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Antimicrobial Activity of Ceftaroline and Comparator Agents against Ceftriaxone-Nonsusceptible *Streptococcus pneumoniae* from the United States (2008–2020)

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CONCLUSIONS

Ceftaroline demonstrated potent and consistent activity (≥99.9%S) over time (2008–2020) against a large collection of *S. pneumoniae* from US medical centers, including ceftriaxone-nonsusceptible, MDR, and XDR isolates.

Only 1 of >20,000 *S. pneumoniae* isolates tested between 2008 and 2020 was nonsusceptible to ceftaroline.

RESULTS

- Ceftaroline was active against >99.9% of ceftriaxone-nonsusceptible *S. pneumoniae* ($MIC_{50/90}$, 0.25/0.25 mg/L); only 1 isolate had a ceftaroline MIC ≥0.5 mg/L (Table 1).
- Ceftriaxone susceptibility varied from 86.9% in 2009 to 98.8% in 2019 and increased from 89.0% in 2008–2011 to 98.1% in 2018–2020 (Figures 1 and 2).
- The ceftaroline-nonsusceptible isolate exhibited
  - Ceftaroline and ceftriaxone MIC values of 1 and 8 mg/L, respectively
  - Multiple substitutions in the penicillin binding proteins (PBP), mainly PBP2x, when compared with reference sequences
  - Showed 31 amino acid alterations in MurM
- The most active comparator agents against ceftriaxone-nonsusceptible *S. pneumoniae* were linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 100.0%S), levofloxacin ($MIC_{50/90}$, 1/1 mg/L; 98.1%S), tigecycline ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 95.5%S), and vancomycin ($MIC_{50/90}$, ≤1/≤1 mg/L; 100.0%S; Table 1).
- Ceftriaxone-nonsusceptible isolates exhibited high resistance rates to azithromycin (98.2%), doxycycline (88.1%), and meropenem (82.1%; Table 1).
- Overall, 20.5% of isolates were MDR and 7.9% were XDR (Table 1).
- MDR and XDR rates decreased from 24.4% and 13.5% in 2008–2011 to 16.8% and 2.4% in 2018–2020, respectively (Figure 3).
- Ceftaroline retained potent activity against MDR ($MIC_{50/90}$, 0.12/0.25 mg/L; >99.9%S) and XDR ($MIC_{50/90}$, 0.25/0.25 mg/L; 100.0%S) isolates. Ceftriaxone exhibited limited activity against both MDR ($MIC_{50/90}$, 1/2 mg/L; 68.9%S) and XDR ($MIC_{50/90}$, 2/2 mg/L; 26.7%S) isolate subsets.
- Among ceftriaxone-nonsusceptible isolates, 97.7% were MDR and 88.2% were XDR.

Table 1. Antimicrobial activity of ceftaroline and comparator agents against ceftriaxone-nonsusceptible, MDR, and XDR *S. pneumoniae* from US medical centers (2008–2020)

Antimicrobial agent	MIC (mg/L)		CLSI[a]	
	MIC_{50}	MIC_{90}	%S	%R
Ceftriaxone-nonsusceptible (1,419)				
Ceftaroline	0.25	0.25	99.9	
Ceftriaxone	2	>2	0.0 [b] 0.0 [c]	15.2 [b] 100.0 [c]
Amox-clav (2:1 ratio)	>4	>4	7.3 [b]	86.7 [b]
Azithromycin	>4	>4	1.1	98.2
Clindamycin	>1	>1	17.3	82.3
Dalbavancin	≤0.03	≤0.03		
Doxycycline	>1	>1	11.2	88.1
Erythromycin	>2	>2	1.9	98.0
Levofloxacin	1	1	98.1	1.6
Linezolid	0.5	1	100.0	
Meropenem	1	1	2.5	82.1
Penicillin	4	>4	10.5 [d] 0.3 [e]	11.1 [d] 99.7 [e]
Tetracycline	>4	>4	10.0	89.9
Tigecycline	≤0.03	0.06	95.5 [f]	
TMP-SMX	>2	>2	3.0	95.3
Vancomycin	≤1	≤1	100.0	
MDR (4,454)				
Ceftaroline	0.12	0.25	>99.9	
Ceftriaxone	1	2	68.9 [b] 49.4 [c]	4.7 [b] 31.1 [c]
Amox-clav (2:1 ratio)	≤1	>4	55.9 [b]	37.7 [b]
Azithromycin	>4	>4	0.5	98.9
Clindamycin	>1	>1	20.6	78.1
Dalbavancin	≤0.03	≤0.03		
Doxycycline	>1	>1	6.6	92.8
Erythromycin	>2	>2	0.2	99.4
Levofloxacin	1	1	97.4	2.4
Linezolid	0.5	1	100.0	
Meropenem	0.5	1	49.9	36.1
Penicillin	1	4	60.3 [d] 10.5 [e]	3.7 [d] 89.5 [e]
Tetracycline	>4	>4	5.1	94.6
Tigecycline	≤0.03	0.06	96.9 [f]	
TMP-SMX	>2	>2	22.7	57.4
Vancomycin	≤1	≤1	100.0	
XDR (1,708)				
Ceftaroline	0.25	0.25	100.0	
Ceftriaxone	2	2	26.7 [b] 1.6 [c]	10.0 [b] 73.3 [c]
Amox-clav (2:1 ratio)	>4	>4	3.8 [b]	89.4 [b]
Azithromycin	>4	>4	0.3	99.4
Clindamycin	>1	>1	5.0	94.5
Dalbavancin	≤0.03	≤0.03		
Doxycycline	>1	>1	1.8	97.9
Erythromycin	>2	>2	0.0	100.0
Levofloxacin	1	1	96.7	2.9
Linezolid	0.5	1	100.0	
Meropenem	1	1	1.5	84.4
Penicillin	4	>4	4.9 [d] 0.2 [e]	9.0 [d] 99.8 [e]
Tetracycline	>4	>4	1.6	98.4
Tigecycline	≤0.03	0.06	96.9 [f]	
TMP-SMX	>2	>2	0.4	98.4
Vancomycin	≤1	≤1	100.0	

