ECCMID 2018
Poster #P1140

Geographic and Temporal Patterns of Antimicrobial Resistance in *Pseudomonas aeruginosa* from the SENTRY Surveillance Program, 1997–2016

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- The SENTRY Antimicrobial Surveillance Program (SENTRY) was established in 1997 and encompasses over 800,000 bacterial isolates from over 200 medical centres worldwide
- Among the pathogens tested, *Pseudomonas aeruginosa* remains a common cause of multidrug-resistant (MDR) bloodstream infections and pneumonias in hospitalized patients
- In the present study, we reviewed geographic and temporal trends in resistant phenotypes of *P. aeruginosa* over 20 years of the SENTRY Program

Materials and Methods

- During the period from 1997 to 2016, 54,185 clinically significant, *P. aeruginosa* isolates were submitted for testing in the SENTRY Program from over 200 medical centres representing the Asia-Pacific, European (including Turkey and Israel), Latin American, and North American regions
  - Only 1 isolate per patient per infection episode was submitted
  - Infection types included bloodstream infection (BSI), pneumonia in hospitalised patients (PIHP), skin and skin structure infection (SSSI), intra-abdominal infection (IAI), and urinary tract infection (UTI)
  - Isolates were identified by standard algorithms and/or matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) at each site and confirmed at the central laboratory
- Susceptibility (S) testing was performed by the CLSI broth microdilution method and interpreted using CLSI and EUCAST 2018 criteria
- Included among the antimicrobials tested were amikacin, cefepime, ceftazidime, ciprofloxacin, colistin (tested 2006–2016), meropenem, and piperacillin-tazobactam
  - Resistant phenotypes analysed using EUCAST criteria were: multidrug-resistant (MDR; nonsusceptible to at least 1 antimicrobial in ≥3 drug classes), extensively drug-resistant (XDR; nonsusceptible to at least 1 agent in all but ≤2 drug classes), pandrug-resistant (PDR), ceftazidime-nonsusceptible (NS), meropenem-NS, and colistin-resistant

Results

- The most common infection type from which *P. aeruginosa* was isolated was PIHP (44.8%) followed by BSI (27.4%) and SSSI (19.7%) as shown in Figure 1
  - PIHP had a higher rate of MDR (33.4%) compared to BSI (27.0%) (Figure 2)
- MDR rates over time are shown in Table 1, ranging from a high of 34.2% in 2005–2008 to a low of 27.1% in 2013–2016
  - XDR rates also peaked in 2005-2008 at 20.1%
  - PDR isolates were rare throughout the study period, totaling 47 isolates over 20 years
  - Rates of ceftazidime-NS isolates were highest (27.5%) in the 2005–2008 period and have decreased to 19.4% most recently
  - Rates of meropenem-NS isolates were highest (27.6%) in 2009–2012 and have decreased to 22.7%
- Activity of antimicrobial agents tested is shown in Table 2 for all isolates and MDR, XDR, and PDR phenotypes with CLSI and EUCAST clinical breakpoints
  - Colistin was the most active agent against isolates with MDR and XDR phenotypes at 98.7% and 98.3% susceptible, respectively (Table 2)
  - PDR isolates that were tested against colistin (n=46) were resistant
  - Amikacin was the second most active agent, inhibiting 85.6% of all isolates and 14.9% of PDR isolates, at a breakpoint of ≤8 mg/L

Table 1 Frequency of resistance phenotypes for *P. aeruginosa* from 1997–2016

Resistance group[a]	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	1997–2016
Multidrug-resistant	27.1%	30.7%	34.2%	31.8%	27.1%	29.7%
Extensively drug-resistant	12.4%	16.4%	20.1%	18.5%	14.5%	16.1%
Pandrug-resistant	0.0%	0.0%	0.2%	0.1%	0.1%	0.1%
Ceftazidime-NS	22.8%	23.4%	27.5%	25.5%	19.4%	23.1%
Meropenem-NS	19.2%	24.9%	27.3%	27.6%	22.7%	24.1%
Colistin-resistant	N/A[b]	N/A	1.2%	0.8%	0.5%	0.7%
Total	9,600	7,928	8,154	11,773	16,730	54,185

