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Prevalence of antibiotic resistance among *P. aeruginosa* in US hospitals, 2000–2009

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ABSTRACT

Introduction: *P. aeruginosa* (PA) represents an important cause of severe infection in hospitalized patients. Initially appropriate empiric antibiotic therapy is a key determinant of outcome. Appropriate initial antibiotic selection is predicated on understanding the epidemiology of resistance to commonly used antibiotics either as single agents or as parts of combination regimens. We explored resistance among PA to frequently utilized antibiotic regimens over time in the US.

Methods: We analyzed a nationally representative US-based microbiology database, Eurofins TSN, between years 2000 and 2009. We examined the prevalence of PA's resistance to the following antibiotics: piperacillin/tazobactam (PTZ), ceftazidime (TAZ), imipenem (IMI), or meropenem (MER) alone, and combinations of PTZ+ciprofloxacin (CIP), TAZ+CIP, IMI+CIP, MER+CIP, PTZ+gentamicin (GEN), TAZ+GEN, IMI+GEN, MER+GEN. We evaluated specimens from pneumonia (PNE), blood stream (BSI), urinary tract (UTI) and complicated intra-abdominal (IAI) infections.

Results: Among the 327,912 PA specimens 57.1% were PNE, 35.1% UTI, 5.6% BSI and 2.2% IAI. Overall, the highest prevalence of resistance to single therapy was TAZ (24.8%) and combination IMI+CIP (17.3%). The lowest rate of resistance was to PTZ as a single agent (13.4%) and PTZ+GEN as combination (7.9%). PNE accounted for the highest proportion of resistance to all regimens examined, ranging from 9.5% PTZ+GEN to 29.5% TAZ. Between 2000 and 2009, while resistance rates rose to PTZ (12.4% to 15.0%), IMI (20.8% to 25.2%), MER (19.5% to 24.2%), PTZ+CIP (8.8% to 10.1%), IMI+CIP (14.7% to 18.3%) and MER+CIP (14.9% to 17.4%), those to the other regimens remained stable with some fluctuations.

Conclusions: Resistance among PA to routine anti-pseudomonal regimens is high, with the highest levels observed in PNE. While they have remained stable to some potential regimens, resistance rates to others have increased over the decade examined. The most pronounced rise in PA resistance was to regimens containing carbapenems, irrespective of concomitant fluoroquinolone use. These trends must inform not only empiric treatment of serious infections, but also the approaches to antibiotic stewardship.

INTRODUCTION

- *Pseudomonas aeruginosa* (PA) represents an important cause of severe infection in hospitalized patients.
- Multidrug resistance among PA represents a major treatment challenge (1).
  - For example, a recent US-based surveillance study reported that one-quarter of device-related infections in hospitalized patients were caused by carbapenem-resistant PA (2).
- Initially appropriate empiric antibiotic therapy is a key determinant of outcome (1–10).
- Appropriate initial antibiotic selection is predicated on understanding the epidemiology of resistance to commonly used antibiotics either as single agents or as parts of combination regimens.

STUDY AIM

- To explore resistance among PA to frequently utilized antibiotic regimens over time in the US

METHODS

Data source

- The Surveillance Network (TSN) database from Eurofins
  - Database used extensively for surveillance purposes since 1994 (11–15).
  - Routine clinical data collected from a nationally representative sample of microbiology laboratories in 217 hospitals in the US
  - Only clinically significant samples reported
  - No personal identifying information for source patients available
  - Only source laboratories that perform antimicrobial susceptibility testing according to standard FDA-approved testing methods and interpret susceptibility in accordance with the Clinical Laboratory Standards Institute breakpoints included (16)
  - All enrolled laboratories undergo a pre-enrollment site visit
  - Logical filters used for routine quality control to detect unusual susceptibility profiles and to ensure appropriate testing methods
  - Repeat testing and reporting done as necessary
  - Laboratory samples reported as susceptible, intermediate, or resistant according to CLSI breakpoints (16)
  - Grouped intermediate samples together with the resistant ones for the purposes of the current analysis
  - Duplicate isolates excluded

Sample frame

- Time: between years 2000 and 2009
- Only samples representing one of the four infections of interest included:
  - Pneumonia
  - Blood stream infection (BSI)
  - Urinary tract infection (UTI)
  - Complicated intra-abdominal infection (cIAI)
- Examined the prevalence of PA's resistance to the following antibiotics (Table 1):

TABLE 1 Antibiotics examined

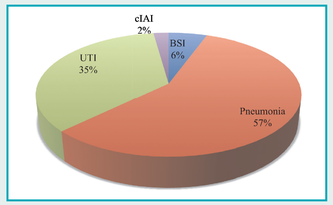
Single agent	*Combinations*
pip-tazo	pip-tazo+cipro
ceftaz	ceftaz+cipro
imi	imi+cipro
mero	mero+cipro
	pip-tazo+gent
	ceftaz+gent
	imi+gent
	mero+gent

Pip-tazo = piperacillin-tazobactam; ceftaz = ceftazidime; imi = imipenem; mero = meropenem; gent = gentamicin

RESULTS

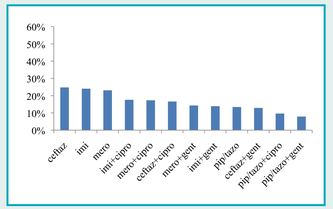
We identified 327,912 pseudomonal specimens between 2000 and 2009, the majority of which were from pneumonia (Figure 1).

