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Evaluation of Pneumococci From the United States (USA) Pediatric Patients Isolated During the 2009 AWARE Program

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Amended Abstract

Background: Ceftaroline, the active form of ceftaroline fosamil, is a novel broad-spectrum cephalosporin with activity (MIC ≥ 0.25 µg/mL) against *S. pneumoniae* (SPN), including penicillin-resistant (PRSP; penicillin MIC ≥ 8 µg/mL) isolates. Ceftaroline fosamil is approved in the USA for CABP caused by SPN and is also under review in Europe. We analyzed the data from the 2009 AWARE Surveillance Program to compare SPN recovered from pediatric and adult patients in the USA.

Methods: Consecutive SPN (n = 1222) were collected from patients at 52 sites representing all 9 USA census regions. Isolates were stratified for analysis by age of patients in years: ≤ 2 (n = 170), 3 - 5 (n = 82), 6 - 14 (n = 94), 15 - 17 (n = 14), 18 - 64 (n = 578) and ≥ 65 (n = 284). MICs were determined centrally using CLSI methods.

Results: PRSP were rare, ranging from no isolates in patients aged 15 - 17 years to 4.3% in 6 - 14 year olds. Ceftriaxone resistance (R) occurred in up to 5.9% of isolates from patients ≤ 2 years. Amoxicillin-clavulanate R was prominent in isolates of patients aged ≤ 2 years (30%) but decreased to 8.8% in patients ≥ 65 years. Inverse correlations between age and MIC were also noted with clindamycin, tetracycline, and trim/sulfa, with MICs decreasing from 31.8% to 18.3%, 36.5% to 20.1%, and 40.6% to 19.7%, respectively. MDR isolates (R to ≥ 2 classes) were also most common in patients ≤ 14 years (50%), decreased to 21.4% amongst 15 - 17 year olds and leveled off at approximately 26% in adults. These trends may reflect the impact of the pneumococcal conjugate vaccine, which was introduced in the USA in 2000.

Ceftaroline was active against isolates from all infection sources/patient age groups and with varying resistance profiles. Using the FDA breakpoint of 0.25 µg/mL, 98.5% of SPN recovered in this study were susceptible to ceftaroline.

Conclusion: Activity of ceftaroline was consistent against SPN isolates obtained from all age groups during the 2009 AWARE program. Varying R patterns for other agents were noted that may correlate with antimicrobial prescribing habits and the use of the pneumococcal conjugate vaccine in younger patients. Further investigation of ceftaroline in pediatric patients is warranted.

Introduction

Ceftaroline, the active form of ceftaroline fosamil, is a new broad-spectrum cephalosporin with activity against *Streptococcus pneumoniae* including penicillin-resistant *S. pneumoniae* (PRSP) isolates. Like other β-lactams, the mechanism of action of ceftaroline includes binding to penicillin-binding proteins (PBPs) and interference with new bacterial cell wall synthesis. Unlike most other β-lactams, ceftaroline retains activity against PRSP isolates as a result of its high affinity for PBP2x. Ceftaroline fosamil was recently approved by the United States Food and Drug Administration (FDA) and is under review in Europe for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia in patients over 18 years of age.

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program has been initiated to monitor the susceptibility of ceftaroline and comparator agents against contemporary clinical isolates from around the world. The data for US *S. pneumoniae* isolates from the 2009 study were analyzed to determine if there were differences in susceptibility and isolate demographics across various patient age groups. Percentages of isolates that were PRSP, resistant rates, and isolate antibiograms were compared.

Methods

Consecutive *S. pneumoniae* isolates (n = 2311) were collected from patients at 52 sites representing the 9 US Census Bureau regions. Only 1 isolate was collected per patient. Isolates were divided for analysis by patient age in years: ≤ 2 (n = 170), 3 - 5 (n = 82), 6 - 14 (n = 94), 15 - 17 (n = 14), 18 - 64 (n = 578), ≥ 65 (n = 284). MICs were determined using the Clinical and Laboratory Standards Institute (CLSI) method as outlined in document M07-A8 (2008) and using validated broth microdilution dry-form panels acquired from TREK Diagnostics (Cleveland, OH). Susceptibility interpretive criteria were as outlined in CLSI M100-S20 (2010) for all comparator agents (the non-meningitis resistance breakpoint of ≥ 8 µg/mL was used for penicillin). US FDA-approved MIC breakpoints (susceptible ≤ 0.25 µg/mL; Teflaro® package insert) were used in lieu of CLSI breakpoints for ceftaroline. Data were analyzed by patient age to identify trends in antibiotic resistance.

