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Minocycline Activity Against Unusual Clinically Significant Gram-Negative Pathogens

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Introduction

- Unusual non-glucose fermenting Gram-negative (NFGN) pathogens, including *Achromobacter* spp., *Alcaligenes* spp., *Aeromonas* spp., and other genera, can cause serious hospital-acquired infections in immunocompromised patients.
  - Some genera are inherently resistant to common drug classes, and can acquire other resistance mechanisms, making them difficult to treat.
  - Publications with susceptibilities of NFGN isolates are uncommon.
- In this study, we analyzed the susceptibility of unusual NFGN isolates to minocycline. Isolates were collected as part of the SENTRY Antimicrobial Surveillance Program from 2014–2019.
  - The most common NFGN species (*Pseudomonas aeruginosa, Acinetobacter baumannii-calcoaceticus* species complex, and *Stenotrophomonas maltophilia*) were excluded from this analysis.

Materials and Methods

- From 2014–2019, 1,813 unusual NFGN isolates were collected from hospitalized patients in 102 hospitals in 35 countries on 4 continents. Hospitals submitted 1 isolate per patient per infection episode that met local criteria for being the likely causative pathogen.
- Identification was performed by the submitting laboratory and confirmed by JMI Laboratories with matrix-assisted laser desorption ionization-time of flight mass spectrometry or other molecular methods if needed.
- The most common NFGN species (*Pseudomonas aeruginosa, Acinetobacter baumannii-calcoaceticus* species complex, and *Stenotrophomonas maltophilia*) were excluded from this analysis.
  - Each genus/species analyzed had at least 10 isolates.
  - Some genera had a large number of species, each with a small number of isolates. In these cases, isolates were combined for analysis. If a single species was the main species within a genus, that species is shown.
- Isolates were tested for minocycline susceptibility using the CLSI broth microdilution method at JMI Laboratories (CLSI, 2018).
  - CLSI breakpoints from M100 or M45 were used as appropriate.
  - If breakpoints were not available, *Acinetobacter* minocycline CLSI breakpoints (≤4/8/≥16 mg/L) were applied.
- All infection types were included in the susceptibility analysis.

Results

- Pneumonia in hospitalized patients was the most common infection from which the NFGN were isolated (Figure 1).
- The top 5 unusual NFGN species were: *Achromobacter* species (n=411), including *A. xylosoxidans* (n=202); *Burkholderia* spp. (n=246), including *B. cepacia* species complex (n=229); *Aeromonas* spp. (n=127), including *Aeromonas hydrophila* (n=35); *Chryseobacterium* spp. (n=59); and *Alcaligenes faecalis* (n=42).
- The MIC frequency distribution and $MIC_{50/90}$ values of minocycline for these species are shown in Table 1.
- Minocycline susceptibility was >90% for all organisms shown, except *Alcaligenes faecalis, Burkholderia* spp., and *non-aeruginosa Pseudomonas* spp.
  - Minocycline susceptibility of *A. faecalis* was 88.1%.
  - Susceptibility of *Burkholderia* spp. was 87.0% and *B. cepacia* species complex was 86.5%.
  - Susceptibility of *non-aeruginosa Pseudomonas* spp. was 89.7%.
- The susceptibilities of minocycline and other comparators are shown for the 2 largest groups, *non-baumannii-calcoaceticus Acinetobacter* spp. (Table 2) and *Achromobacter* spp. (Table 3).
  - For *Acinetobacter* spp., minocycline had the highest susceptibility (98.8%) of the comparators tested. The agent with the lowest susceptibility was ceftazidime (79.5%).
  - For *Achromobacter* spp., minocycline had the highest susceptibility, 92.7%. The agent with the lowest susceptibility was aztreonam (1.0%).

Conclusions

- Minocycline had >85% susceptibility for the most frequently isolated unusual NFGN, including 99.2% for *Aeromonas* spp., 98.8% for *non-baumannii Acinetobacter*, and 92.7% for *Achromobacter* spp.
- These data suggest that minocycline remains a useful treatment option for infections caused by unusual NFGN.

