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Factors Associated with Antimicrobial Resistance and Mortality in Pneumococcal Bacteremia

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Abstract

We conducted a multicenter, retrospective cohort study of patients with *Streptococcus pneumoniae* bacteremia to determine factors associated with antibiotic resistance and mortality. Risk factors were identified using multivariate logistic regression. 1,574 patients at 34 sites were enrolled. Compared to isolates from patients not receiving an antibiotic before the index blood culture, patients receiving an antibiotic were less likely to harbor an antibiotic susceptible organism. Susceptibility to penicillin decreased from 78% (95% confidence interval [CI], 75−80) to 49% (95%CI, 39−59); to cefotaxime/ceftriaxone, from 92% (95%CI, 90−93) to 82% (95%CI, 72−89); and to macrolide, from 84% (95% CI, 82−87) to 55% (95%CI, 41−68). Factors associated with macrolide non-susceptibility include: >24 hours of antibiotic therapy at time of the index culture (odds ratio [OR] 4.0), residing in southern U.S. (OR 1.7), and having an antibiotic allergy (OR 1.7). Harboring an antibiotic non-susceptible strain (OR 1.4) and male sex (OR 1.4) were associated with increased risk of mortality, whereas Black race (OR 0.6) and evidence of focal infection (OR 0.6) were associated with decreased risk.

Keywords

Streptococcus pneumoniae; antibiotic resistance; mortality; bacteremia

Introduction

Despite the long standing use of the 23-valent pneumococcal vaccine in specific at risk groups over the age of two years, and the recent introduction of the conjugate pneumococcal vaccine into the childhood immunization schedule in the United States, *Streptococcus pneumoniae* remains the leading bacterial cause of community-acquired pneumonia, otitis media, and meningitis among both adults and children. As recently as 1980, 99% of *Streptococcus pneumoniae* were fully susceptible to penicillin, and thus treatment of community-acquired pneumonia with a beta-lactam antibiotic was justified. Due to concerns about increasing pneumococcal resistance to penicillin, and to provide coverage for atypical pathogens, the American Thoracic Society and Infectious Disease Society of America now recommend considering the use of a macrolide antibiotic plus high dose beta-lactam antibiotic for the empiric outpatient treatment of community acquired pneumonia.(1-4) Recent surveillance studies of invasive pneumococcal isolates have demonstrated that only 73% of isolates remain susceptible to penicillin, and 78% susceptible to erythromycin. (5)

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The use of low dosages and long treatment duration with beta-lactam antibiotics have been identified as risk factors for the nasopharyngeal carriage of penicillin resistant organisms. (6) Underlying disease, immunosupression and prior antibiotic use have also been associated with penicillin non-susceptibility in prior studies.(7,8) Despite the recognized increased rates of antimicrobial resistance among pneumococci, the clinical significance of this resistance is largely unknown. There is literature suggesting that antibiotic resistance may contribute to treatment failure and poor clinical outcomes.(7,9-11) Cases of failed therapy in association with resistance have been reported, but large-scale clinical studies of this phenomenon are lacking. The result is poor consensus regarding the clinical implications of antimicrobial resistance. For example, some authors contend that beta-lactam resistance as currently defined should only impact on the therapy of meningitis, or that macrolide resistance as currently defined does not correlate with clinical failure. Some recent reports, however, are worrisome with reported development of pneumococcal bacteremia among patients receiving azithromycin or clarithromycin therapy, in association with low-level resistant strains. (12-15)

We performed this large multicenter U.S. study including over 1500 patients with pneumococcal bacteremia in order to increase our understanding regarding factors associated with antibiotic resistance and associated mortality. We will describe the susceptibility pattern of pneumococcal isolates in this cohort, and will determine the factors associated with antibiotic resistance and mortality.

Materials and Methods

We performed a multicenter, retrospective case-control study of patients with *Streptococcus pneumoniae* bacteremia. Investigators at 34 U.S. sites reviewed the medical records of these subjects using a standardized protocol. All sites are members of the Emergency Medicine Network (EMNet), a clinical research collaboration with greater than 140 participating medical centers.(6) Site selection for participation was based on the local microbiology lab routinely performing pneumococcal susceptibility testing and with consideration of their geographic location. The study was approved by the institutional review board at each of the 34 participating hospitals.

