Microbial Etiologies of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

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Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) can be caused by a wide variety of bacteria that originate from the patient flora or the health care environment. We review the medical and microbiology literature and the results of the SENTRY Antimicrobial Surveillance Program (1997–2008) to establish the pathogens most likely to cause HABP or VABP. In all studies, a consistent 6 organisms (*Staphylococcus aureus* [28.0%], *Pseudomonas aeruginosa* [21.8%], *Klebsiella* species [9.8%], *Escherichia coli* [6.9%], *Acinetobacter* species [6.8%], and *Enterobacter* species [6.3%]) caused ~80% of episodes, with lower prevalences of *Serratia* species, *Stenotrophomonas maltophilia,* and community-acquired pathogens, such as pneumococci and *Haemophilus influenzae.* Slight changes in the pathogen order were noted among geographic regions; Latin America had an increased incidence of nonfermentative gram-negative bacilli. In addition, VABP isolates of the same species had a mean of 5%–10% less susceptibility to frequently used extended-spectrum antimicrobials, and the rate of drug resistance among HABP and VABP pathogens has been increasing by 1% per year (2004–2008). In conclusion, the empirical treatment of HABP and VABP due to prevailing bacterial causes and emerging drug resistance has become more challenging and requires use of multidrug empirical treatment regimens for routine clinical practice. These facts have profound impact on the choices of comparison therapies to be applied in contemporary new drug clinical trials for pneumonia.

The antimicrobial management of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) is heavily influenced by the understanding of causative pathogens that affect patients with disease onset >48 h after hospital admission [1]. Those organisms, along with complicating risk factors and comorbidities, result in extended hospitalization periods, escalated health care costs, and the requirement of potent, broad-spectrum antimicrobial agents often used in expensive combination regimens [1–6]. The organisms causing HABP and VABP require prompt and appropriate choices to prevent poor clinical outcomes, especially for increasing incidence of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) [7] and nonfermentative gram-negative bacilli in VABP [8].

To appreciate the challenges of empirical therapy of HABP and VABP, the lesser problems of treating other types of pneumonia, such as community-acquired bacterial pneumonia (CABP), must be considered. Echols et al [9] summarized the pathogens causing mild-to-moderate CABP from the records of the US Food and Drug Administration, as found in a review of the Summary Basis of Approvals for 1996–2007 (5025 cases). In those data, only 44.7% of episodes had a pathogen cultured: 26.1% of pathogens were typical bacterial species, and 18.6% were atypical organisms (>90% mycoplasmas or *Chlamydophila pneumoniae*). Of the culturable bacterial species, 32.7% and 25.6% were *Streptococcus pneumoniae* and *Haemophilus influenzae,* respectively [9]. A personal review of recently published reports of phase 3 clinical trials of tigecycline for treatment of CABP [10–12] confirmed the dominant path-

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Clinical Infectious Diseases 2010; 51(S1):S81–S87

1058-4838/2010/5103S1-0013$15.00
DOI: 10.1086/653053

Table 1. Pathogen Rates from 3 Recent Phase 3 Clinical Trials of Tigecycline for Treatment of Community-Acquired Bacterial Pneumonia.

Rank	Pathogen (rate, %)
1	*Streptococcus pneumoniae* (41.8)
2	*Mycoplasma pneumoniae* (19.1)[a]
3	*Chlamydophila pneumoniae* (10.1)[a]
4	*Haemophilus influenzae* (8.6)
5	*Staphylococcus aureus* (5.5)
6	*Haemophilus parainfluenzae* (4.4)
7	*Legionella pneumophila* (3.5)[a]
8	*Klebsiella pneumoniae* (3.3)
9	*Moraxella catarrhalis* (2.0)
10	*Escherichia coli* (1.8)

NOTE. Data are from [10–12].

[a] These pathogens were found using serological examination and/or special culture. All other pathogens were found using routine culture.

ogenic roles of *S. pneumoniae* (41.8%), *Mycoplasma pneumoniae* (19.1%), *C. pneumoniae* (10.1%), and *H. influenzae* (8.6%) (Table 1). The remaining top 10 pathogens causing CABP include only 5.5% *S. aureus* and 5.1% Enterobacteriaceae—small numbers of cases that would require expanded-spectrum agents or combination chemotherapies as frequently applied regimens (Table 1).

