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High Rates of Non-Susceptibility to Common Oral Antibiotics Among *Streptococcus pneumoniae* Clinical Isolates from the United States (2019–2021)

Lalitagauri M. Deshpande, Michael D. Huband, Sarah Charbon, Mariana Castanheira, Rodrigo E. Mendes
JMI Laboratories, North Liberty, IA, USA

Introduction

- Major guidelines, such as those from the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Canadian Guidelines, recommend macrolides, β-lactams, doxycycline, or respiratory quinolone monotherapy for the initial management of community-acquired bacterial pneumonia (CABP) for outpatients who are otherwise generally healthy.
- Outpatients with comorbidities represent the greatest disease burden, and combination therapy (e.g., macrolide or doxycycline plus β-lactam) is recommended for these cases.
- CDC has issued a cautionary note about the development of resistance on quinolone monotherapy for treating CABP. In addition, these agents are associated with serious adverse events affecting the musculoskeletal, peripheral nervous, and central nervous systems.
- Various studies have reported rates of macrolide resistance ≥25% for *Streptococcus pneumoniae* isolates in all US Census Divisions.
  - According to the SENTRY Antimicrobial Surveillance Program, a total of 45% and 23% of *S. pneumoniae* from the US were not susceptible to macrolides and doxycycline, respectively, in 2022.
  - In addition, 34% of *S. pneumoniae* were not susceptible to oral penicillin agents.
- Omadacycline is an aminomethylcycline antibiotic derived from the tetracycline class, with structural modifications to overcome the most common clinical mechanisms of acquired tetracycline resistance, namely efflux pumps and ribosomal protection proteins.
  - The most prevalent mechanism of tetracycline resistance in *S. pneumoniae* is the *tet*(M) gene encoding a ribosomal protection protein, which reduces the activity of doxycycline and minocycline, but does not impact omadacycline activity.
- In a CABP clinical trial, omadacycline showed clinical efficacy similar to moxifloxacin as monotherapy and was approved by the US FDA in 2018 for treatment of adults with CABP.
- In this study, the activity of omadacycline and comparator agents, including those recommended for CABP, was evaluated against *S. pneumoniae* isolates from the US.
  - The tetracycline resistance mechanisms in *S. pneumoniae* isolates with select doxycycline MIC values were also evaluated.

Conclusions

- The options recommended for empiric treatment of outpatients with CABP demonstrated low susceptibility rates when tested against *S. pneumoniae* causing pneumonia, regardless of US Census Division.
  - Among amoxicillin/clavulanic acid or cefpodoxime non-susceptible isolates, doxycycline and azithromycin had very limited activity.
  - Doxycycline and azithromycin did not have activity against isolates carrying the *tet*(M) gene.
- Omadacycline inhibited >99% of isolates recovered from patients across all US Census divisions, regardless of resistance phenotype, *tet*(M) genotype, or serotype.
- *tet*(M) remained the sole tetracycline resistance mechanism detected, which did not affect omadacycline activity but significantly reduced doxycycline susceptibility.
- These data suggest that omadacycline represents a potential empiric option for treating pneumonia caused by *S. pneumoniae* in the USA, including against isolates carrying the most common tetracycline resistance gene *tet*(M).

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Materials and Methods

- A total of 1,038 *S. pneumoniae* isolates from 31 US centers (2019–2021) were included in the study.
  - Based on the patient's demographic information, 90.0% (933/1,038) of isolates were associated with CABP, whereas 3.0% (33/1,038) were associated with pneumonia from nosocomial origin.
  - Among these isolates, 7.0% (72/1,038) were from invasive infections.
- Isolates were tested for susceptibility by broth microdilution according to CLSI. Quality control (QC) was performed according to the CLSI M100 guidelines.
  - Multidrug-resistant (MDR) *S. pneumoniae* was defined as isolates not susceptible to amoxicillin-clavulanic acid, cefpodoxime, and doxycycline.
- A total of 115 *S. pneumoniae* isolates were selected for further characterization based on the doxycycline MIC results (decreased susceptibility). These *S. pneumoniae* included:
  - 75 isolates with doxycycline MIC results (0.25–2 mg/L) around the CLSI breakpoints (≤0.25 mg/L for susceptible; 0.5 mg/L for intermediate; and ≥1 mg/L for resistant).
  - In addition, a random collection of 40 doxycycline-resistant isolates (MIC, 4–>8 mg/L) was included.
- Whole genome sequencing was conducted using MiSeq (Illumina, San Diego, CA, USA).
  - Total genomic DNA was used as input material for library construction.
  - DNA libraries were prepared using the Illumina DNA™ library construction protocol and index kit (Illumina, San Diego, CA) and sequenced on a NextSeq 1000 Sequencer using NextSeq™ 1000/2000 P2 Reagents (300 cycles; Illumina).
- Assembled contigs were used for *in silico* screening of resistance genes and serotyping.
  - Isolates were screened for >80 acquired tetracycline resistance genes and target site mutations against reference-curated databases.