Each site was asked to produce a list of all patients with pneumococcal bacteremia over at least one year since January 1, 2000. If less than 50 patients were listed in 2000, sites were asked to continue collecting patients into 2001 and 2002 until reaching 50 subjects. Patient lists were produced by the hospital's microbiology laboratory, which identified eligible subjects as those with growth of *S. pneumoniae* in blood culture. Sites submitted completed patient lists to the EMNet Coordinating Center, where lists were checked for repeat patients and assigned randomized numbers. Data was collected for only one visit per patient, such that only the first visit for that patient was included in the analysis, and subsequent visits by that patient for the same or subsequent episodes of bacteremia were excluded. The patient lists were sorted by assigned randomization number and site and the principal investigator at each site completed a data abstraction form for the first 50 patients from their randomly sorted list. If one of the 50 charts was a lost medical record, the next chart on the list was used. Sites that did not accrue 50 patients during the study period collected data on each of the eligible patients seen at the site during the study period.

Data collection was done using a standardized protocol and data abstraction form. For all charts, basic demographic information, diagnosis, the presence of a focal site of infection, and key clinical information was obtained. Documentation was obtained regarding hospitalization and prior antimicrobial therapy within the month prior to developing bacteremia. Investigators also recorded whether the blood culture was obtained in the office/clinic, ED, or as an inpatient and

whether or not the patient was admitted for the illness. The final disposition of admitted patients was also recorded.

The result of laboratory susceptibility testing of the *S. pneumoniae* isolates and specific methodology was recorded. All forms were reviewed by site investigators before submission to the EMNet Coordinating Center in Boston, where they underwent further review by trained personnel and then double data entry. Determination of prior antibiotic therapy was based on the response to the following question: Is there evidence of > 24 hours of antibiotic therapy before the time the blood culture was drawn? Available selections were: yes, no or unsure. We considered a patient to have therapeutic failure if the answer to the above question was yes, i.e. bacteria was identified from a culture of blood obtained from the patient after more than twenty-four hours of antibiotic treatment.

S. pneumoniae is reported as susceptible, intermediate, or resistant to the tested antibiotic. Twenty-nine of the sites used NCCLS criteria to define these categories; five sites used alternate but nearly identical criteria (similar Minimal Inhibitory Concentration (MIC) and Zone Diameter breakpoints as those defined by NCCLS criteria to delineate each category. For the purposes of these analyses, both intermediate and resistant organisms will be considered as non-susceptible strains. Antibiotic susceptibility testing listed on the data form included: penicillin, cefotaxime / ceftriaxone, erythromycin, clindamycin, tetracycline, and trimethoprim / sulfamethoxazole.

All analyses were performed using STATA 7.0 (StataCorp, College Station, TX). Data are presented as proportions (with 95% confidence intervals [CI]), means (with standard deviation [SD]), or medians (with interquartile range [IQR]). The association between antibiotic susceptibility and other factors was examined using Chi-square test, Student's t-test, and Wilcoxon rank sum test, as appropriate. Age, sex, and race were included in the multivariate models because of their potential clinical significance. Other variables associated with resistance at $p<0.10$ in univariate analysis were evaluated for inclusion in multivariate logistic regression. The final models were further evaluated using the Hosmer-Lemeshow test. All p-values are two-sided, with $p<0.05$ considered statistically significant.

Results

A total of 1,574 patients at 34 sites were included in the study. 99 patients (6%:95% CI 5, 8) had received >24 hours of antibiotic therapy before the time that the blood was drawn for culture; of whom 38% had received a macrolide antibiotic, 31% a sulfonamide, 16% a cephalosporin, 16% a quinolone, and 7% of study subjects received a penicillin. 1423 patients had not received an antibiotic prior to the collection of a blood culture, and we were unable to determine prior antibiotic status in 52 patients.

Demographic characteristics of these patients with pneumococcal bacteremia are shown in Table 1. There is a bimodal distribution for age, which peaks at 1−5 years and 40−49 years of age. The median age was 46 years, with a similar number of men and women. Consistent with the urban setting of the study hospitals, half of the subjects were black or Hispanic. Subjects came from all regions of Unites States, with preponderance from Northeast (consistent with location of most EMNet sites). Patients were covered by a diverse array of third-party payers.