[a] Resistance phenotypes using EUCAST (2018) criteria
[b] Not applicable, drug not tested

- Isolates with the MDR or XDR phenotype were most frequently isolated in Latin America with 45.1% MDR and 29.0% XDR, followed by Europe with 32.3%/19.2%, Asia-Pacific with 28.4%/15.1%, and North America with 23.5%/10.2% (Figure 3)
  - Latin America also had a higher frequency of ceftazidime-NS and meropenem-NS isolates than the other regions
- Figure 4 shows the percent MDR by 4-year increments for each region
  - Europe and North America had a relatively stable MDR rate across 2 decades
  - Latin America had the highest rate overall, though it has shown a decline in 2013–2016
  - Asia-Pacific showed a large increase in 2005-2008, with a decline since 2009

Table 2 Activity of antimicrobial agents when tested against MDR, XDR, and PDR isolates of *P. aeruginosa*

Antimicrobial agent	MIC (mg/L)			CLSI[a]			EUCAST[a]		
	50%	90%	Range	%S[b]	%I	%R	%S	%I	%R
All (n=54,185)									
Amikacin	≤4	16	≤4 to >32	90.0	2.5	7.5	85.6	4.5	10.0
Cefepime	4	>16	≤0.5 to >16	78.7	10.9	10.4	78.7		21.3
Ceftazidime	≤2	>16	≤2 to >16	76.9	5.2	17.9	76.9		23.1
Ciprofloxacin	≤0.5	>2	≤0.5 to >2	72.6	4.4	23.0	67.3		32.7
Colistin	1	2	≤0.5 to >4				99.3		0.7
Meropenem	0.5	>8	≤0.12 to >8	75.8	6.5	17.7	75.8	13.0	11.1
Piperacillin-tazobactam	8	>64	≤1 to >64	72.5	12.2	15.3	72.5		27.5
MDR (n=16,091)									
Amikacin	8	>32	≤4 to >32	68.7	7.5	23.8	58.0	10.7	31.3
Cefepime	16	>16	≤0.5 to >16	36.4	31.0	32.6	36.4		63.6
Ceftazidime	>16	>16	≤2 to >16	35.9	12.7	51.4	35.9		64.1
Ciprofloxacin	>2	>2	≤0.5 to >2	28.8	8.0	63.2	20.5		79.5
Colistin	1	2	≤0.5 to >4				98.7		1.3
Meropenem	8	>8	≤0.12 to >8	27.6	15.6	56.9	27.6	35.3	37.1
Piperacillin-tazobactam	64	>64	≤0.5 to >64	24.6	30.4	45.0	24.6		75.4
XDR (n=8,723)									
Amikacin	16	>32	≤4 to >32	54.7	10.0	35.3	42.6	12.1	45.3
Cefepime	>16	>16	≤0.12 to >16	14.3	36.9	48.8	14.3		85.7
Ceftazidime	>16	>16	≤2 to >16	14.9	14.9	70.2	14.9		85.1
Ciprofloxacin	>2	>2	≤0.5 to >2	14.0	7.4	78.6	8.3		91.7
Colistin	1	2	≤0.5 to >4				98.3		1.7
Meropenem	>8	>8	≤0.12 to >8	7.7	13.7	78.5	7.7	35.4	56.9
Piperacillin-tazobactam	>64	>64	≤0.5 to >64	6.0	33.7	60.4	6.0		94.0
PDR (n=47)									
Amikacin	>32	>32	≤4 to >32	29.8	14.9	55.3	14.9	14.9	70.2
Cefepime	>16	>16	0.25 to >16	12.8	27.7	59.6	12.8		87.2
Ceftazidime	>16	>16	4 to >16	8.5	17.0	74.5	8.5		91.5
Ciprofloxacin	>2	>2	2 to >2	4.3	8.5	87.2	2.1		97.9
Colistin	4	>4	4 to >4				0.0		100.0
Meropenem	>8	>8	0.5 to >8	10.6	12.8	76.6	10.6	34.0	55.3
Piperacillin-tazobactam	>64	>64	32 to >64	0.0	46.8	53.2	0.0		100.0

MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant using EUCAST (2018) criteria
[a] Criteria as published by CLSI (2018) and EUCAST (2018)
[b] S, susceptible; I, intermediate; R, resistant