Acknowledgements

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Table 1 MIC distribution of minocycline tested against various unusual non-fermentative Gram-negative species with at least 10 isolates

Organism (number)	Dilution (mg/L) 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	MIC_{50}	MIC_{90}
Acinetobacter non-baumannii complex spp. (424)		166	131	80	32	9	0	1	1			4	0.12	0.5
		39.2%	70.0%	88.9%	96.5%	98.6%	98.6%	98.8%	99.1%			100.0%		
Achromobacter spp. (411)		2	7	21	62	141	97	51	22			8	1	4
		0.5%	2.2%	7.3%	22.4%	56.7%	80.3%	92.7%	98.1%			100.0%		
A. xylosoxidans (202)		1	3	6	36	73	35	32	10			6	1	4
		0.5%	2.0%	5.0%	22.8%	58.9%	76.2%	92.1%	97.0%			100.0%		
Aeromonas spp. (127)		0	2	10	60	35	16	3	0	0	0	1	0.5	2
		0.0%	1.6%	9.4%	56.7%	84.3%	96.9%	99.2%	99.2%	99.2%	99.2%	100.0%		
A. hydrophila (35)		0	1	4	17	10	2	1					0.5	1
		0.0%	2.9%	14.3%	62.9%	91.4%	97.1%	100.0%						
Alcaligenes faecalis (42)			0	1	1	8	19	8	3			2	2	8
			0.0%	2.4%	4.8%	23.8%	69.0%	88.1%	95.2%			100.0%		
Burkholderia spp. (246)		1	1	2	14	57	91	48	12			20	2	8
		0.4%	0.8%	1.6%	7.3%	30.5%	67.5%	87.0%	91.9%			100.0%		
B. cepacia complex (229)		1	0	2	13	51	84	47	11			20	2	8
		0.4%	0.4%	1.3%	7.0%	29.3%	65.9%	86.5%	91.3%			100.0%		
Burkholderia non-cepacia spp. (47) [a]		0	1	0	4	14	17	7	1			3	2	4
		0.0%	2.1%	2.1%	10.6%	40.4%	76.6%	91.5%	93.6%			100.0%		
Chryseobacterium spp. (59)		0	1	0	6	14	21	14	3				2	4
		0.0%	1.7%	1.7%	11.9%	35.6%	71.2%	94.9%	100.0%					
Delftia spp. (13)	0	1	2	5	5								0.25	0.5
	0.0%	7.7%	23.1%	61.5%	100.0%									
Elizabethkingia spp. (23)			0	1	12	8	1	0	1				0.5	1
			0.0%	4.3%	56.5%	91.3%	95.7%	95.7%	100.0%					
Ochrobactrum spp. (16)		0	1	1	8	6							0.5	1
		0.0%	6.2%	12.5%	62.5%	100.0%								
Pseudomonas non-aeruginosa spp. (340)		0	1	9	24	76	119	76	20			15	2	8
		0.0%	0.3%	2.9%	10.0%	32.4%	67.4%	89.7%	95.6%			100.0%		
Rhizobium spp. (15)		3	6	5	0	1							0.12	0.25
		20.0%	60.0%	93.3%	93.3%	100.0%								
Shewanella spp. (14)		0	1	6	6	1							0.25	0.5
		0.0%	7.1%	50.0%	92.9%	100.0%								
Sphingomonas spp. (19)		13	4	0	1	1							≤0.06	0.5
		68.4%	89.5%	89.5%	94.7%	100.0%								
Stenotrophomonas non-maltophilia spp. (12)		2	6	1	3								0.12	0.5
		16.7%	66.7%	75.0%	100.0%									

CLSI minocycline breakpoints are shown by green shading for susceptible, yellow for intermediate, and orange for resistant (CLSI M100 or M45). *Acinetobacter* spp. breakpoints were used for species without breakpoints.
[a]Organisms included: *Burkholderia cenocepacia* (11), *B. gladioli* (17), *B. multivorans* (19)