Clinical characteristics of patients with pneumococcal bacteremia are shown in Table 2. Forty-four percent of patients with prior antibiotic therapy were immunocompromised, compared to 23% of those not receiving antibiotics at the time of blood collection. Human Immunodeficiency Virus infection accounted for 56% of immunocompromise overall, and 29% were chemotherapy related. A primary site of infection was documented for 78% of patients, with pneumonia being most common (63% of all patients, and 82% of those with a

documented site of infection). Twenty-two percent of patients had no focal site of infection identified. The majority of subjects (74%) had blood drawn for culture within an emergency department. For those with blood drawn within the ED or clinic (total of 79%), 88% were admitted to the hospital. Thirteen percent of hospitalized patients with *S. pneumoniae* bacteremia died.

Antibiotic susceptibilities of *S. pneumoniae* isolates are detailed in Table 3. Testing varied widely across sites, with most hospitals testing for penicillin (99%) and cephalosporins (85%). Fewer tested for susceptibility to macrolides (62%) and quinolones (47%). Patients already receiving an antibiotic at the time they developed bacteremia were more likely than patients not currently receiving antibiotics, to harbor an antibiotic non-susceptible organism. For example, penicillin susceptibility decreased from 78% to 49%, and macrolide susceptibility decreased from 84% to 55%. Among patients taking a penicillin (n=7) at the time they developed pneumococcal bacteremia, 43% had a penicillin susceptible isolate. Similarly, 20% of patients receiving a cephalosporin (n=15), and 60% of those receiving a macrolide (n=38) antibiotic had a pneumococcal isolate which was susceptible to the antibiotic they were receiving.

Of the 344 pediatric patients under 18 years of age, 28 (8.1%) had received antibiotic therapy prior to obtaining blood for culture. A similar reduction in proportion of antibiotic susceptible strains was observed in this group. Pneumococcal isolates from children receiving a macrolide prior to blood culture collection were more likely to be a macrolide non-susceptible organism (33% susceptible vs. 81% susceptible). Additionally, among children taking a non-macrolide antibiotic (penicillin, cephalosporin, etc.), the proportion with isolates susceptible to penicillins (75% vs. 59% susceptible), cephalosporins (91% vs. 86%), as well as macrolides (81% vs. 73%) were decreased. Similar reductions in the proportion of susceptible isolates were observed among elderly patients (≥65 years of age).

Univariate predictors of macrolide resistance include: residence in Southern US (as defined by U.S. Census Bureau Estimates), prior antibiotic therapy, and immunocompromise (data not shown). Multivariate models for macrolide, penicillin, and cephalosporin non-susceptibility are shown in Table 4. Adjusting for covariates, predictors that confer increased risk of macrolide resistance include: evidence of prior antibiotic therapy (OR = 4.0), residing in the Southern United States (OR = 1.7), and having an allergy to an antibiotic (OR = 1.7). Predictors for penicillin and cephalosporin non-susceptibility were similar; prior antibiotic therapy remained significant in the penicillin and cephalosporin models with OR's = 3.3 and 2.0 respectively. Admission to the hospital within the preceding month was a risk factor for both penicillin (OR = 1.5) and cephalosporin (OR = 2.6) non-susceptibility, whereas having an allergy to an antibiotic did not reach statistical significance in these two models. Increasing age was not a risk factor for macrolide, penicillin or cephalosporin non-susceptibility. Exclusion of children (n=344) did not materially change the results (data not shown).

Thirteen percent of patients with pneumococcal bacteremia died. A multivariate model of mortality among patients with pneumococcal bacteremia is shown in Table 5. Antibiotic nonsusceptibility (macrolide or penicillin or cephalosporin) was found to be a significant predictor of mortality among patients with pneumococcal bacteremia (OR = 1.4). Univariate analysis of antibiotic non-susceptibility on mortality are as follows: macrolide non-susceptibility (OR=1.2, 95% CI 0.9, 1.8), penicillin non-susceptibility (OR=1.2, 95% CI 1.0, 1.5), and ceftriaxone or cefotaxime non-susceptibility (OR=1.3, 95% CI 0.9, 1.5). Male patients (OR =1.4), as well as patients that were either admitted to the hospital or were an inpatient at the time the blood culture was drawn (OR = 5.1) had an increased risk of mortality compared with those not admitted to the hospital. Increasing age was also associated with risk of mortality (OR = 1.3). Current antibiotic use was not associated with increased risk of mortality. The

presence of a reported focal infection conferred a decreased risk of mortality (OR 0.6). Additionally, Blacks had a lower risk of mortality (OR = 0.6) compared to whites. Limiting the analysis to adults did not alter our results (data not shown).

