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Frequency of Occurrence and Antimicrobial Susceptibility of Bacteria Isolated from Patients Hospitalised with Community-Acquired Bacterial Pneumonia: Evaluation of Ceftaroline Potency and Antimicrobial Spectrum

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Introduction

- Pneumonia is the second most common infection in hospitalised patients, and it is associated with significant morbidity and mortality
- The initial antimicrobial management of patients with pneumonia is driven mainly by the understanding of causative pathogens, and there is very little current information regarding the frequency and antimicrobial susceptibility of organisms causing community-acquired bacterial pneumonia (CABP) that requires hospitalisation
- Ceftaroline is a cephalosporin with broad-spectrum *in vitro* bactericidal activity against gram-positive and common gram-negative pathogens causing CABP, including oxacillin (methicillin)-susceptible (MSSA) and -resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) *Streptococcus pneumoniae*, and β-lactamase-producing *Haemophilus influenzae*
- The SENTRY Antimicrobial Surveillance Program monitors the frequency of occurrence and antimicrobial susceptibility of organisms from various infection types worldwide
- In the SENTRY Program, bacterial isolates are consecutively collected (1 per infection episode) according to the infection type and sent to a monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), where they are tested for susceptibility by reference broth microdilution methods against most antimicrobial agents currently used to treat systemic gram-positive and gram-negative infections
- In this investigation, we present the results for organisms isolated from patients hospitalised with CABP

Materials and Methods

Organism collection

- A total of 2,267 bacterial isolates were consecutively collected in 2014–2016 from 62 medical centres distributed as follows (Table 1)
  - Western Europe (W-EUR): 1,361 isolates from 19 medical centres in 9 nations
  - Eastern Europe and the Mediterranean region (E-EUR): 399 isolates from 16 medical centres in 12 nations
  - Asia-Pacific region (APAC): 345 isolates from 16 medical centres in 9 nations
  - Latin America (LATAM): 162 isolates from 11 medical centres in 9 nations
- Each participating centre was asked to collect consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia
- Qualified sputum samples and isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, etc.) were accepted
- An isolate obtained from an outpatient or collected earlier than 48 hours after hospitalisation was considered community-acquired
- An extended-spectrum β-lactamase screening-positive phenotype (ESBL-phenotype) was defined as MIC ≥2 mg/L for ceftriaxone, ceftazidime, or aztreonam (CLSI, 2018)

Susceptibility methods

- Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) documents determined antimicrobial susceptibility of ceftaroline and numerous comparator antimicrobials used to treat patients with pneumonia
- MIC panels were prepared at JMI Laboratories (2015-2016) or manufactured by ThermoFisher Scientific® (2014; Cleveland, Ohio, USA)
- *S. aureus* and *Enterobacteriaceae* were tested in cation-adjusted Mueller-Hinton broth (CAMHB), *S. pneumoniae* isolates were tested in CAMHB supplemented with 2.5%-5% lysed horse blood, and *Haemophilus* spp. strains were tested in *Haemophilus* test medium (HTM) according to CLSI document M07 (2018)
- Quality control (QC) strains included *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *H. influenzae* 49247
- Susceptibility percentages and QC results validation were based on the EUCAST (2018) and CLSI (2018) guidelines

Table 1 List of nations and number of participating centres surveyed in each geographic region

Western Europe (W-EUR)	Eastern Europe (E-EUR)	Asia-Pacific (APAC)	Latin America (LATAM)
Belgium (1)	Belarus (1)	Australia (6)	Argentina (1)
France (4)	Croatia (1)	Japan (1)	Brazil (2)
Germany (2)	Czech Republic (1)	Malaysia (1)	Chile (1)
Greece (1)	Hungary (1)	New Zealand (2)	Colombia (1)
Ireland (2)	Israel (1)	Philippines (1)	Costa Rica (1)
Italy (3)	Poland (1)	Singapore (1)	Ecuador (1)
Portugal (1)	Romania (2)	South Korea (2)	Mexico (2)
Spain (3)	Russia (3)	Taiwan (1)	Peru (1)
United Kingdom (2)	Slovakia (1)	Thailand (1)	Venezuela (1)
	Slovenia (1)		
	Turkey (2)		
	Ukraine (1)		