[a] Criteria as published by CLSI (2021).
[b] Using non-meningitis breakpoints.
[c] Using meningitis breakpoints.
[d] Using parenteral, non-meningitis breakpoints.
[e] Using parenteral, meningitis breakpoints.
[f] US FDA breakpoints were applied.
Abbreviations: Amox-clav, amoxicillin-clavulanate; TMP-SMX, trimethoprim-sulfamethoxazole; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Figure 1. Ceftriaxone yearly susceptibility rates when tested against *S. pneumoniae* from US medical centers

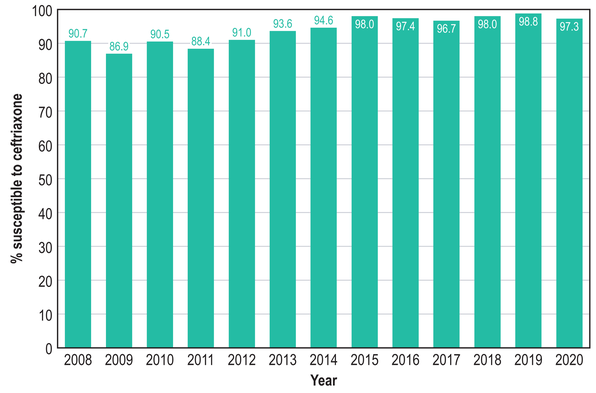


Figure 2. Susceptibility of *S. pneumoniae* to ceftaroline, ceftriaxone, and amoxicillin-clavulanate over time (2008–2020)

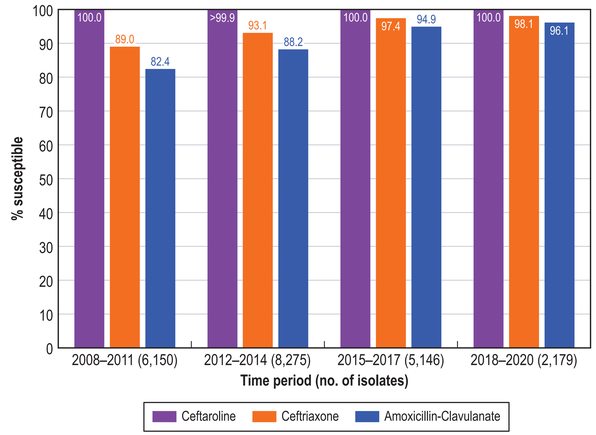
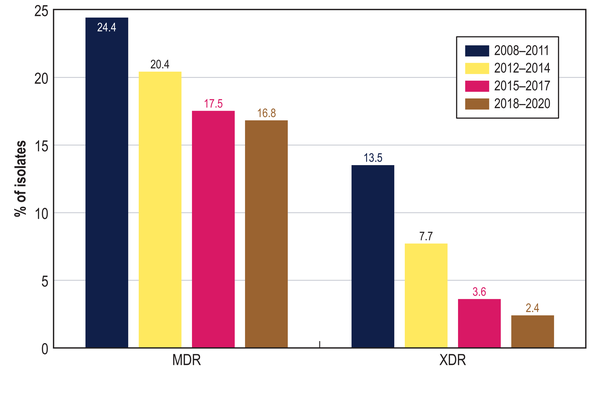


Figure 3. Frequencies of multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes



INTRODUCTION

- Ceftaroline is a broad-spectrum cephalosporin with potent activity against *Streptococcus pneumoniae*, including multidrug-resistant (MDR) strains.
- Ceftaroline fosamil was approved by the US Food and Drug Administration (US FDA) in 2010 for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSSI).
- We evaluated the activity of ceftaroline against isolates of ceftriaxone-nonsusceptible *S. pneumoniae* from US medical centers.

METHODS

- A total of 21,750 *S. pneumoniae* isolates were consecutively collected (1 per patient) from 201 medical centers in 2008–2020.
- Among these isolates, 1,419 (6.5%) were ceftriaxone-nonsusceptible (MIC, ≥2 mg/L).
- Other resistant subgroups analyzed included:
  - Multidrug-resistant (MDR): 4,454 isolates
    - Nonsusceptible to ≥3 classes
  - Extensively drug-resistant (XDR): 1,708 isolates
    - Nonsusceptible to ≥5 classes

METHODS

- Drug classes were represented by penicillin (MIC, ≥4 mg/L), ceftriaxone (MIC, ≥2 mg/L), erythromycin (MIC, ≥0.5 mg/L), clindamycin (MIC, ≥0.5 mg/L), levofloxacin (MIC, ≥4 mg/L), tetracycline (MIC, ≥2 mg/L), and trimethoprim-sulfamethoxazole (MIC, ≥1 mg/L)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).
- Participating laboratories identified isolates and JMI confirmed bacterial identifications by standard algorithms and/or MALDI-TOF.
- Isolates were tested for susceptibility by broth microdilution following CLSI M07 (2018) standards.

DISCLOSURES

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