21%)	48 (21%)	0.89
Primary Diagnosis:			
Bacteremia	78 (10%)	36 (16%)	0.006
Pneumonia	653 (80%)	176 (79%)	0.562
Meningitis	44 (5%)	15 (7%)	0.462
Other	42 (5%)	3 (1%)	0.01
ICU admission	196 (24%)	121 (54%)	<.0001
Mechanical Ventilation	114 (14%)	99 (44%)	<.0001

Overall 30-day mortality was 22%
Figure 1. 30-day case fatality by age



Results (con't)

Table 2: Characteristics of case isolates

Isolate Characteristics	Survived N=813	Died N=224	P-value
No (%) Resistant to:			
Penicillin	25 (3%)	7 (3%)	0.96
Erythromycin	94 (12%)	23 (10%)	0.58
Ceftriaxone	8 (1%)	3 (0.4%)	0.68
Levofloxacin	9 (1%)	2 (1.2%)	0.78
Moxifloxacin	3 (0.4%)	1 (0.4%)	0.86
Serotype:			
14	139 (17%)	28 (13%)	0.09
6B	67 (8%)	15 (7%)	0.4
3	70 (9%)	33 (14%)	0.006
4	77 (10%)	12 (5%)	0.051
19F	30 (6%)	22 (9%)	0.002
11A	9 (1%)	11 (5%)	0.002
9V	48 (6%)	9 (4%)	0.27

Table 3. Non treatment factors associated with 30-day mortality in multivariable analysis

Non treatment factors associated with 30-day mortality	Odds ratio (95% confidence interval)	P-value
Age	1.04 (1.03-1.06)	<0.0001
Chronic underlying disease	1.61 (1.03-2.53)	0.04
Nursing home acquisition	3.82 (2.45-5.94)	<0.0001
ICU admission	2.99 (1.68-5.31)	0.0002
Required mechanical ventilation	3.30 (1.83-5.95)	<0.0001
Infection with serotype 11A	2.95 (1.10-7.91)	0.03
Infection with serotype 19F	2.94 (1.50-5.74)	0.002

Table 4. Treatment regimens used for patients who received ICU vs non-ICU care

Treatment choices	ICU		Non- ICU	
	Survived N=196	Died N=121	Survived N=617	Died N=103
Cepholosporin alone	9 (4.6%)	23 (19%)	77 (12.5%)	14 (13.6%)
Fluoroquinolone alone	18 (9.2%)	8 (6.6%)	167 (27%)	23 (22%)
Fluoroquinolone + other antibiotic	70 (36%)	53 (44%)	180 (29%)	39 (38%)
Cephalosporin/Pen + macrolide	48 (24%)	20 (16.5%)	99 (16%)	9 (9%)
Cephalosporin + other antibiotic	37 (19%)	10 (8.3%)	47 (7%)	7 (7%)
Others	14 (7%)	7 (6%)	47 (7%)	11 (11%)

Results (con't)

All patients in this cohort received at least one antibiotic active against their isolate of *S. pneumoniae* within the first 24 hours of hospitalization. The presence of resistance to one or more antibiotic classes had no impact on outcome.

In multivariable analysis, an increasing number of antibiotics in the treatment regimen was associated with survival if the regimens did not include a fluoroquinolone (Table 5), but not if it did. Survival was significantly higher in patients treated with fluoroquinolone-containing regimens

Table 5. Treatment characteristics associated with 30-day survival

	Odds ratio	P-value
Number of antibiotics in the regimen (per antibiotic added)		
Regimens NOT including a fluoroquinolone	1.87(0.46, 2.37)	0.01
Regimens including a fluoroquinolone	0.91 (0.65, 1.27)	0.57
Any fluoroquinolone in the regimen vs no fluoroquinolone	16.7 (2.6, 107)	.003

Conclusions

In this cohort of patients with community-acquired pneumococcal bacteremia receiving concordant antibiotic therapy, the odds of survival increased with increasing numbers of antibiotics in initial treatment regimens, if the regimen did NOT contain a respiratory fluoroquinolone, but not if it did. Fluoroquinolone containing regimens were associated with improved outcomes.

Analyses of different cohorts of patients with pneumonia or pneumococcal disease have reached different conclusions about the impact of antibiotic choices on outcomes. This may be due to different patient populations, or to undetected confounding in such analysis. Caution should be exercised in making conclusions about the effectiveness of different therapeutic regimens from such observational cohorts.

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