Results

- The top 4 organisms observed were the same in all 4 regions: *S. aureus*, *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp. (Figures 1a to 1d)
- *Serratia* spp., *H. influenzae*, and *S. pneumoniae* ranked fifth, sixth, and seventh overall, respectively, but their frequencies and rank orders varied among regions (Figures 1a to 1d)
- *S. pneumoniae* accounted for only 3.1% of the isolates overall, with prevalence varying from 1.2% in LATAM to 6.5% in E-EUR; and *H. influenzae* represented only 5.1% of the isolates overall, varying from 0.0% in LATAM to 6.1% in the APAC region (Figures 1a to 1d)
- Overall, 26.7% of *S. aureus* isolates were resistant to methicillin (MRSA), with rates varying from 16.7% in E-EUR to 29.0% in W-EUR (Figure 2)
- *S. aureus* susceptibility to ceftaroline was highest in the APAC region (98.6%), followed by E-EUR (97.2%), W-EUR (96.0%), and LATAM (93.2%); all nonsusceptible isolates were intermediate (MIC, 2 mg/L) and no resistant isolates were detected in any geographic region (0.0% resistance; Figure 3)
- Ceftaroline ($MIC_{50/90}$, 0.25/0.25 mg/L) was 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 mg/L) against methicillin-susceptible *S. aureus* (MSSA; data not shown)
- Ceftaroline was active against all *S. pneumoniae* isolates (100.0% susceptible) from W-EUR, E-EUR, and LATAM, and only 1 nonsusceptible isolate was detected in the APAC region, an isolate from Taiwan with a ceftaroline MIC of 0.5 mg/L (Figure 3)
- *S. pneumoniae* resistance rates to ceftriaxone were highest in LATAM (50.0% nonsusceptible; only 2 isolates tested), followed by the APAC region (37.5%), W-EUR (26.5%), and E-EUR (only 7.7% nonsusceptible; Figure 2)
- β-lactamase production among *H. influenzae* varied from 47.6% (APAC) to 16.7% (W-EUR), with 96.6% and 100.0% of isolates being susceptible to ceftaroline at the EUCAST (≤0.03 mg/L) and CLSI/US FDA (≤0.5 mg/L) susceptible breakpoints, respectively (Figures 2 and 3)
- ESBL-phenotype rates varied from 9.9% (APAC) to 63.0% (E-EUR) among *Klebsiella* spp. and from 17.6% (W-EUR) to 57.9% (LATAM) among *E. coli* (Figure 2)
- Ceftaroline was active against non-ESBL-phenotype isolates but generally not active against ESBL-phenotype isolates
- Ceftaroline susceptibility among *Enterobacter* spp. varied from 69.7% (W-EUR) to 85.7% (LATAM), 73.6% overall (Figure 3)

Figure 1 Frequency of occurrence of organisms isolated from patients hospitalised with community-acquired bacterial pneumonia (CABP) stratified by geographic region

