A Multi-center Evaluation of the US Prevalence and Regional Variation in Macrolide-resistant Streptococcus pneumoniae from Blood or Respiratory Cultures Among Adult Patients

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INTRODUCTION & PURPOSE

- *S. pneumoniae* is the most common etiology for community-acquired bacterial pneumonia (CABP).[1-2]
- Because of the significant healthcare burden associated with *S. pneumoniae*, the US Centers for Disease Control and Prevention (CDC) designated drug-resistant *S. pneumoniae* a pathogen of serious threat.[3]
- Macrolides have long been an important component of empiric CABP therapy; but increasing resistance has diminished effectiveness and prompted a change in the 2019 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for CABP treatment.[2]
- Namely, although macrolide monotherapy is still considered an option for initial treatment of CABP in outpatients with no comorbid conditions, the ATS/IDSA 2019 update specifies that this therapy should only be used if local Pneumococcal resistance is <25%.[2]

OBJECTIVE

- We used microbiological laboratory data from a large US hospital database to determine the prevalence of macrolide-resistant *S. pneumoniae* in hospitalized and ambulatory patients throughout the US.

METHODS

Study Design

- This retrospective cohort study included microbiological results from adult patients with positive *S. pneumoniae* blood or respiratory cultures evaluated between October 2018 and September 2019 at 329 US facilities in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ, US).
- The primary objective was to determine the proportion of *S. pneumoniae* isolates resistant to macrolides in blood and respiratory cultures.
- The study dataset was approved as a limited, de-identified dataset for retrospective analysis and was exempted from patient consent by the New England Institutional Review Board (Wellesley, Massachusetts).

Susceptibility Testing

- Non-duplicate *S. pneumoniae* isolates, defined as first isolate of a species per 30-day period, were obtained from blood or respiratory cultures. Isolates from each source were considered separately.
- Assessment of macrolide-resistance was based on facility reports using commercial panels in local automated susceptibility testing platforms and application of locally defined laboratory breakpoints.
- Resistance to any member of the macrolide class (i.e. azithromycin, clarithromycin, or erythromycin) was considered macrolide resistant.

METHODS (continued)

Statistical Analysis

- Macrolide resistance rates were compared by use of the chi-square test with *P* values <0.05 indicating statistical significance. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Nationwide *S. pneumoniae* Macrolide Resistance

- **Table 1** depicts the results of the nationwide macrolide resistance rates.
- A total of 3,626 *S. pneumoniae* isolates from blood (n=1,591; 43.9%) or respiratory (n=2,035; 56.1%) cultures were included.
- 22.8% of isolates where obtained from patients in the ambulatory setting, with the remaining 77.2% coming from inpatient settings.
- The overall rate of macrolide resistance in *S. pneumoniae* isolates was 39.5%
- The resistance rate in respiratory isolates (47.3%) was significantly higher than the rate in blood isolates (29.6%; $P < 0.0001$).
- Isolates obtained from ambulatory encounters had a significantly higher rate of macrolide resistance compared with isolates from inpatients (45.3% vs 37.8%; $P < 0.001$).

Table 1. Macrolide Resistance rates among *S. pneumoniae* across the USA

Setting	Number of Facilities	% Macrolide Resistant (n)		
		Blood Isolates	Respiratory Isolates	All Isolates
Total	329	29.6% (1,591)[a]	47.3% (2,035)[a]	39.5% (3,626)
Inpatient	313	28.2% (1,211)	45.2% (1,587)	37.8% (2,798)[b]
Ambulatory	231	33.9% (380)	54.9% (448)	45.3% (828)[b]

[a]Respiratory vs. blood (p<0.0001)
[b]Ambulatory vs. inpatient (p<0.001)

Geographic Differences in *S. pneumoniae* Macrolide Resistance

- Statistically significant differences ($P < 0.0001$) were observed in macrolide resistance in different US census regions (**Table 2**).
- Respiratory isolates from all US census regions revealed ≥25% macrolide resistance.
- The highest overall rate (i.e. combined respiratory and blood) of macrolide resistance was observed in the West North Central region (54.2%), followed by the South Atlantic (48.0%).

