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Minocycline Activity against *Stenotrophomonas maltophilia* Isolated from Patients in US Hospitals

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Introduction

- *Stenotrophomonas maltophilia* has emerged as a common hospital-associated opportunistic pathogen isolated from immunocompromised and immunocompetent patients
- *S. maltophilia* is intrinsically resistant to many common drug classes, including carbapenems, cephalosporins, and aminoglycosides
- Four commonly used antibiotics with Clinical and Laboratory Standards Institute (CLSI) breakpoints for *S. maltophilia* were tested in this study: minocycline, ceftazidime, levofloxacin, and trimethoprim-sulfamethoxazole
  - Ticarcillin-clavulanate is no longer available
  - Chloramphenicol is rarely used due to toxicity concerns
- Minocycline is frequently used to treat *S. maltophilia* infections
- In this study, we analyzed susceptibilities of 990 *S. maltophilia* US isolates collected as part of the SENTRY Antimicrobial Surveillance Program from 2014–2018
- We also examined the frequency of *S. maltophilia* isolation from respiratory tract specimens in 9,120 patients hospitalized with pneumonia among all Gram-negative isolates from 2014–2018

Materials and Methods

- From 2014–2018, 990 *S. maltophilia* isolates were collected from hospitalized patients in 32 US hospitals with any infection type
- Hospitals submitted 1 isolate per patient per infection episode that met local criteria for being the likely causative pathogen and submitted consecutive isolates
- Isolates were tested for minocycline susceptibility (S) using the CLSI broth microdilution method at JMI Laboratories, according to CLSI interpretive criteria: susceptible ≤4 mg/L, intermediate 8 mg/L, and resistant ≥16 mg/L (M100, 2019)
- Other antimicrobials tested were ceftazidime, levofloxacin, and trimethoprim-sulfamethoxazole
  - Trimethoprim-sulfamethoxazole was tested 3 of 5 years
  - All infection types were included in the susceptibility analysis
- The prevalence of *S. maltophilia* isolates in patients with pneumonia caused by a Gram-negative organism during this period was also analyzed to determine frequency of the causative pathogen

Results

- There were 9,120 Gram-negative pathogens isolated from patients in US medical centers with pneumonia during the 2014–2018 study period
- The most commonly isolated species was *Pseudomonas aeruginosa* (n=3,161, 34.7%), followed by *Klebsiella pneumoniae* (n=1,145, 12.6%), *Escherichia coli* (n=918, 10.1%), and *S. maltophilia* (n=716, 7.9%), shown in Figure 1
- Among the infections from which *S. maltophilia* was isolated, pneumonia was the most common infection type at 72.4%, followed by bloodstream infections (14.4%) and skin/skin structure infections (6.9%), shown in Figure 2
- The %S and $MIC_{50/90}$ values of the 4 antimicrobials with CLSI breakpoints in this study are shown in Table 1
  - Minocycline susceptibility was 99.5%, trimethoprim-sulfamethoxazole susceptibility was 94.7%, levofloxacin susceptibility was 77.8%, and ceftazidime was 28.5% susceptible
- The MIC distributions are shown in Table 2
  - Only 2 isolates were resistant to minocycline (MIC >8 mg/L)
  - There were 32 trimethoprim-sulfamethoxazole resistant isolates (MIC >4/76 mg/L), and 31 of those were susceptible to minocycline
- Figure 3 shows the activity of minocycline against isolates resistant to trimethoprim-sulfamethoxazole, levofloxacin, or ceftazidime

Conclusions

- *S. maltophilia* was the fourth most frequent cause of Gram-negative pneumonia in hospitalized patients from US medical centers from 2014–2018
- Minocycline was the most active drug tested against *S. maltophilia* with 99.5% susceptible, followed by trimethoprim-sulfamethoxazole (94.7%), levofloxacin (77.8%), and ceftazidime, which was the least active with 28.5% susceptible
  - Minocycline was active against 31/32 trimethoprim-sulfamethoxazole-resistant isolates
  - Only 2 isolates were minocycline resistant (>8 mg/L)
- This study suggests that minocycline may be considered as a treatment for infections caused by *S. maltophilia* that has a very low resistance rate based on CLSI breakpoints