Results

The number of isolates by body site is shown in Table 1. MICs for ceftaroline and comparator agents by age group are shown in Table 2.

- PRSP isolates (MIC ≥ 8 µg/mL) were very rare across all age groups. Approximately 2.5% of *S. pneumoniae* isolates from adult patients and approximately 4% from patients aged 0 - 2 and 6 - 14 years were penicillin-resistant. One of 82 isolates (1.2%) from patients aged 3 - 5 years was PRSP. No penicillin-resistant isolates were recovered from patients aged 15 – 17 years. Penicillin-non-susceptible (intermediate and resistant) isolates, however, were more common, particularly amongst children and adolescents (Figure 1)
- In general, inverse correlations between patient age and the incidences of isolates resistant to amoxicillin-clavulanate, clindamycin, erythromycin, tetracycline and trimethoprim-sulfamethoxazole (SXT) were noted (Figures 2 - 6). Amoxicillin-clavulanate resistance was prominent in isolates of patients aged ≤ 2 years (30.0%) but decreased to 8.8% in patients ≥ 65 years. Resistance to clindamycin, erythromycin, tetracycline and SXT decreased from 31.8% to 18.3%, 55.9% to 35.2%, 36.5% to 20.1% and 40.6% to 19.7%, across the same age groups, respectively
- A similar trend was observed between patient age and the incidence of multidrug-resistant (MDR; resistant to ≥ 2 classes of antimicrobials) isolates. In patients from the following age groups (in years), MDR rates were 0 - 2, 50.0%; 3 - 5, 36.6%; 6 - 14, 31.9%; 15 - 17, 21.4%; 18 - 64, 26.8% and ≥ 65, 26.1% (Figure 7)
- Non-susceptibility to ceftriaxone varied from 24.1% in patients aged ≤ 2 years to 7.1% in patients aged 15 - 17 years
- Non-susceptibility to levofloxacin was rarely observed (0.7% of all isolates). As expected, no linezolid- or vancomycin-non-susceptible isolates were recovered in this study (Table 2)
- Ceftaroline was consistently active against isolates from all age groups, with 98.5% of isolates being susceptible according to the US FDA breakpoint of 0.25 µg/mL.

Table 1. Numbers of *Streptococcus pneumoniae* Isolates Recovered by Infection Body Site

Body site	0 - 2 years (N = 170)	3 - 5 years (N = 82)	6 - 14 years (N = 94)	15 - 17 years (N = 14)	18 - 64 years (N = 578)	≥ 65 years (N = 284)
Bloodstream	39	15	23	3	151	72
Respiratory tract	103	63	66	10	395	204
Skin/skin structure	7	-	2	-	10	1
Urinary tract	-	1	1	-	-	-
Other	21	3	2	1	22	7

Table 2. MIC_{90} Values of Ceftaroline and Comparator Agents Against *Streptococcus pneumoniae* From the 2009 AWARE Surveillance Program

	MIC_{90} (µg/mL; % susceptible)					
Antimicrobial agent	0 - 2 years (N = 170)	3 - 5 years (N = 82)	6 - 14 years (N = 94)	15 - 17 years (N = 14)	18 - 64 years (N = 578)	≥ 65 years (N = 284)
Ceftaroline	0.25 (96.5)	0.25 (100)	0.25 (97.9)	0.12 (100)	0.25 (98.4)	0.12 (99.3)
Amox/clav	8 (65.0)	8 (74.4)	8 (80.9)	8 (85.7)	8 (85.3)	4 (89.4)
Ampicillin	8 (NA)	8 (NA)	8 (NA)	8 (NA)	8 (NA)	4 (NA)
Ceftriaxone	2 (75.9)	2 (80.5)	2 (86.2)	1 (92.9)	2 (89.4)	1 (91.5)
Cefuroxime	> 8 (53.5)	> 8 (60.5)	8 (66.0)	4 (85.7)	8 (77.4)	8 (79.5)
Clindamycin	> 2 (68.2)	> 2 (69.5)	> 2 (80.9)	> 2 (78.6)	> 2 (82.0)	> 2 (81.3)
Erythromycin	> 2 (43.5)	> 2 (56.1)	> 2 (59.6)	> 2 (64.3)	> 2 (65.2)	> 2 (64.1)
Levofloxacin	1 (100)	1 (100)	1 (98.9)	1 (100)	1 (99.0)	2 (99.3)
Linezolid	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
Penicillin	4 (69.4)	4 (78.0)	4 (81.9)	2 (92.9)	4 (86.2)	2 (90.1)
Tetracycline	> 8 (63.5)	> 8 (69.5)	> 8 (77.7)	> 8 (85.7)	> 8 (77.0)	> 8 (79.6)
SXT	> 2 (47.6)	> 2 (58.5)	> 2 (64.9)	> 2 (71.4)	> 2 (68.7)	> 2 (71.5)
Vancomycin	≤ 1 (100)	≤ 1 (100)	≤ 1 (100)	≤ 1 (100)	1 (100)	≤ 1 (100)