Discussion

Streptococcus pneumoniae remains the leading cause of invasive bacterial diseases such as community-acquired pneumonia and meningitis in the United States. (5,16-19) Despite widespread reports of decreased susceptibility of *S. pneumoniae* to penicillins, cephelosporins, and macrolides, these remain the most commonly prescribed antibiotics for both children and adults with community acquired pneumonia in the United States and Canada. (4,12) With increasing rates of antibiotic resistance of *S. pneumoniae*, decisions on treatment of patients with such infections may depend on local antimicrobial susceptibility, as well as clinical outcomes of patients treated with these antibiotics. Prior studies investigating the clinical relevance of antibiotic resistance and mortality in pneumococcal disease have been based on a much smaller number of patients.(11,12)

In this large, retrospective mulitcenter cohort study of patients with pneumococcal bacteremia, we determine the relationship between prior antibiotic use and antibiotic resistance, and also determine which factors are associated with antibiotic resistance. We found that in addition to prior antibiotic use, having *S. pneumoniae* isolated from another site in addition to blood, residing the Southern US, and having an allergy to an antibiotic are independent risk factors for harboring a macrolide resistant organism.

Six percent of patients with identified pneumococcal bacteremia were already receiving an antibiotic as treatment for an infection at the time blood was drawn for culture. If the pneumococcus in these patients were fully susceptible to the antibiotic used, we suspect that these patients would have cleared the bacteremia, or when secondary to other focal infections, not have developed bacteremia.(20,21) Thus we consider these patients to have failed antimicrobial therapy. Among these patients, we observed a significantly higher rate of antimicrobial resistance, not only for the antibiotic they were currently receiving, but for other tested antibiotics as well. Thus, if a patient develops pneumococcal bacteremia while taking an antibiotic, the clinician should consider changing the antibiotic selected, or changing the dose or the route of therapy- taking into consideration the likelihood that the isolate will have reduced susceptibility or be non-susceptible to the current and other antibiotics. Due to the case-control design of this study, and the analysis of only patients that developed pneumococcal bacteremia, these results should not be extrapolated to all patients at risk of pneumococcal disease, particularly those with community-acquired pneumonia.

In our study, macrolides were the most common prior antibiotic used among patients that developed pneumococcal bacteremia, followed closely by sulfonamides. Penicillins and cephalosporins were used less frequently. Perhaps this is due to the fact that the use of beta-lactam antibiotics has been limited by the increasing prevalence of pneumococcal resistance to these agents. It should be noted that most of the decrease in cephalosporin and penicillin susceptibility attributed to prior antibiotic use appears to be due to an increase in intermediate resistant strains. Nearly all isolates, even among patients that had received prior antibiotic therapy, remained susceptible to quinolones.

Since the emergence of resistance of *S. pneumoniae* to beta-lactams such as penicillins, and to provide coverage against atypical pathogens, macrolides have become a mainstay of therapy for adults with pneumonia. Their use however has been questioned due to the rising rate of resistance of *S. pneumoniae* to macrolides over the past decade. Two types of macrolide resistance patterns have been identified among pneumococcal strains. “High level resistance”

is associated with the MLS_B phenotype, and the presence of the *erm* gene, which codes for ribosomal methylase. “Low/ intermediate level resistance” (M phenotype), is associated with presence of the mef gene, which codes for a macrolide efflux pump. Most macrolide resistance within the United States has been of the low level type; these pneumococci remain susceptible to clindamycin.(22) There are conflicting data on whether this type of resistance correlates with clinical failure among patients with invasive pneumococcal disease treated with macrolide antibiotics.(7,9,10,13,17,23,24)

The strongest predictor of macrolide resistance among patients with pneumococcal bacteremia was prior antibiotic use. Patients who have received > 24 hours of antibiotics therapy at the time the blood culture was drawn were four times more likely to harbor a macrolide resistant organism, compared to those not receiving prior antibiotic therapy. Prior antibiotic therapy was also a significant risk factor for harboring a penicillin and cephalosporin resistant organism. This is consistent with the results of numerous other studies, (7,8,12,25,26) and is not surprising, considering that the selective pressure exerted on organisms by antibiotics, forces species to develop mechanisms of resistance to allow for its survival. These results should be framed in the context that it is likely that the patients included in this study had organisms which were already resistant to the antibiotic prescribed. It is also not surprising that the most common antibiotics we observed used among patients that developed pneumococcal bacteremia were macrolides, as the current guidelines for treatment of community-acquired pneumonia recommend the use of a macrolide for outpatient treatment. Since this is a case-control study, we are essentially only including patients that did not successfully treat their infections, and thus, we are unable to draw any conclusions about the effectiveness of macrolides overall.