Results

- In general, 99.8% of *S. pneumoniae* isolates were inhibited by omadacycline at the FDA breakpoint for susceptibility (i.e., ≤0.12 mg/L). The remaining 0.2% of isolates (n=2) had intermediate susceptibility results for omadacycline (i.e., 0.25 mg/L) (Table 1).
  - High susceptibility rates were also observed for levofloxacin (99.7%; CLSI guidelines) and tigecycline (98.4%; FDA criteria) (Table 1).
- Other agents, such as penicillin (63.5% susceptible; oral breakpoint), doxycycline (80.2% susceptible), and azithromycin (54.3% susceptible), had limited activity overall against the entire collection.

Table 1. Activity of omadacycline and comparator agents tested against 1,038 *S. pneumoniae* isolates

Antimicrobial agent	MIC (mg/L)			CLSI[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Omadacycline	0.06	0.06	≤0.015 to 0.25	99.8 [b, c]	0.2	0.0
Doxycycline	0.12	4	≤0.008 to >8	80.3	0.8	19.0
Tetracycline	0.25	>4	0.06 to >4	79.6	0.4	20.1
Tigecycline	0.03	0.06	≤0.008 to 0.12	98.4 [b]		
Penicillin	0.03	2	≤0.008 to >4	63.5 [d] 63.5 [e] 96.8 [f]	26.0 3.1	10.5 36.5 0.1
Amoxicillin-clavulanic acid [g]	≤0.03	2	≤0.03 to >4	95.7	2.3	2.0
Cefpodoxime	0.03	2	≤0.004 to >8	76.8	6.6	16.7
Ceftriaxone	0.03	1	≤0.015 to >2	98.1 [g]	1.3	0.6
Levofloxacin	1	1	0.25 to >4	99.7 [h]	0.0	0.3
Erythromycin	0.06	>16	≤0.03 to >16	54.0	0.8	45.2
Azithromycin	0.12	>4	≤0.03 to >4	54.4	0.9	44.7
Clindamycin	≤0.25	>2	≤0.25 to >2	86.6	0.7	12.7
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	71.8	12.3	15.9

[a] Criteria as published by CLSI (2023).
[b] US FDA breakpoints applied.
[c] Using breakpoints for CABP.
[d] Using oral breakpoints.
[e] Using parenteral, meningitis breakpoints.
[f] Using parenteral, non-meningitis breakpoints.
[g] Testing amoxicillin-clavulanic acid with a 2:1 ratio.