RESULTS AND DISCUSSION

Etiologies of HABP. In contrast to CABP, HABP has a long history of causative pathogens dominated by *S. aureus,* nonfermentative gram-negative bacilli, and Enterobacteriaceae species. Data from studies (Table 2) reviewing isolates from the period 1985–1998 from 3 investigations [1] clearly show that *S. aureus* (15%–32% of cases) and *Pseudomonas aeruginosa* (16%–30% of cases) were common causes of HABP, followed by *Enterobacter* species, *Klebsiella* species, and *Escherichia coli.* The CABP-causing pathogen *H. influenzae* achieved high ranking (second) only in the Eole study [13], which involved surgical patients. In more recent publications, few geographically comprehensive analyses were available; thus, this article summarizes the experience of the SENTRY Antimicrobial Surveillance Program during the period 1997–2008 from the data retrieved for hospitalized patients with pneumonia [14–18]. The data were collected from patients in North America, Europe, and Latin America (Asia-Pacific region not presented), each having demographic profiles that allowed categorization of HABP or VABP (41,821 total cases). All pathogens were available for central laboratory processing by reference broth microdilution methods of the Clinical and Laboratory Standards Institute [19], with appropriate interpretive breakpoints [20]. Results were processed by geographic region, HABP, VABP, and all results for pathogen prevalence and antimicrobial susceptibility and resistance rates.

Table 3 shows the incidence of etiologic organisms causing the HABP cases (31,436 episodes) in the recent SENTRY Program files. The results tabulated across all regions showed that the top 6 pathogens caused nearly 80% of all cases, and only 5.6% of patients had CABP-causing pathogens (eg, *S. pneumoniae* and *H. influenzae).* Regional variation in pathogen rank was encountered, but the same top 6 organisms prevailed (in 75.8% of cases in Europe and 85.4% of cases in Latin America; data not shown). A significant change in rank was that *P. aeruginosa* was the most frequent pathogen causing HABP in Latin America (28.2%), with *Acinetobacter* species ranked third (13.3%, compared with only 4.8%–5.6% in the other regions) (Table 3). *E. coli* was a prominent pathogen (third) in Europe. All other pathogens did not vary by >1 rank among regions. The percentage of identified pathogens causing CABP was only 5.6% overall but was highest (7.3%) in Europe and lowest in Latin America (3.7%). Some nations have reported increased incidence of nonfermentative gram-negative bacilli (eg, *Pseu-*

Table 2. Frequency of Bacterial Pathogens Isolated from Patients with Hospital-Acquired Bacterial Pneumonia, 1985–1998.

		Frequency, %				
		NNIS				
Rank	Organism	1985–1988	1989	1992–1997	1992	1997–1998
1	*Staphylococcus aureus*	15	20	20	32	27
2	*Pseudomonas aeruginosa*	17	16	21	30	17
3	*Enterobacter* species	10	11	9	8	4
4	*Klebsiella* species	7	7	8	8	4
5	*Escherichia coli*	6	4	4	7	13
6	*Haemophilus influenzae*	6	5	–	10	19
7	*Acinetobacter* species	–	4	6	10	2
8	*Serratia* species	5	–	4	–	4

NOTE. Data are from the National Nosocomial Infection Surveillance (NNIS) Study (1985–1997), the European Prevalence of Infection in Intensive Care Study (1992), and the Eole Study (1997–1998) [1, 13].

Table 3. Regional Incidence of Pathogens Isolated from Patients Hospitalized with Pneumonia in the Last 5 Years of the SENTRY Antimicrobial Surveillance Program (31,436 Cases).

	Incidence, %			
Pathogen	All regions	United States	Europe	Latin America
Staphylococcus aureus	28.0	36.3	23.0	20.1
Pseudomonas aeruginosa	21.8	19.7	20.8	28.2
Klebsiella species	9.8	8.5	10.1	12.1
Escherichia coli	6.9	4.6	10.1	5.5
Acinetobacter species	6.8	4.8	5.6	13.3
Enterobacter species	6.3	6.5	6.2	6.2
Serratia species	3.5	4.1	3.2	2.4
Stenotrophomonas maltophilia	3.1	3.3	3.2	2.3
Streptococcus pneumoniae	2.9	2.5	3.6	2.4
Haemophilus influenzae	2.7	2.5	3.7	1.3

domonas species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*) causing HABP, compared with that in the United States (28% in the SENTRY Program) [21]; these countries in the Asia-Pacific area included Pakistan (67%), India (58%), Philippines (55%), Malaysia (52%), Thailand (46%), Taiwan (44%), China (34%), and Korea (31%).