In our multivariate model, we found that residence in the Southern U.S. confers an increased risk of harboring a macrolide and penicillin resistant pneumococcal organism. This is consistent with the findings from the PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States) surveillance program conducted in 2000 / 2001, which found a high rate of penicillin and macrolide resistance among respiratory tract pathogens in the Southern U.S..(27) Higher rates of antibiotic resistance in general has been documented in the Southern U.S., where up to 38% of *Streptococcus pneumoniae* species are reported to be non-susceptible to penicillin, compared to approximately 25% nationwide.(17,25)

It is not entirely understood why patients with allergies to antibiotics would be more likely to harbor macrolide resistant organism. The presence or knowledge of an antibiotic allergy may serve as a proxy for prior or frequent antibiotic use. Hospitalization within the preceding month is also associated with harboring a penicillin and cephalosporin non-susceptible organism. This may be due to antibiotic therapy during hospitalization, to associated co-morbid conditions and / or immunosupression, or exposure to virulent strains.

Antibiotic non-susceptibility, male sex, increasing age, and admission to the hospital were associated with increased odds of mortality among patients with pneumococcal bacteremia. There is much debate over whether antibiotic resistance, and macrolide resistance in particular, contributes to clinical failure among individuals with invasive pneumococcal disease. We found that after adjusting for other factors, harboring an antibiotic non-susceptible organism conferred 40% higher odds of mortality. We did not collect detailed information regarding severity of illness, co-morbidities, hospital course (including antibiotics given), and thus the only predictors of mortality that we are able to comment on are those available at the time the patient developed bacteremia. These unmeasured factors are likely to affect mortality, and will require further study.

Although antibiotic therapy at the time the blood culture was obtained was found to be a risk factor for antibiotic resistance, it did not contribute to overall mortality. As noted above, there are many factors relating to hospital course that were not obtained as part of this study, and which may affect these results. Black race, and the presence of a focal infection, such as pneumonia, were associated with a decreased risk of mortality among patients with pneumococcal bacteremia. To our knowledge, this is the first study documenting a decreased risk of mortality among Blacks with pneumococcal bacteremia; the reason for this is not clear. Additionally, we would have predicted that patients without a focus of infection would have a better outcome, as a majority of children with *Streptococcus pneumoniae* bacteremia without an identified focus generally have an excellent outcome. Perhaps patients with a focus of infection are presenting for medical care earlier than patients without a focus of infection, who may be more critically ill upon arrival to the health care system.

Although this study involved 34 sites, it is possible that these sites were not representative of patients with pneumococcal bacteremia within the U.S., and may not be generalizable to all patients with pneumococcal bacteremia. Additionally, the type of macrolide resistance predominately seen in the U.S. (M phenotype) differs from that seen in Europe and other parts of the world (MLS_B phenotype). Thus outcomes of patients with pneumococcal bacteremia treated with macrolide antibiotics are likely to be different between the two populations. Due to our small number of pediatric patients (seven deaths), we are unable to assess risk factors for mortality in this age group.

One limitation of our case-control design is that the study population may not be representative of all patients that were prescribed antibiotics for presumed or possible pneumococcal infections. Macrolides were the most common antibiotic used among patients who developed pneumococcal bacteremia in our study, however they may not have been the most common antibiotic prescribed for infections that subsequently resulted in pneumococcal bacteremia. For example, patients that received penicillins or cephalosporins for their initial infection may have clinically improved and would not have developed pneumococcal bacteremia, and thus, would not be included in our study.

In summary, among patients with pneumococcal bacteremia we have identified the following risk factors for harboring a *S. pneumoniae* macrolide non-susceptible strain: residence in southern U.S., evidence of prior antibiotic therapy, and presence of an antibiotic allergy. We have also demonstrated that antibiotic non-susceptibility and male sex are risk factors for mortality among patients with pneumococcal bacteremia. Taken together, these observations increase our understanding of antibiotic resistance among patients with pneumococcal bacteremia, and provide a strong foundation for future prospective studies of therapy for pneumococcal infections.

