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Activity and Spectrum of Antimicrobial Coverage against Pathogens Collected from Patients with Hospital-acquired and Ventilator-associated Bacterial Pneumonia in USA Medical Centers

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SENTRY ANTIMICROBIAL SURVEILLANCE

Amended Abstract

Objective: To evaluate the frequency of occurrence and antimicrobial susceptibility of bacterial organisms collected from patients with hospital-acquired (HABP) and ventilator-associated bacterial pneumonia (VABP) in USA hospitals. We also evaluated the expected empirical coverage for broad-spectrum antimicrobials alone and 2 drug combinations.

Methods: Organisms were consecutively collected from patients hospitalized with pneumonia in 65 hospitals from all USA nine Census regions in 2010-2011 directed by a common prevalence style protocol. Susceptibility testing was performed by reference CLSI broth microdilution methods.

Results: 2,657 organisms were evaluated, 2,187 from HABP and 470 from VABP. The proportion of Gram-negative/Gram-positive was nearly 60%/40%. 63.6% of patients were male and 36.4% female. The median age values were 57 and 54 for HABP and VABP, respectively. Overall, 53.1% of patients were from ICU, including 44.5% of patients with HABP and 83.9% of patients with VABP. The five most common organisms were (% of total for HABP/VABP): *S. aureus* (36.3%/33.4%), *P. aeruginosa* (20.8%/17.9%), *Klebsiella* spp. (10.1%/10.6%), *Enterobacter* spp. (5.5%/8.3%) and *E. coli* (5.5%/4.9%), and these accounted for 77.6% of the total. 47.1% of *S. aureus* were oxacillin-resistant (MRSA) and 30.1% of *P. aeruginosa* were non-susceptible to imipenem. Among *Klebsiella* spp., 12.6% had an ESBL phenotype and 1.5% of strains were non-susceptible to imipenem. None of the antimicrobials alone provided adequate spectrum against the 5 most common organisms as a group. The 2 drug combination with best coverage (susceptibility to at least one of the compounds) for the top 5 organisms was amikacin plus vancomycin (VAN) or linezolid (LZD; 98.6% coverage), tobramycin plus VAN or LZD (95.2%), gentamicin plus VAN or LZD (94.7%), cefepime plus VAN or LZD (93.0%) and meropenem plus VAN or LZD (92.9%) and. The 6th and 7th most frequently isolated organisms were *S. maltophilia* (4.0%) and *Acinetobacter* spp. (3.8%), and exhibited high resistance rates to all antimicrobial agents tested.

Conclusion: Empirical antimicrobial therapy for HABP/VABP requires at least 2 agents to provide adequate coverage for the most common organisms. The best antimicrobial coverage was obtained with the combination of an aminoglycoside (amikacin, tobramycin or gentamicin) with VAN or LZD.

Introduction

The antimicrobial treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) is frequently initiated empirically and the selection of agents is deeply influenced by the understanding of causative pathogens. The organisms causing HABP and VABP require prompt and appropriate antimicrobial choices to prevent poor clinical outcomes, especially for increasing incidence of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and nonfermentative Gram-negative bacilli.

In the present study, we evaluated the frequency of occurrence and antimicrobial susceptibility of bacterial organisms collected from patients with HABP and VABP in USA hospitals through the SENTRY Antimicrobial Surveillance Program (2010-2011). We also evaluated the expected empirical coverage for broad-spectrum antimicrobials used alone and by two drug combinations.

Materials and Methods

Organism collection: Organisms were consecutively collected from patients hospitalized with pneumonia in 65 hospitals from all nine USA Census regions in 2010-2011, directed by a common prevalence style protocol. The participating medical centers were requested to collect and refer 100 consecutive pathogens each year from lower respiratory tract sites determined to be significant by local specimen quality criteria as the reported probable cause of pneumonia.

Methods-continued

Susceptibility testing: Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine antimicrobial susceptibility of broad-spectrum agents commonly used to treat HABP and VABP. Validated MIC panels were manufactured by Thermo Fisher Scientific Inc. (formerly TREK Diagnostics; Cleveland, Ohio, USA). Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included: *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619.

Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime MIC values were ≥2 mg/L were considered to be phenotype-positive for ESBL production (CLSI, 2012).

