ASM Microbe 2018
Sunday-404

Global Trends in Prevalence and Diversity of Carbapenemases Carrying *Enterobacteriaceae* Identified through SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- Carbapenem-nonsusceptible (NS) *Enterobacteriaceae* (ENT) pose a major challenge to treating serious infections caused by these organisms
  - These pathogens are often multidrug resistant, making treatment options limited
  - NS ENT rates vary widely according to geography
- IMP- (first identified in *Serratia marcescens* in Japan, 1994) and VIM- (first identified in *Pseudomonas aeruginosa* in Italy, 1999) metallo-beta-lactamases were the first carbapenemases to be described in human pathogens
  - These carbapenemases have been replaced largely by KPC and NDM carbapenemases worldwide among NS ENT
  - OXA-48-like carbapenemases are endemic in some regions of Asia and Europe and appear sporadically in other parts of the world
- We analyzed the diversity, prevalence, and evolution of carbapenemase genes among *Enterobacteriaceae* isolates collected through the longitudinal SENTRY Antimicrobial Surveillance Program from 1997 to 2016

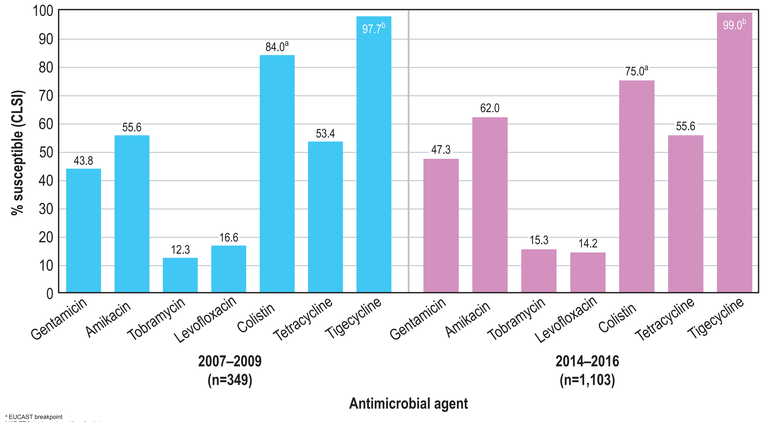
Materials and Methods

- Among 112,979 *Enterobacteriaceae* isolates collected between 1997–2016, 2,877 isolates (2.5%) displayed NS ENT phenotype (imipenem MIC at ≥2 mg/L or meropenem MIC at ≥1 mg/L) and were further evaluated
  - These isolates originated from >200 medical centers in 40 countries worldwide
- Isolates were tested for susceptibility by contemporary CLSI broth microdilution methods and MIC interpretations used current CLSI and EUCAST criteria, as available
- Isolates were screened for carbapenemases by PCR followed by Sanger sequencing or whole genome sequencing and analysis
  - Screening from 1997–2014 was done by multiplex PCR for carbapenemase-encoding genes followed by confirmation with singleplex PCR and sequencing of amplicons
  - Since 2015, screening has been performed by whole genome sequencing of high-quality genomic DNA on the MiSeq (Illumina, San Diego, California, USA) platform
    - NS ENT isolates were submitted to whole genome sequencing on a MiSeq instrument targeting a 30X coverage
    - Sequences were *de novo* assembled (SPAdes 3.9.0) and queried for the presence of acquired carbapenemases using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage
- Prevalence of carbapenemases among NS ENT isolates from 2007–09 and 2014–16 were compared
  - These time periods were chosen as the molecular data were more robust and were temporally separated enough to document changes in trends