Figure 1 Distribution of infection types



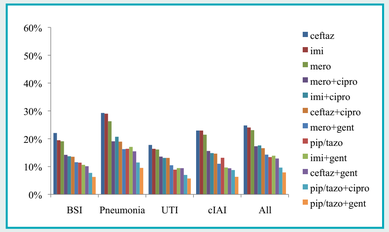
- For all years and infection types combined (Figure 2)
  - The highest prevalence of resistance
    - Single therapy: ceftaz (24.8%)
    - Combination therapy: imi+cipro (17.6%)
  - The lowest rate of resistance
    - Single therapy: pip-tazo (13.4%)
    - Combination therapy: pip-tazo+gent (7.9%)

Figure 2 Resistance rates by agent



- For all years combined, pneumonia accounted for the highest proportion of resistance to all regimens examined, ranging from 9.5% pip-tazo+gent to 29.5% ceftaz (Figure 3)

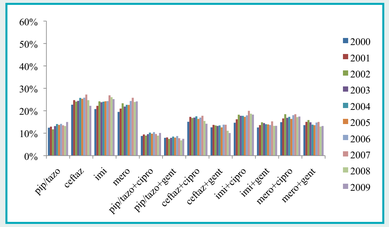
Figure 3 Rates of resistance by agent and infection type



BSI = blood stream infection; UTI = urinary tract infection; cIAI = complicated intra-abdominal infection

- For all infections combined, between 2000 and 2009 (Figure 4)
  - Resistance rates rose for
    - pip-tazo (12.4% to 15.0%)
    - imi (20.8% to 25.2%)
    - mero (19.5% to 24.2%)
    - pip-tazo+cipro (8.8% to 10.1%)
    - imi+cipro (14.7% to 18.3%)
    - mero+cipro (14.9% to 17.4%)
  - Resistance to the other regimens remained stable with some fluctuations

Figure 4 Combined resistance rates by year



- Geographic variation in the prevalence of resistance was examined according to the 9 US census divisions (Figure 5)
  - East North Central census division consistently had one of the highest rates of resistance to all regimens examined (Figure 6)
  - There was substantial variability in resistance rates across the other eight divisions (Figure 6)

Figure 5 US Census regions and divisions

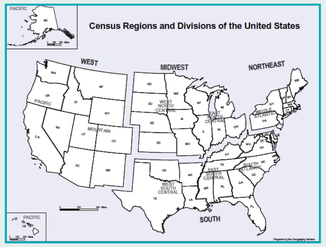
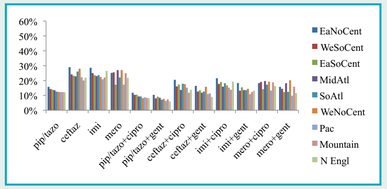


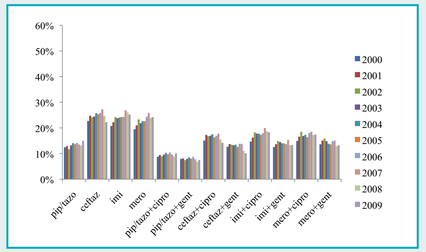
Figure 6 Resistance rates by census division



MidAtl = Mid-Atlantic; EaNoCent = East North Central; N Engl = New England; SoAtl = South atlantic; WeNoCent = West North Central; WeSoCent = West South Central; Pac = Pacific; EaSoCent = East South Central

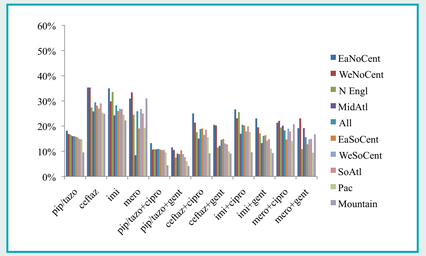
- We additionally examined resistance rates for specimens originating in the ICU
  - Over time, resistance patterns in the ICU echoed those outside the ICU with some minor variations (Figure 7)

Figure 7 Resistance rates of specimens originating in the ICU by year



- Geographically, resistance patterns in the ICU also echoed those outside the ICU with some minor variations (Figure 8)

Figure 8 Resistance rates of specimens originating in the ICU by census division



MidAtl = Mid-Atlantic; EaNoCent = East North Central; N Engl = New England; SoAtl = South atlantic; WeNoCent = West North Central; WeSoCent = West South Central; Pac = Pacific; EaSoCent = East South Central

STRENGTHS AND LIMITATIONS

- Nationally representative database → highly generalizable results
- TSN database consists of microbiology samples from hospital laboratories.
  - While we attempted to reduce the risk of duplication, because of how samples are numbered in the database, repeat sampling remains a possibility.

CONCLUSIONS

- Resistance among PA to routine anti-pseudomonal regimens is high, with the highest levels observed in pneumonia.
- While they have remained stable to some potential regimens, resistance rates to others have increased over the decade examined.
- Resistance rates among organisms isolated in the ICU are generally higher than those among all the organisms examined.
- The most pronounced rise in PA resistance was to regimens containing carbapenems, irrespective of concomitant fluoroquinolone use.
- These trends must inform not only empiric treatment of serious infections, but also the approaches to antibiotic stewardship.

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