VABP etiology, compared with that of HABP. In recent phase 3 clinical trials of doripenem and tigecycline for treatment of HABP and/or VABP [22, 23], the rank order of pathogens for the combined pneumonia types in doripenem trials was *S. aureus* (28.0%), *P. aeruginosa, Klebsiella* species, *E. coli, Acinetobacter* species, and *Enterobacter* species. The rank in tigecycline trials was *S. aureus, Acinetobacter* species, *Klebsiella* species, *E. coli, P. aeruginosa,* and *Enterobacter* species. In the tigecycline trial, the microbiology results provided by Wyeth [10–12] showed that *S. aureus* was the most common pathogen causing HABP and VABP, but *P. aeruginosa* and *Acinetobacter* isolates were significantly more prevalent among patients with VABP. The tigecycline trials encouraged enrollment of patients infected with MRSA and attempted to minimize the number of episodes possibly caused by nonfermentative gram-negative bacilli *(P. aeruginosa)*. Similarly, the experience of Abrahamian et al [2] and Kollef et al [7] (Table 4) shows that the incidence of gram-negative bacillary species increases (markedly for *Haemophilus* species, from 5.6% to 12.2%) in VABP, compared with HABP. More accurate, higher quality, invasive diagnostic sample obtainment methods (eg, bronchoalveolar lavage and brush biopsy) probably facilitated the greater recovery of these fastidious pathogens in VABP cases. Paradoxically, rates of *S. aureus* as an etiologic agent and of MRSA among those strains appeared to decrease.

These differences between HABP and VABP etiologies were confirmed by the SENTRY Program results from the last 5 surveillance years (2004–2008; 10,081 cases) [14, 18]. Table 5 shows the comparisons of HABP and VABP pathogens (top 6) causing episodes in the United States and worldwide. The key observations for the all-region data were that (1) *P. aeruginosa* (26.6%) and *Acinetobacter* species were more common in VABP, (2) incidence of *S. aureus* was lower among patients with VABP than among patients with HABP (19.5% vs 26.6%), (3) the top 6 pathogens accounted for 79.4%–81.7% of cases, and (4) the incidence of pathogens causing CABP was greater in VABP (2.6%–4.1%). The results from the United States were generally similar to the worldwide statistics, with the exception that the incidence of *Acinetobacter* species was not as high (4.4% in HABP and 5.3% in VABP) (Table 5).

Patient age can also influence the incidence of pathogens, as noted in a study by Foglia et al [3] in which the most common etiologies of HABP and VABP were *P. aeruginosa* (25.2%–38.4%), other gram-negative bacilli (26.6%–51.4%), and *S. aureus* (14.6%–28.4%). The criteria of pathogen prediction using early versus late onset revealed dominant maternal transmission

Table 4. Frequency of Bacterial Pathogens Associated with Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP)

	Percentage of isolates (no)	
Organism	HABP (n = 835)	VABP (n = 499)
MRSA	47.1 (48.6)	42.5 **(34.4)**
Pseudomonas species	18.4	21.2
Klebsiella species	7.1	8.4
Haemophilus species	5.6	**12.2**
Enterobacter species	4.3	5.6
Streptococcus pneumonaie	3.1	5.8
Acinetobacter species	2.0	3.0

NOTE. Data are from [2, 7]. Boldface indicates a significant change or difference in incidence compared with HABP. MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 5. Differences in Causative Pathogens of Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) in the United Stated and 3 Other Regions in the SENTRY Antimicrobial Surveillance Program, 2004–2008.

	Percentage of cases			
	United States (n = 2585)		All regions (n = 7496)	
Pathogen	HABP	VABP	HABP	VABP
Staphylococcus aureus	36.5[a]	31.9[a]	26.6[a]	19.5[a]
Pseudomonas aeruginosa	19.0[a]	21.4[a]	22.4[a]	26.6[a]
Enterobacter species	8.6	8.8	7.5	7.0
Klebsiella species	8.0	6.6	10.5	10.2
Serratia species	5.5	6.5	4.1	4.1
Acinetobacter species	4.4	5.3	8.3[a]	14.3[a]
Top 6 species	80.4	80.5	79.4	81.7
Pathogens causing CABP[b]	3.3	6.6	2.6	4.1

[a] Significant difference in incidence rate between the United States and all regions.