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Table 1

Demographic Characteristics of Patients with Pneumococcal Bacteremia.

	Prior antibiotic therapy		NO prior antibiotic	
	n=99	**% (95%CI)**	**n=1423**	**% (95%CI)**
Age, years (median [IQR])	99	40 (33 − 48)	1423	47 (45 − 48)
Male sex	57	58 (47 − 67)	763	54 (51 − 56)
Race				
White	48	48 (38 − 59)	650	46 (43 − 48)
Black	28	28 (20 − 38)	535	38 (35 − 40)
Hispanic	18	18 (11 − 27)	171	12 (10 − 14)
Other*	5	5 (2 − 11)	67	5 (4 − 6)
Region				
Northeast	34	34 (25 − 45)	630	44 (42 − 47)
Midwest	19	19 (12 − 28)	359	25 (23 − 28)
South	19	19 (12 − 28)	243	17 (15 − 19)
West	27	27 (19 − 37)	191	13 (12 − 15)
Insurance Type				
Commercial/private HMO	36	36 (27 − 47)	483	34(31 − 36)
Medicaid	32	32 (23 − 42)	366	26(23 − 28)
Other public	19	19 (12 − 28)	318	22(21 − 25)
None	11	11 (6 − 19)	194	14 (12 − 16)
Missing/unknown	1	1 (0.03 − 5)	62	4(3 − 6)

* includes other race, Asian, missing, and, unknown

Table 2

Clinical Characteristics of Patients with Pneumococcal Bacteremia.

	Prior Antibiotic (n=99)	% (95% CI)	No Prior Antibiotic (n=1423)	% (95% CI)
Admitted within past 30 days	16	16 (10 − 25)	122	9 (7 − 10)
Immunocompromised	44	44 (34 − 55)	322	23 (20 − 25)
Antibiotic allergy	27	27 (19 − 37)	224	16 (14 − 18)
Focal Infection	77	78 (68 − 86)	1101	77 (75 − 80)
Site of infection *				
Pneumonia	62	63 (53 − 72)	910	64 (61 − 66)
Meningitis	10	10 (4 − 16)	39	3 (2 − 4)
Septic arthritis	1	1 (0 − 3)	15	1 (1 − 2)
Skin	0	0 (0 − 1)	10	1 (0 − 1)
Multiple sites	2	2 (0 − 7)	30	2 (1 − 3)
Otitis media, endocarditis, catheter, other	13	13 (6 − 20)	94	7 (5 − 8)
Missing	1	1 (0 − 5)	5	<1 (0 − 1)
If blood drawn in ED or Clinic:	N=78		N=1131	
ED/Clinic disposition				
Admit/observation	44	56 (45 − 68)	663	59 (56 − 62)
Admit ICU	26	33 (23 − 45)	259	23 (20 − 25)
Sent home/outpatient only	7	9 (4 − 18)	193	17 (15 − 19)
AMA / other	1	1 (.03 − 7)	16	1 (.8 − 2)
Final hospital disposition				
Sent home	70	71 (61 − 79)	1053	74 (72 −76)
Long term / rehab	8	8 (4 − 15)	143	10 (9 − 12)
Deceased	14	14 (8 − 23)	188	13 (11 − 15)
Other/missing	7	7 (3 − 14)	39	3 (2 − 4)

* not mutually exclusive

Table 3

Susceptibility testing

	Prior Antibiotic Use (n=99)				No Prior Antibiotic Use (n=1423)			
Antibiotic	Tested (n)	Susceptible % (95%CI)	Intermed %	Resistant %	Tested (n)	Susceptible % (95%CI)	Intermed %	Resistant %
Penicillins	98	49% (39−59)*	35%	16%	1404	78% (75−80)*	14%	8%
Cephalosporins§	88	82% (72−89)*	15%	3%	1203	92% (90−93)*	6%	2%
Macrolides	53	55% (41−68)*	4%	42%	889	84% (82−87)*	1%	15%
Clindamycin	43	84% (69−93)	0%	16%	528	95% (92−96)	2%	4%
Quinolones	47	96% (84−99)	0%	4%	665	99% (98−100)	<1%	1%
Tetracyclines	29	72% (53−87)*	3%	24%	454	94% (91−96)*	1%	6%
Sulfonamides	34	59% (41−75)	6%	35%	572	74% (70−77)	6%	20%

Comparisons made between proportion susceptible among two groups.