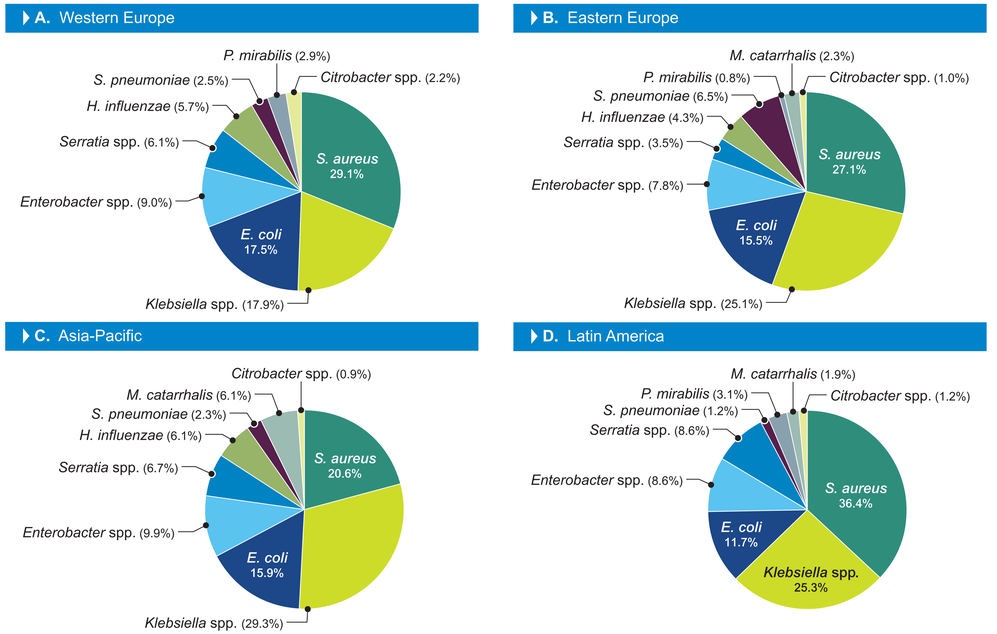
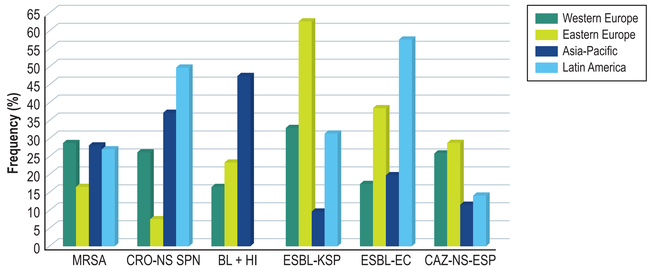
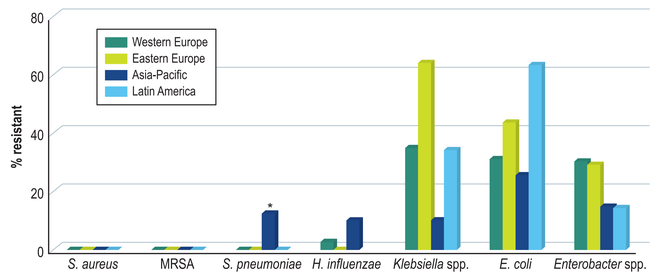


Figure 2 Frequency of occurrence of key resistance phenotypes among the main organisms isolated from patients hospitalised with CABP



Abbreviations: MRSA, methicillin-resistant *S. aureus*; CRO-NS SPN, ceftriaxone-nonsusceptible *S. pneumoniae*; BL + HI, β-lactamase-positive *H. influenzae*; ESBL-KSP, ESBL-phenotype *Klebsiella* spp.; ESBL-EC, ESBL-phenotype *E. coli*; CAZ-NS-ESP, ceftazidime-nonsusceptible *Enterobacter* spp.

Figure 3 Ceftaroline resistance rates (EUCAST criteria) among the main organisms isolated from patients hospitalised with community-acquired bacterial pneumonia (CAPB)



* 1 resistant isolate per EUCAST with ceftaroline MIC of 0.5 mg/L (susceptible per CLSI)

Conclusions

- Rank order and antimicrobial susceptibility of bacteria isolated from patients hospitalised with CABP varied widely by geographic region
- The prevalence of *S. pneumoniae* and *H. influenzae* was low in all geographic regions
- Ceftaroline exhibited potent activity against *S. aureus* overall (93.2%-98.6% susceptible), and its activity against MRSA varied substantially by geographic region (75.0%-95.0% susceptible); all nonsusceptible isolates were intermediate (MIC, 2 mg/L) and no resistant isolates were detected in any geographic region
- Ceftaroline was highly active against *S. pneumoniae*, including ceftriaxone-nonsusceptible isolates, and *H. influenzae*, including β-lactamase-producing isolates
- When tested against *Enterobacteriaceae*, ceftaroline spectrum of activity was similar to those of ceftriaxone and ceftazidime

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