- Several agents also had limited activity in every US Census Division (Table 2), including oral penicillin (≤83.9% susceptible), doxycycline (≤88.9% susceptible), and azithromycin (≤84.0% susceptible), with the sole exception of doxycycline (93.3% susceptible) against isolates from the Pacific region.
- Among 115 *S. pneumoniae* selected for characterization of resistance mechanisms, 61 (53.0%) isolates carried *tet*(M).
  - These included 52/52 doxycycline-resistant (MIC, ≥1 mg/L), 5/7 -intermediate (MIC, 0.5 mg/L), and 4/56 -susceptible (MIC, 0.25 mg/L) isolates.
  - *tet*(M) positive isolates showed low susceptibility to tetracycline (1.6%) and azithromycin (3.3%) (Table 2).
  - Cefpodoxime (68.9% susceptible) and amoxicillin-clavulanic acid (82.0% susceptible) had suboptimal activity against this molecularly characterized subset, whereas other agents showed even lower susceptibility rates of ≤36.1% (Table 2).
- Additional tetracycline resistance mechanisms, such as target site mutations or acquired genes other than *tet*(M), were not observed.
- Only omadacycline (100% susceptible), levofloxacin (98.4%–100% susceptible), and tigecycline (96.7%–97.8% susceptible) remained active against amoxicillin-clavulanic acid or cefpodoxime non-susceptible, *tet*(M), and MDR *S. pneumoniae* (non-susceptibility to amoxicillin-clavulanic acid, cefpodoxime, and doxycycline) (Table 2).
- The 115 *S. pneumoniae* isolates that were further evaluated belonged to 21 serotypes in total.
  - Serotypes 22F (15/115; 13.0%), 15A (14/115; 12.2%), 35B (12/115; 10.4%), and 23A (12/115; 10.4%) were the most common (>10 isolates) among the doxycycline susceptible and non-susceptible *S. pneumoniae* (Table 2).

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Contact

Rodrigo E. Mendes, Ph.D., FIDSA
Director, JMI Laboratories
345 Beaver Kreek Center, Suite A
North Liberty, Iowa 52317 USA
rodrigo.mendes@element.com

Table 2. Susceptibility profiles of *S. pneumoniae* isolate subsets

Isolates (No. tested)	Antimicrobial agent (% susceptible)[a]								
	Omadacycline	Penicillin	Cefpodoxime	Tetracycline	Doxycycline	Tigecycline	Azithromycin	Amoxicillin/ clavulanic acid	Levofloxacin
Overall (1,038)	**99.8**	**63.5**	**76.8**	**79.5**	**80.2**	**98.4**	**54.4**	**95.6**	**99.7**
US Census Division									
New England (130)	100	73.1	85.4	66.1	69.2	100	49.2	99.2	99.2
Middle Atlantic (119)	100	62.2	73.9	74.6	74.8	97.5	58.0	94.0	100
East North Central (184)	99.5	60.3	76.6	87.0	86.4	98.4	58.7	95.6	100
West North Central (114)	100	64.9	79.8	84.2	85.1	96.5	47.4	99.1	100
South Atlantic (114)	99.1	56.1	68.4	75.4	76.3	99.1	43.0	93.0	100
East South Central (71)	100	56.3	70.4	76.0	76.1	100	47.9	88.6	100
West South Central (150)	100	51.3	65.3	76.7	76.7	97.3	41.3	94.0	99.3
Mountain (81)	100	83.9	88.9	87.6	88.9	97.5	76.5	96.3	98.8
Pacific (75)	100	74.7	90.7	92.0	93.3	100	84.0	100	100
Antibiotic resistant subsets									
Amoxicillin-clavulanic acid NS (45)	100	0.0	0.0	24.4	16.1	97.8	0.0	0.0	100
Cefpodoxime NS (241)	99.6	0.4	0.0	67.1	67.6	97.9	8.3	81.3	99.2
MDR (34)	100	0.0	0.0	0.0	0.0	97.1	0.0	0.0	100
Molecularly characterized (115)	99.1	48.7	70.4	47.8	48.7	96.5	30.4	89.6	99.1
tet(M) isolates (61)	100	36.1	68.9	1.6	6.6	96.7	3.3	82.0	98.4
Serotypes									
22F (15)	100	100	100	93.3	86.7	93.3	73.3	100	100
15A (14)	100	0.0	71.4	7.1	7.1	100	0.0	92.9	100
35B (12)	100	0.0	0.0	83.3	83.3	100	8.3	83.3	100
23A (12)	100	41.7	83.3	33.3	33.3	91.7	33.3	100	100

[a] CLSI breakpoints applied to all agents, except for omadacycline and tigecycline (US FDA); NS, non-susceptible; oral breakpoint for penicillin against isolates causing infections other than meningitis; MDR, defined as *S. pneumoniae* isolates non-susceptible to amoxicillin-clavulanic acid, cefpodoxime, and doxycycline per CLSI criteria.