Figure 1 Infection types from which isolates were cultured

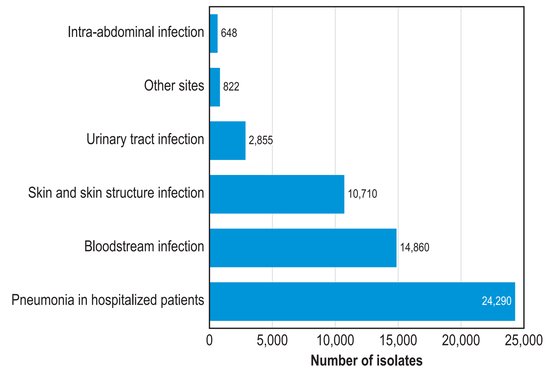


Figure 2 Percent multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* isolates by infection type

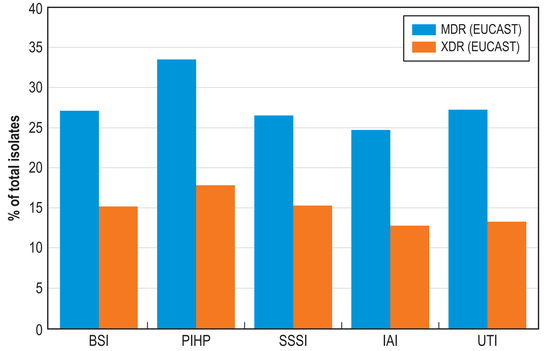


Figure 3 Percent of multidrug-resistant (MDR), extensively drug-resistant (XDR), ceftazidime-nonsusceptible (NS), and meropenem-nonsusceptible (NS) *P. aeruginosa* by region

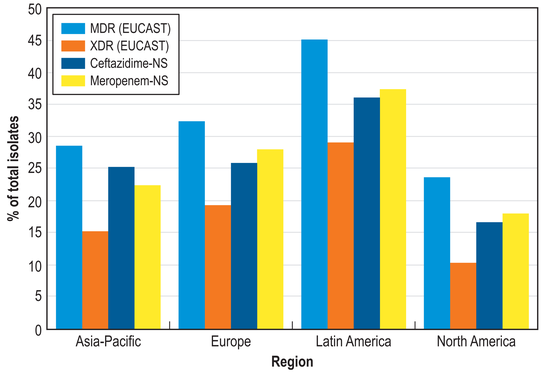
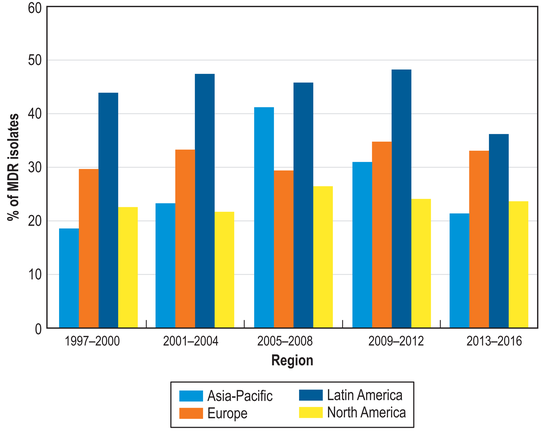


Figure 4 Percent multidrug-resistant *P. aeruginosa* by region and 4-year period



Conclusions

- Over the 20 years of SENTRY surveillance, the rates of MDR and other resistant phenotypes for *P. aeruginosa* were highest in 2005–2008 and decreased more recently
  - The continent with the highest rate of MDR isolates was Latin America
  - Latin America and Asia-Pacific showed a decrease of MDR phenotype in 2013–2016
- Colistin and amikacin were the most active drugs tested against all phenotypes except PDR
- Due to the differences in breakpoints between the 2 breakpoint setting groups, EUCAST resistance rates are generally higher than CLSI, with the exception of meropenem
  - The higher resistance rates for EUCAST are due, at least in part, to the lack of an intermediate category
- Whether the trend of decreasing resistance in *P. aeruginosa* is maintained will be determined in future SENTRY and other international-level surveillance reports

Acknowledgements

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

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