Abbreviations: Amox/clav = amoxicillin-clavulanate; AWARE = Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance program; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; SXT = trimethoprim-sulfamethoxazole.

Figure 1. Frequency of Penicillin Non-susceptibility by Patient Age Group

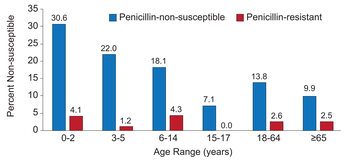


Figure 2. Frequency of Amoxicillin-clavulanate-resistant *Streptococcus pneumoniae*

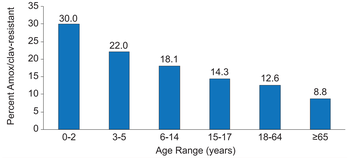


Figure 3. Frequency of Clindamycin-resistant *Streptococcus pneumoniae*

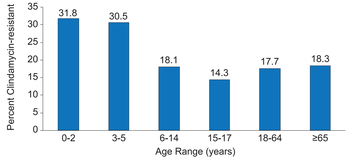


Figure 4. Frequency of Erythromycin-resistant *Streptococcus pneumoniae*

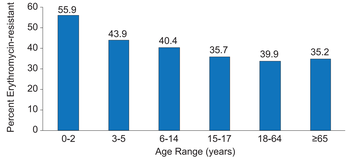


Figure 5. Frequency of Tetracycline-resistant *Streptococcus pneumoniae*

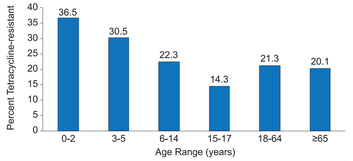


Figure 6. Frequency of Trimethoprim-sulfamethoxazole-resistant *Streptococcus pneumoniae*

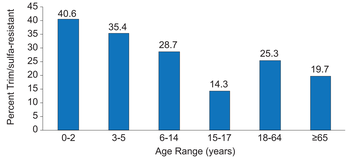
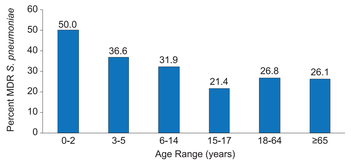


Figure 7. Frequency of Multidrug-resistant *Streptococcus pneumoniae*



Conclusions

- The data in this study suggest that PRSP (MIC ≥ 8 µg/mL) are rare amongst patients from all age groups in the US
- Resistance trends appeared to correlate well with antibiotic prescribing habits and the use of the pneumococcal conjugate vaccine in younger patients, as resistance for most classes of antibiotics appeared to generally decrease with patient age
- As expected, resistance to levofloxacin, linezolid, and vancomycin was rare or not found amongst the *S. pneumoniae* in this study
- Ceftaroline maintained consistent activity against the *S. pneumoniae* isolates evaluated as part of the 2009 AWARE program, irrespective of patient age or infection source. The ceftaroline MIC_{90}s for the isolates evaluated in this study were either 0.12 or 0.25 µg/mL for the isolate groups. Ceftaroline susceptibility ranged from 96.5% - 100% using the FDA interpretive criteria. These data support the further evaluation of ceftaroline against SPN, including PRSP and MDR isolates, in pediatric patients.

References

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CLSI. M100-S20 Performance Standards for Antimicrobial Susceptibility testing, 20th ed. Wayne, PA.

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