[b] *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis.*

of β-haemolytic streptococci and, rarely, *H. influenzae* causing early onset pneumonia [3]; however, other authors [24] have presented data challenging this concept, because the pathogens have evolved to be the same for early- and late-onset disease and for HABP and VABP, regardless of age. Furthermore, extreme differences in the incidences of etiologic agents causing VABP have been documented between institutions and treatment units (usually intensive care units); generation of local data about etiologic organisms and their antibiograms is required [5, 25, 26]

Resistance trends and/or rates comparing HABP and VABP. The SENTRY Program results derived from reference broth microdilution tests were again used to assess susceptibility rates in the top 6 pathogens causing HABP and VABP (Table 6). The data were generated from all cases from the last 5 surveillance years (2004–2008) and across all 3 geographic regions. With use of data on *S. aureus* for 7 selected antimicrobial agents, isolates from patients with VABP were more susceptible to β-lactams (including methicillin and fluoroquinolones) but more resistant to aminoglycosides. These results confirm previous results [2, 7]. In contrast, the 5 tabulated gram-negative bacilli showed >5% reduction in the susceptibility rate (Table 6) for 17 (56.7%) of 30 drug-organism comparisons. In fact, decreases of >10% in susceptibility rates were (3 occurrences) noted among these 30 comparisons (2004–2008), with a mean 4.3% lower susceptibility rate for gram-negative bacilli when VABP isolates were compared with HABP organisms.

Other newer agents (eg, ceftobiprole, doripenem, and tigecycline) were also evaluated, and decreases in the in vitro susceptibility for VABP isolates were also documented, even without significant exposure to these drugs during the last 5 years of surveillance (data not shown). An examination of the levofloxacin minimum inhibitory concentration (MIC) distributions and percentage susceptibility indicated a significant shift in MICs to levels predicting compromised target attainment for some VABP isolates via pharmacokinetic and/or pharmacodynamic profiles (8% lower rate of susceptibility for *Klebsiella* species) (Table 6).

Geographic trends in drug resistance among HABP and VABP isolates. The SENTRY Program [14–18] was used to determine trends in antimicrobial resistance (8–9 agents) for 3 separate years (2004, 2006, and 2008). The top 6 pathogens were analyzed against all HABP and/or VABP strains worldwide. Table 7 shows trends for *S. aureus* and *Klebsiella* species and 2 recently released broad-spectrum products (doripenem and tigecycline) in North America. Clearly, drug susceptibilities in *S. aureus* increased, and susceptibility rates in *Klebsiella* species

Table 6. Variations in Drug Susceptibility Rates between Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Isolates from All SENTRY Antimicrobial Surveillance Program Regions, 2004–2008.

	Susceptibility, % (HABP/VABP)					
Antimicrobial agent	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella* species	*Escherichia coli*	*Acinetobacter* species	*Enterobacter* species
Oxacillin	41/49[a]	…	…	…	…	…
Gentamicin	87/78	**72/66**	**82/71**	85/84	**25/18**	**87/81**
Levofloxacin	42/52[a]	60/58	**84/76**	72/74	**16/11**	88/89
Cefepime	41/49	**70/65**	**87/78**	91/87	**27/20**	93/91
Ceftazidime	41/49	**68/63**	**77/68**	**84/78**	12/10	62/64
Meropenem	41/49	**72/66**	>99/99	100/100	**58/46**	100/99
Piperacillin-tazobactam	41/49	**76/71**	**76/71**	86/82	**19/11**	71/70

NOTE. Data are from [14–18]. Boldface indicated ⩾5% decrease in susceptibility for VABP isolates, compared with HABP isolates. More than a 10% lower susceptibility occurred with 3 drug-pathogen analyses.

[a] VABP *S. aureus* isolates were generally more susceptible to oxacillin and fluoroquinolones.

Table 7. Drug Resistance in Isolates of *Staphylococcus aureus* and *Klebsiella* Species Causing Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia in North America from the SENTRY Antimicrobial Surveillance Program, 2004–2008

	Susceptibility, %		
Pathogen, antimicrobial agent	2004	2006	2008
S. aureus (n = 1213)			
Oxacillin	42	38	46
Gentamicin	95	96	98
Levofloxacin	44	44	49
Cefepime	42	38	46
Ceftazidime	34	37	43
Piperacillin-tazobactam	42	38	46
Meropenem	42	38	46
Doripenem[a]	42	38	46
Tigecycline[a]	100	>99	100
Klebsiella species (n = 291)			
Gentamicin	88	98	87
Levofloxacin	94	90	84[b]
Cefepime	98	97	90[b]
Ceftazidime	94	94	85[b]
Piperacillin-tazobactam	90	90	87
Meropenem	99	97	94[b]
Doripenem[a]	99	97	93[b]
Tigecycline[a]	96	98	99

NOTE. Data are from R.N.J.