§ Cephalosporin testing includes testing for Ceftriaxone and Cefotaxime

* Non-overlapping confidence intervals signify significant at p< 0.05 level.

Table 4

Multivariate Models for Macrolide, Penicillin, and Cephalosporin (Ceftriaxone and Cefotaxime) Non-susceptibility

	Model for Macrolide Non-Susceptibility OR (95% CI)	Model for Penicillin Non-Susceptibility OR (95% CI)	Model for Cephalosporin Non-Susceptibility OR (95% CI)
Age (per 10 years ↑)	1.0 (0.92, 1.07)	1.0 (0.92, 1.03)	1.0 (0.90, 1.06)
Male	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.1 (0.7, 1.6)
White	1.3 (0.9, 1.9)	1.2 (0.9, 1.5)	1.0 (0.6,1.5)
Region			
Northeast	Reference	Reference	Reference
Midwest	0.9 (0.6, 1.5)	0.8 (0.6, 1.2)	0.8 (0.5, 1.4)
South	1.7 (1.1, 2.8)*	1.9 (1.4, 2.7)*	1.6 (0.9, 2.6)
West	1.2 (0.6, 2.2)	0.9 (0.6, 1.3)	0.3 (0.1, 0.7)*
Medicaid insurance	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	0.6 (0.3, 0.96)*
Evidence of prior antibiotic drug therapy	4.0 (2.1, 7.3)*	3.3 (2.1, 5.1)*	2.0 (1.04, 3.8)*
Immunosuppressed patient	1.5 (1.0, 2.2)	1.5 (1.1, 2.0)*	1.3 (0.8, 2.1)
Admitted over night in past month	1.5 (0.9, 2.5)	1.5 (1.01, 2.3)*	2.6 (1.5, 4.5)*
Focal infection	0.9 (0.6, 1.4)	0.9 (0.7,1.3)	0.7 (0.4, 1.1)
Antibiotic allergy	1.7 (1.1, 2.6)*	1.3 (0.9, 1.8)	1.4 (0.9, 2.3)

Macrolide Model

Of n=893 in model, n=159 had intermediate/resistant test results.

Area under the ROC curve: 0.67, Hosmer-Lemeshow goodness of fit p-value: 0.56

Penicillin Model

Of n=1412 in model, n=350 with intermediate/resistant test results.

Area under the ROC curve: 0.65, Hosmer-Lemeshow p-value: 0.57

Cephalosporin Model

Of n=1210 in model, n=111 with intermediate/resistant test results.

Area under the ROC curve: 0.69, Hosmer-Lemeshow p-value: 0.49

*Confidence intervals that do not cross 1 are statistically significant

Table 5

Multivariate model of mortality

	Odds Ratio	95% CI	
Any antibiotic non-susceptible strain (including macrolide, penicillin, cephalosporin)	1.4*	1.01	2.1
Evidence of prior antibiotic drug therapy	1.0	0.5	1.9
Inpatient or admitted from ED §	5.1*	2.0	13.0
Age (per 10 year increase)	1.3*	1.2	1.4
Male	1.4*	1.02	2.0
Race			
White	1.0	Reference	
Black	0.6*	0.4	0.9
Hispanic	1.3	0.7	2.2
Other	0.8	0.3	2.0
Region			
Northeast	1.0	Reference	
Midwest	1.2	0.8	1.7
South	0.7	0.4	1.2
West	1.0	0.6	1.6
Insurance status			
Private/commercial	1.0	Reference	
Medicaid	0.9	0.5	1.4
Other public	1.0	0.7	1.5
None	1.3	0.8	2.2
Admitted overnight in past month	1.6	0.99	2.6
Immunosuppressed	1.2	0.98	1.5
Focal infection	0.6*	0.4	0.9
Allergy to antibiotics	1.0	0.7	1.4

Of n=1433 in model, there were 189 deaths

Area under ROC 0.73, Hosmer-Lemeshow p-value =0.42

* Confidence intervals that do not cross 1 are statistically significant

§ Definition of "Inpatient or admitted from ED": If blood culture location is inpatient OR if blood culture location is ED and disposition=admitted OR if blood culture location is clinic and disposition=admitted