Results

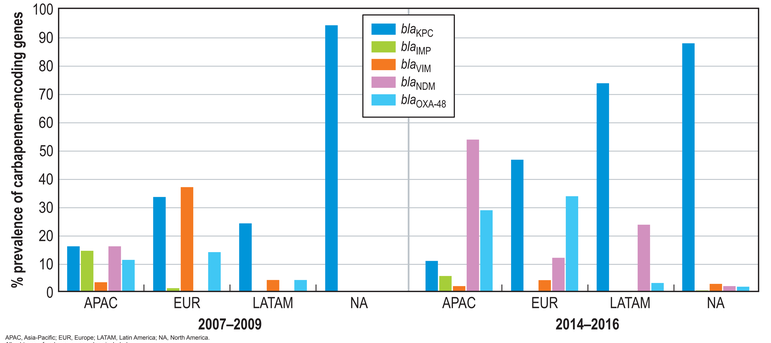
- Global prevalence of NS ENT isolates increased from 1.5% in 2007–09 to 2.7% in 2014–16 (p=0.09)
  - Among 23,078 isolates submitted during 2007-09, 349 (1.5%) were NS ENT with the majority from bloodstream infections (BSIs; 65.3%)
  - Among 40,514 isolates submitted during 2014–16, 1,104 (2.7%) were NS ENT, most commonly recovered from pneumonia in hospitalized patients (32%) followed by BSIs (27%)
- *Klebsiella pneumoniae* (81.1%) was the most abundant NS ENT species, followed by *Enterobacter cloacae* (10.7%) and *Escherichia coli* (4.7%)
  - *Citrobacter freundii* and *Klebsiella oxytoca* isolates were <2% overall per species
  - Prevalence of *K. pneumoniae* among NS ENT increased from 77.4% in 2007–09 to 84.4% in 2014–16
    - A corresponding decrease in the prevalence of *Enterobacter cloacae* species complex was from 12.6% to 8.7% in the 2 time periods evaluated
    - *K. oxytoca* occurrence dropped from 3.1% to just 1.8%
- Overall, tigecycline was the only agent that was highly active (>98% S) against this set of isolates; amikacin (56.8% susceptible) and tetracycline (54.9% susceptible) had moderate activity
  - 79.4% of isolates were susceptible to colistin per EUCAST criteria; colistin susceptibility dropped from 84.0% in 2007–09 to just 75.0% in 2014–16 isolates (Figure 1)
- The most common carbapenemase was bla_{KPC} (Figure 2)
  - bla_{KPC} was detected in 71.2% of all carbapenemase-producing isolates in 2007–09 and in 64.5% of isolates in 2014–16
  - *K. pneumoniae* was the predominant species with 86.8% of all bla_{KPC} carriers in these time frames
  - bla_{KPC} was the only carbapenemase determinant detected in North America in 2007-09 (140 of 149 NS ENT isolates; 94%)
  - Prevalence of KPC-producing isolates increased in Europe and Latin America during 2014–16 (33.3% in 2007–09 to 46.5% in 2014–16 in Europe and 24.0% in 2007–09 to 73.5% in 2014–16 in Latin America)
- Only 10 isolates (2.9% overall, all from medical centers in India) carried bla_{NDM-1} during 2007–09, and incidence of bla_{NDM}-positive isolates increased to 127 (11.5%; p<0.0001) in 2014–16 and were detected on all continents (Figure 2)
  - All bla_{NDM-1}-positive isolates from 2007–09 were also positive for $bla_{CTX-M-15}$[1] but no other carbapenemase
  - bla_{NDM-1} and bla_{OXA-48}-like genes were detected together in 15 isolates in 2014–16
  - bla_{NDM-1} and bla_{KPC} were detected in 2 *K. pneumoniae* isolates from 2015, 1 each from the United States (bla_{NDM-1} and bla_{KPC-17}) and Brazil (bla_{NDM-1} and bla_{KPC-2})
  - bla_{NDM-1}, bla_{KPC-3}, and bla_{OXA-48}-like genes were detected in one isolate from Turkey in 2015
- Prevalence of isolates harboring bla_{VIM} and bla_{IMP} declined over the time periods, except in North America; bla_{OXA-48} genes were most prevalent in Europe (Figure 2)

Figure 1 Comparative activity of antimicrobial agents when tested against carbapenem nonsusceptible isolates in the SENTRY Program (2007–09 and 2014–16)



[a] EUCAST breakpoint
[b] US FDA package insert breakpoint

Figure 2 Percent prevalence of carbapenemase encoding genes in the time periods 2007–2009 and 2014–2016



APAC, Asia-Pacific; EUR, Europe; LATAM, Latin America; NA, North America.
All subtypes of carbapenemase class included.

- Prevalence of bla_{OXA-48}-like increased significantly, from 13.8% in 2007–09 to 33.6% in 2014–16, in Europe
- Among NS ENT, the prevalence of carbapenemase increased from 76.8% in 2007–09 to 95.6% in 2014–16

Conclusions

- Prevalence of carbapenemases among *Enterobacteriaceae* is increasing worldwide with changing trends in different geographic regions
- bla_{KPC} remains the most prevalent carbapenemase in this collection
  - bla_{NDM} has spread globally as demonstrated in smaller scale by other investigators
    - bla_{NDM} is currently the most prevalent in the Asia-Pacific region, accounting for more than 50% of this region's carbapenemases
- Continued screening for NS ENT and underlying mechanisms to control the spread of these pathogens is warranted
  - The SENTRY Antimicrobial Surveillance Program supplies a valuable platform for surveillance of these organisms

Acknowledgements

The authors thank all participants of the SENTRY Program for their work in providing bacterial isolates.

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