[a] US Food and Drug Administration package insert breakpoint criteria (2009) [23].

[b] Decreases in susceptibility at ⩾5%.

decreased during the 5-year period. The decreases equate to ~1% per year.

Regional geographic patterns of drug resistance can markedly influence these statistics, and Table 8 summarizes these data from North America (6 pathogens; only 2 represented in Table 7), Europe, and Latin America. A generalized decrease in drug susceptibility was observed in HABP and/or VABP isolates over the last 5 years of surveillance; the decrease was greatest in Latin America, and except for the carbapenems (doripenem and meropenem for treatment of infection due to *Acinetobacter*) and fluoroquinolones (for treatment of selected Enterobacteriaceae infection), drug susceptibility remained stable in North America. Greater decreases in drug susceptibility (⩾10%) were most often observed in Latin America among *Acinetobacter* species (doripenem, meropenem, and piperacillin-tazobactam), *Klebsiella* species (cefepime, gentamicin, and piperacillin-tazobactam), and *Enterobacter* species (ceftazidime). Clearly, drug resistance was more common for the VABP isolates and was consistently increasing, regardless of monitored geographic location of the organisms.

Drug resistance was interpreted in accordance with the Clinical Laboratory Standards Institute breakpoints, which are significantly different (higher MICs) from those recently approved by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and European Medicines Evaluation Agency (EMEA) for European chemotherapy [19, 20, 27]. By applying EUCAST breakpoints to SENTRY Program data on the HABP and/or VABP pathogen results for each analyzed antimicrobial (Tables 6–8), the resistance rates become significantly higher, and a greater number of trends toward resistance would be recognized (β-lactams tested against enteric bacilli and fluoroquinolones and carbapenems against nonfermentative gram-negative species). Obviously, a unified and harmonized series of breakpoints should be selected by the US Food and Drug Administration and EUCAST (EMEA) to guide appropriate HABP and VABP therapies.

SUMMARY

Clinical trials, international surveillance data, and published studies of the causes of pneumonia in hospitalized patients were reviewed [1–8, 13–18, 21–26] for indicators of consistent trends in the incidence of pathogens, differences in antimicrobial resistance between HABP and VABP isolates, and trends in drug-resistance patterns over time and among geographic areas [14–18], as interpreted by criteria from standardized susceptibility breakpoint organizations [19, 20, 27]. Findings indicate that HABP and VABP bacterial etiologies and incidences of pathogens are remarkably consistent over time (past 10–12 years), among continents, and for ventilator-associated or nonassociated nosocomial pneumonia. For VABP, our findings are similar to those in articles from the National Healthcare Safety Network at the Centers for Disease Control and Prevention (2006–2007) [28–30], in which incidence rates were highest in the burn (12.3 cases per 1000 ventilator-days), trauma (10.2 cases per 1000 ventilator-days), and neurosurgical (7.0 cases per 1000 ventilator-days) intensive care units, compared with an overall mean rate in the intensive care unit of 2.7–3.6 cases per 1000 ventilator-days. A trend of decreasing numbers of VABP cases in intensive care units was noted in data from the period 1992–2004 through 2006 [28, 29].

These conclusions can be limited by local epidemic and/or endemic spread of some organisms, but the top 6 most prevalent pathogens (*S. aureus, P. aeruginosa, Klebsiella* species, *E. coli, Acinetobacter* species, and *Enterobacter* species) consistently cause 80% of all HABP or VABP episodes, in contrast to only 3.7%–7.3% by *S. pneumoniae* and *Haemophilus* species. Any treatment guideline [1, 3, 31, 32] must take into account that the routine empirical use of 2- or 3-drug regimens may be required to cover >90% of these contemporary pathogens. Hidron et al [30] also tabulated the number of yeast found in VABP and concluded that 2.7% of cases have fungal isolates.

Furthermore, emerging drug resistance to frequently used broad-spectrum agents (third- or fourth-generation cephalo-

Table 8. Drug Resistance in the Top 6 Pathogens Causing Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia in North America, Europe, and Latin America from the SENTRY Antimicrobial Surveillance Program, 2004–2008.