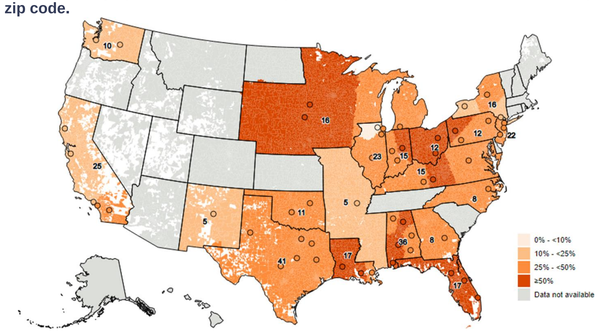
RESULTS (continued)

- Regions with overall *S. pneumoniae* macrolide resistance rates <25% were Mountain (13.9%), New England (18.2%), and Pacific (18.3%), driven primarily by the relatively low resistance rates in blood isolates, whereas respiratory isolates were ≥25%.
- Further delineation of the geographic distribution by zip codes (**Figure 1**) identified sub-regional and within-state differences in overall resistance rates. (e.g. California showed higher macrolide resistance in the southern part of the state.
  - Data therein represented 3,464 isolates collected from 314 facilities aggregated into geographic clusters of 5 or more hospitals from 2 or more integrated delivery networks. Shaded circles show the geographic centroid for each geographic cluster and numbers indicate the total number of included medical centers at the state level; facilities contributing <5 isolates were excluded.

Table 2. *S. pneumoniae* macrolide resistance rates by USA census region.

Census region (states)	Number of Facilities	% Macrolide Resistant (n)		
		Blood Isolates	Respiratory Isolates	All Isolates
West North Central: (IA, KS, MN, MO, ND, NE, SD)	12	52.1% (48)	55.0% (131)	54.2% (179)
South Atlantic: (DE, DC, FL, GA, MD, NC, SC, VA, WV)	40	30.3% (145)	60.8% (199)	48.0% (344)
East South Central: (AL, KY, MS, TN)	49	38.0% (229)	55.6% (252)	47.2% (481)
West South Central: (AR, LA, OK, TX)	71	35.6% (455)	48.5% (643)	43.2% (1098)
East North Central: (IL, IN, MI, OH, WI)	56	29.0% (217)	49.7% (320)	41.3% (537)
Middle Atlantic: (NJ, NY, PA)	50	28.3% (191)	39.8% (236)	34.7% (427)
Pacific: (AK, CA, OR, WA)	36	13.2% (257)	25.3% (190)	18.3% (447)
New England: (CT, MA, ME, NH, RI, VT)	5	4.0% (25)	25.0% (52)	18.2% (77)
Mountain: (AZ, CO, ID, MT, NM, NV, UT, WY)	10	4.2% (24)	33.3% (12)	13.9% (36)

Figure 1. Geographic distribution of *S. pneumoniae* macrolide resistance rates by zip code.



CONCLUSIONS

- *S. pneumoniae* blood and respiratory isolates from US facilities reveal a high burden of macrolide resistance with an overall 39.5% resistant rate.
- Macrolide resistance among *S. pneumoniae* obtained in the ambulatory setting was higher than those cultured in the inpatient setting.
- Macrolide resistance rates in respiratory *S. pneumoniae* across all census regions ranged from 25 – 60.8% and were higher than those observed in blood isolates.
- Given the ≥25% macrolide resistance threshold proposed by the ATS/IDSA CABP treatment guidelines, our data suggest alternative antibiotics, other than macrolide monotherapy, should be considered for empiric CABP therapy in the US.

REFERENCES

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Disclosures

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