Results

- A total of 2,657 organisms were evaluated, 2,187 from HABP and 470 from VABP. The proportion of Gram-negative/Gram-positive was nearly 60%/40%. Overall, 53.1% of patients were from ICU, including 44.5% of patients with HABP and 83.9% of patients with VABP. Furthermore, 63.6% of patients were male, and the median age was 57 and 54 for HABP and VABP, respectively.
- The five most common organisms were (% of total for HABP/VABP): *S. aureus* (36.3%/33.4%), *P. aeruginosa* (20.8%/17.9%), *Klebsiella* spp. (10.1%/10.6%), *Enterobacter* spp. (5.5%/8.3%) and *E. coli* (5.5%/4.9%), and these accounted for 77.6% of the total (2,061 organisms; Tables 1 and 2).
- Linezolid ($MIC_{50/90}$, 1/1 mg/L), vancomycin ($MIC_{50/90}$, 1/1 mg/L) and tigecycline ($MIC_{50/90}$, 0.06/0.25 mg/L) showed complete activity (100.0% susceptibility) against *S. aureus*; while 47.1% of strains were oxacillin-resistant (MRSA; Table 2).
- Against the three most frequently isolated Enterobacteriaceae species/genera (*E. coli, Klebsiella* spp. and *Enterobacter* spp.), the most active compounds were amikacin (97.4 to 100.0% susceptible by CLSI criteria), the carbapenems meropenem and imipenem (98.1 to 99.3% susceptible) and tigecycline (98.1 to 100.0% susceptible). An ESBL phenotype was observed in 16.8% of *E. coli* and 12.6% of *Klebsiella* spp., and 1.5% of *Klebsiella* spp. strains were non-susceptible to imipenem (Table 2).
- The most active compounds against *P. aeruginosa* were colistin (99.4% susceptible), amikacin (96.1% susceptible) and tobramycin (91.8% susceptible; Table 2); 30.1% of *P. aeruginosa* strains were non-susceptible to imipenem.
- None of the antimicrobials alone provided adequate spectrum against the five most common organisms as a group. The two drug combination with best coverage (susceptibility to at least one of the compounds) for the top five organisms was amikacin plus vancomycin or linezolid (98.6% coverage), followed by tobramycin plus vancomycin or linezolid (95.2%), gentamicin plus vancomycin or linezolid (94.7%), cefepime plus vancomycin or linezolid (93.0%) and meropenem plus vancomycin or linezolid (92.9%; Table 3).
- The 6th and 7th most frequently isolated organisms were *S. maltophilia* (4.0%) and *Acinetobacter* spp. (3.8%), and these pathogens exhibited high resistance rates to all antimicrobial agents tested.

Table 1. The most frequently isolated pathogens from HABP and VABP.

	Organism: no. of isolates (% of total)	
	HABP	VABP
1.	*S. aureus* - 794 (36.3)	*S. aureus* - 157 (33.4)
2.	*P. aeruginosa* - 455 (20.8)	*P. aeruginosa* - 84 (17.9)
3.	*Klebsiella* spp. - 220 (10.1)	*Klebsiella* spp. - 50 (10.6)
4.	*Enterobacter* spp. - 121 (5.5)	*Enterobacter* spp. - 39 (8.3)
5.	*E. coli* - 120 (5.5)	*Acinetobacter* spp. - 35 (7.4)
6.	*S. maltophilia* - 91 (4.2)	*E. coli* - 23 (4.9)
7.	*Serratia* spp. - 69 (3.2)	*Serratia* spp. - 19 (4.0)
8.	*Acinetobacter* spp. - 67 (3.1)	*S. maltophilia* - 17 (3.6)
9.	*H. influenzae* - 62 (2.8)	*H. influenzae* - 15 (3.2)
10.	*S. pneumoniae* - 52 (2.4)	

Table 2. Antimicrobial susceptibility of the five top organisms isolated from HABP and VABP.