Continent, pathogen	Rank (%)	Antimicrobials with ⩾5% increase in resistance[a]
North America		
Staphylococcus aureus	1 (36.3)	None
Pseudomonas aeruginosa	2 (19.7)	Meropenem
Klebsiella species	3 (8.5)	**Levofloxacin**, cefepime, ceftazidime, meropenem, doripenem
Enterobacter species	4 (6.5)	None
Acinetobacter species	5 (4.8)	Levofloxacin, cefepime, **meropenem**, **doripenem**
Escherichia coli	6 (4.6)	Piperacillin-tazobactam
Europe		
S. aureus	1 (23.0)	None
P. aeruginosa	2 (20.8)	None
E. coli	3 (10.1)	Gentamicin, levofloxacin, cefepime, ceftazidime, piperacillin-tazobactam
Klebsiella species	3 (10.1)	Levofloxacin, cefepime, ceftazidime
Enterobacter species	5 (6.2)	Levofloxacin
Acinetobacter species	6 (5.6)	Gentamicin, levofloxacin, ceftazidime, piperacillin-tazobactam, doripenem
Latin America		
P. aeruginosa	2 (28.2)	None
S. aureus	2 (20.1)	Oxacillin, gentamicin, cefepime, ceftazidime, piperacillin-tazobactam, meropenem, doripenem
Acinetobacter species	3 (13.3)	Levofloxacin, ceftazidime, **piperacillin-tazobactam**, **meropenem**, **doripenem**
Klebsiella species	4 (12.1)	**Gentamicin**, levofloxacin, **cefepime**, ceftazidime, **piperacillin-tazobactam**
Enterobacter species	5 (6.2)	Levofloxacin, **ceftazidime**
E. coli	6 (5.5)	None

NOTE. Data are from [14–18]. Nine selected agents were tabulated. Broad-spectrum antimicrobials analyzed were cefepime, ceftazidime, gentamicin, levofloxacin, piperacillin-tazobactam, doripenem, meropenem, oxacillin, and tigecycline. Boldface indicates antimicrobials that had ⩾10% increase in resistant rate.

[a] Interpretive criteria of the Clinical Laboratory Standards Institute or the US Food and Drug Administration (doripenem and tigecycline), 2009.

sporins, carbapenems, β-lactam and/or β-lactamase inhibitor combinations, fluoroquinolones, aminoglycosides, and new classes [tigecycline]) requires further modifications of treatment guidelines [1, 3, 31, 32] or clinical trial designs for new, candidate agents. Tables 6–8 shows alarming proof of emerging drug resistance in numerous antimicrobial classes and increases over the last 5 years of surveillance for isolates causing HABP and VABP (greatest for VABP). Obvious geographic differences in drug resistance phenotypes will require specific national and regional empirical therapies, and local (hospital) epidemiologic studies and antibiograms focused on HABP and/or VABP treatments should always be preferred.

The most positive drug susceptibility finding from this review was the apparent shift of *S. aureus* isolates (most common cause of HABP and VABP) toward lower occurrence and at a lower rate of MRSA infection. These facts should be considered in the designs of future clinical trials to select ethical comparison treatments (combinations to achieve >90% empirical coverage and greatest success [33–36]) for testing new agents. As the pathogens causing hospital-based pneumonia become more drug resistant, clinical trial designs become more complex, thus making monotherapeutic protocols nearly impossible and the analyses of trial results extremely difficult. When modified trial designs become available, thought must be given to use of early-phase clinical trial or wild-type study drug MIC distributions to prospectively model the most appropriate doses for optimized pharmacokinetic and/or pharmacodynamic target attainment and reduced adverse event profiles.

Acknowledgments

Potential conflicts of interest. RNJ and JMI Laboratories have received research/educational grants from AB Bioisk, Abbott, Anacor, API, Arpida, Astellas, AstraZeneca, Avexa, Bayer, bioMérieux, Cadence, Calixa, Cempra, Cerexa, Cornerstone, Cubist, Daiichi, Elan, Elanco, Enanta, GlaxoSmithKline, Johnson & Johnson (Ortho McNeil), Merck, Nabriva, Novartis, Novexel, Optimer, Ordway, Osmotics, Pacific Beach, Peninsula,

Pfizer, Protez, Schering-Plough, Shionogi, Targanta (The Medicines Co), Theravance, TREK Diagnostics, ViroPharma, and Wyeth.

Supplement sponsorship. This article was published as part of a supplement entitled "Workshop on Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia," sponsored by the US Food and Drug Administration, Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and the Society of Critical Care Medicine, with financial support from the Pharmaceutical Research and Manufacturers of America, AstraZeneca Pharmaceuticals, and Forest Pharmaceuticals.

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