Table 1 Activities of minocycline and comparator agents when tested against 990 *S. maltophilia* isolates (US 2014–2018)

Antimicrobial agent	No. of isolates	MIC_{50}	MIC_{90}	Range	CLSI*		
					%S	%I	%R
Minocycline	990	0.5	2	≤0.06 to >8	99.5	0.3	0.2
Ceftazidime	990	32	>32	0.25 to >32	28.5	10.2	61.3
Levofloxacin	990	1	>4	≤0.12 to >4	77.8	8.9	13.3
Trimethoprim-sulfamethoxazole	609	≤0.5	1	≤0.5 to >4	94.7		5.3

* CLSI (2019).

Figure 1 Gram-negative pathogens isolated from patients hospitalized with pneumonia

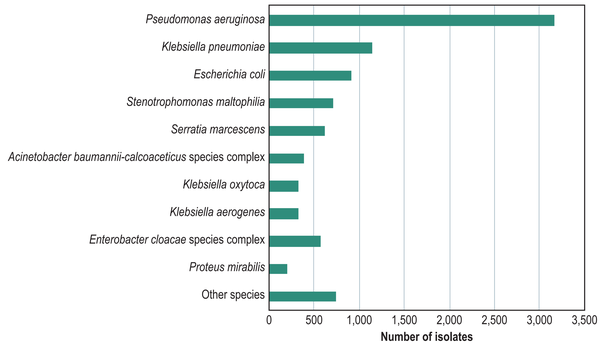
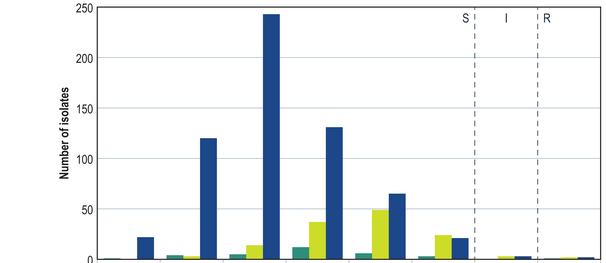


Figure 3 Minocycline MIC against *S. maltophilia* isolates resistant to trimethoprim-sulfamethoxazole (TMP-SMX), levofloxacin (LEV), or ceftazidime (CAZ)



	0.12	0.25	0.5	1	2	4	8	>8
TMP-SMX-R	1	4	5	12	6	3		1
LEV-R	0	3	14	37	49	24	3	2
CAZ-R	22	120	243	131	65	21	3	2

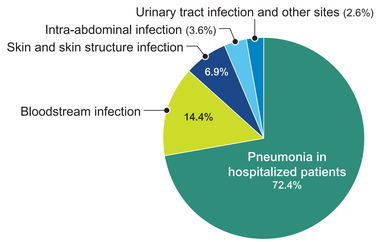
CLSI breakpoints indicated by lines (Susceptible, ≤4/Intermediate, 8/Resistant, ≥16 mg/L)

Table 2 MIC distribution of minocycline and comparator antimicrobial agents when tested against *Stenotrophomonas maltophilia* isolates collected from medical centers in the United States (2014–2018)

Antimicrobial agent	MIC (mg/L)														Total	MIC_{50}	MIC_{90}
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>			
Minocycline			2	53	226	372	210	90	32	3				2	990	0.5	2
			0.2%	5.6%	28.4%	66.0%	87.2%	96.3%	99.5%	99.8%				100.0%			
Ceftazidime				0	1	5	39	84	76	77	101	147		460	990	32	>32
				0.0%	0.1%	0.6%	4.5%	13.0%	20.7%	28.5%	38.7%	53.5%		100.0%			
Levofloxacin				8	37	182	364	179	88					132	990	1	>4
				0.8%	4.5%	22.9%	59.7%	77.8%	86.7%					100.0%			
Trimethoprim-sulfamethoxazole						545	19	13	9					23	609	≤0.5	1
						89.5%	92.6%	94.7%	96.2%					100.0%			

CLSI (2019) breakpoints are indicated: green, susceptible; yellow, intermediate; red, resistant

Figure 2 Infection types from which *S. maltophilia* was isolated



Acknowledgements

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