Table 2 Activity of minocycline and comparator antimicrobial agents tested against 424 *Acinetobacter* isolates (excluding *Acinetobacter baumannii-calcoaceticus* species complex)

Antimicrobial agent	No. of isolates	mg/L MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%I	%R	EUCAST[a] %S	%I	%R
Minocycline	424	0.12	0.5	≤0.06 to >8	98.8	0.2	0.9			
Meropenem-vaborbactam	424	0.25	1	≤0.015 to >32						
Meropenem	424	0.25	1	≤0.015 to >32	95.0	0.5	4.5	95.0	0.9	4.0
Imipenem	423	≤0.12	0.5	≤0.12 to >8	95.3	0.2	4.5	95.3	0.2	4.5
Tetracycline	358	2	4	≤0.5 to >8	94.1	2.2	3.6			
Amikacin	423	1	4	≤0.25 to >32	95.3	1.7	3.1	92.4 [b]		7.6
Aztreonam	424	>16	>16	0.5 to >16						
Ceftazidime	424	4	>16	≤0.25 to >16	79.5	8.3	12.3			
Colistin	423	≤0.5	2	≤0.5 to >8		90.5	9.5	90.5		9.5
Gentamicin	424	≤1	2	≤1 to >8	94.3	1.7	4.0	94.3 [b]		5.7
Levofloxacin	424	≤0.12	0.5	≤0.12 to >4	97.2	0.9	1.9	95.0	1.4	3.5

[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.
Organisms include: *Acinetobacter beijerinckii* (3), *A. berezinae* (34), *A. calcoaceticus* (2), *A. courvalinii* (6), *A. guillouiae* (8), *A. haemolyticus* (14), *A. johnsonii* (20), *A. junii* (27), *A. lwoffii* (78), *A. nosocomialis* (8), *A. pittii* (35), *A. proteolyticus* (2), *A. radioresistens* (49), *A. schindleri* (3), *A. soli* (10), *A. towneri* (2), *A. ursingii* (83), *A. variabilis* (6), *A. vivianii* (1), unspeciated *Acinetobacter* (33)

Table 3 Activity of minocycline and comparator antimicrobial agents tested against 411 *Achromobacter* spp. isolates

Antimicrobial agent	No. of isolates	mg/L MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%I	%R	EUCAST[a] %S	%I	%R
Minocycline	411	1	4	≤0.06 to >8	92.7	5.4	1.9			
Meropenem-vaborbactam	411	0.12	4	0.03 to >32						
Meropenem	411	0.25	16	0.03 to >32	85.9	3.9	10.2			
Imipenem	411	1	4	0.25 to >8	90.3	4.9	4.9			
Amikacin	411	>32	>32	≤0.25 to >32	9.5	5.6	84.9			
Aztreonam	411	>16	>16	2 to >16	1.0	1.0	98.1			
Cefepime	411	>16	>16	≤0.12 to >16	10.7	27.3	62.0			
Ceftazidime	411	4	16	0.25 to >16	76.9	13.1	10.0			
Gentamicin	411	>8	>8	≤0.12 to >8	6.1	2.7	91.2			
Levofloxacin	411	4	>4	≤0.12 to >4	36.0	30.7	33.3			
Piperacillin-tazobactam	411	≤0.5	16	≤0.5 to >64	92.2	3.6	4.1			

[a] Criteria as published in the "Other non-*Enterobacterales*" table in M100. (CLSI, 2020). EUCAST does not have breakpoints for this genus.
Organisms include: *Achromobacter denitrificans* (12), *A. insolitus* (6), *A. marplatensis* (1), *A. xylosoxidans* (202), unspeciated *Achromobacter* (190)

Figure 1 Infection types from which non-fermentative Gram-negative (NFGN) species were isolated, number of isolates