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Staphylococcus aureus (949)					
Oxacillin	1	>2	≤0.25 – >2	52.9 / 47.1	52.9 / 47.1
Ciprofloxacin	1	>4	0.06 – >4	51.2 / 47.5	51.2 / 48.8
Clindamycin	≤0.25	>2	≤0.25 – >2	72.8 / 26.8	72.4 / 27.2
Gentamicin	≤1	≤1	≤1 – >8	96.9 / 2.6	96.4 / 3.6
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.06	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Escherichia coli (143)					
Amikacin	2	8	0.5 – >32	99.3 / 0.7	97.9 / 0.7
Cefepime	≤0.5	8	≤0.5 – >16	90.9 / 8.4	84.6 / 11.2
Ceftazidime	0.25	8	≤0.015 – >32	89.5 / 9.1	83.2 / 10.5
Ciprofloxacin	≤0.03	>4	≤0.03 – >4	59.4 / 40.6	58.7 / 40.6
Colistin	≤0.5	≤0.5	≤0.5 – 1	- / -	100.0 / 0.0
Gentamicin	≤1	>8	≤1 – >8	86.0 / 13.3	81.8 / 14.0
Imipenem	≤0.12	≤0.12	≤0.12 – 2	99.3 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	59.4 / 39.9	59.4 / 40.6
Meropenem	≤0.12	≤0.12	≤0.12 – 4	99.3 / 0.7	99.3 / 0.0
Piperacillin/tazobactam	2	64	≤0.5 – >64	88.1 / 7.7	84.6 / 11.9
Tigecycline[b]	0.12	0.25	0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Tobramycin	1	8	0.25 – >16	83.9 / 9.1	81.1 / 16.1
Klebsiella spp (270)[c]					
Amikacin	1	2	≤0.25 – >32	97.4 / 0.4	96.7 / 2.6
Cefepime	≤0.5	1	≤0.5 – >16	95.2 / 4.4	90.0 / 5.9
Ceftazidime	0.12	2	0.03 – >32	91.1 / 8.9	88.9 / 8.9
Ciprofloxacin	≤0.03	1	≤0.03 – >4	90.4 / 8.1	88.9 / 9.6
Colistin	≤0.5	≤0.5	≤0.5 – >4	- / -	98.9 / 1.1
Gentamicin	≤1	≤1	≤1 – >8	94.4 / 4.1	94.4 / 5.6
Imipenem	≤0.12	0.25	≤0.12 – >8	98.5 / 1.5	98.5 / 0.7
Levofloxacin	≤0.5	1	≤0.5 – >4	92.2 / 7.0	90.4 / 7.8
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.1 / 1.5	98.5 / 1.1
Piperacillin/tazobactam	4	16	≤0.5 – >64	90.4 / 7.0	83.0 / 9.6
Tigecycline[b]	0.25	1	0.06 – >4	98.1 / 0.4	92.6 / 1.9
Tobramycin	0.5	1	≤0.12 – >16	92.2 / 4.4	91.1 / 7.8
Enterobacter spp (160)[d]					
Amikacin	1	2	0.5 – 8	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.5	4	≤0.5 – >16	95.6 / 2.5	86.3 / 4.4
Ceftazidime	0.25	>32	0.03 – >32	70.6 / 25.6	67.5 / 29.4
Ciprofloxacin	≤0.03	0.25	≤0.03 – >4	93.8 / 5.6	92.5 / 6.3
Colistin	≤0.5	>4	≤0.5 – >4	- / -	86.9 / 13.1
Gentamicin	≤1	≤1	≤1 – >8	95.0 / 3.8	95.0 / 5.0
Imipenem	0.5	1	≤0.12 – >8	98.1 / 0.6	99.4 / 0.6
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.4 / 5.0	93.1 / 5.6
Meropenem	≤0.12	≤0.12	≤0.12 – >8	99.4 / 0.6	99.4 / 0.6
Piperacillin/tazobactam	4	64	≤0.5 – >64	73.1 / 8.1	70.6 / 26.9
Tigecycline[b]	0.25	1	0.06 – 4	98.1 / 0.0	95.0 / 1.9
Tobramycin	0.5	1	≤0.12 – >16	93.8 / 3.8	93.8 / 6.3
Pseudomonas aeruginosa (539)					
Amikacin	4	8	≤0.25 – >32	96.1 / 2.2	91.7 / 3.9
Cefepime	4	16	≤0.5 – >16	79.2 / 9.3	79.2 / 20.8
Ceftazidime	4	>32	0.25 – >32	77.4 / 17.6	77.4 / 22.6
Ciprofloxacin	0.25	>4	≤0.03 – >4	70.9 / 23.0	62.2 / 29.1
Colistin	1	1	≤0.5 – >4	99.4 / 0.2	99.4 / 0.6
Gentamicin	2	8	≤1 – >8	87.6 / 9.3	87.6 / 12.4
Imipenem	1	>8	≤0.12 – >8	69.9 / 24.7	75.3 / 13.7
Levofloxacin	1	>4	≤0.5 – >4	66.4 / 24.3	54.5 / 33.6
Meropenem	0.5	8	≤0.12 – >8	74.2 / 17.7	74.2 / 8.2
Piperacillin/tazobactam	8	>64	≤0.5 – >64	69.0 / 17.1	69.0 / 31.0
Tigecycline[b]	4	>4	0.06 – >4	- / -	- / -
Tobramycin	0.5	2	≤0.12 – >16	91.8 / 7.1	91.8 / 8.2

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].
c. Includes: *Klebsiella oxytoca* (63 strains), *K. ozaenae* (1 strain), *K. planticola* (1 strain), *K. pneumoniae* (202 strains), and unspeciated *Klebsiella* (3 strains).
d. Includes: *Enterobacter aerogenes* (45 strains), *E. asburiae* (2 strains), *E. cloacae* (104 strains), and unspeciated *Enterobacter* (9 strains).

Table 3. Antimicrobial combinations that provided best coverage for the top five organisms isolated from HABP/VABP[a].

Antimicrobial agents	% susceptible to at least one agent
1. Amikacin + vancomycin or linezolid	98.6%
2. Tobramycin + vancomycin or linezolid	95.2%
3. Gentamicin + vancomycin or linezolid	94.7%
4. Cefepime + vancomycin or linezolid	93.0%
5. Meropenem + vancomycin or linezolid	92.9%

a. Includes the top five organisms from both hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP).

Conclusions

- Empirical antimicrobial therapy for HABP/VABP requires at least two agents to provide adequate coverage (>92.9% susceptible) for the most common pathogens.
- The best antimicrobial coverage was obtained with the combination of an aminoglycoside (amikacin, tobramycin or gentamicin) with vancomycin or linezolid.

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