ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2008, p. 813–821 Vol. 52, No. 3
0066-4804/08/$08.00+0 doi:10.1128/AAC.01169-07

MINIREVIEW

Clinical and Economic Impact of Common Multidrug-Resistant Gram-Negative Bacilli▽

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During the last decade, the efforts to combat multidrug-resistant (MDR) microorganisms mainly focused on gram-positive bacteria, namely, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. While a large number of hospitals have implemented more rigorous infection control measures, drug companies have developed novel antimicrobial agents to combat these bacteria, resulting in several new compounds with novel mechanisms of action, e.g., linezolid and daptomycin (66). Paralleling the developments in gram-positive bacteria, infections caused by MDR gram-negative bacilli have become a growing problem (71). In a recent report the Infectious Diseases Society of America specifically addressed three categories of MDR gram-negative bacilli, namely, extended-spectrum cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp., MDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter* spp. (70). Unfortunately, and contrary to what happened with gram-positive bacteria, no antibiotic from a new class has been developed specifically for MDR gram-negative bacilli. It might be argued that the glycylcycline tigecycline is an exception from the statement made above, but although this drug has in vitro activity against many MDR gram-negative bacilli, the drug was not developed specifically for the purpose of treating infections caused by such bacteria (64). Moreover, there are now a growing number of reports of cases of infections caused by gram-negative organisms for which no adequate therapeutic options exist (20). This return to the preantibiotic era has become a reality in many parts of the world (14, 55, 80). The present report aims at estimating the prevalence of infections due to MDR gram-negative bacilli, as well as the consequences with respect to mortality, hospital length of stay (LOS), and increased hospital costs.

The topics covered in this report are resistance to extended-spectrum cephalosporins in *E. coli* and *Klebsiella pneumoniae*, MDR (resistance to three or more antipseudomonal agents) (17) in *P. aeruginosa*, and carbapenem resistance in *Acinetobacter* spp. PubMed (www.ncbi.nih.gov; accessed on 31 October 2007) searches were performed by using the following search terms: (*Escherichia coli* OR *Klebsiella pneumoniae*) AND ESBL, (*Escherichia coli* OR *Klebsiella pneumoniae*) AND cephalosporin resistance, *Pseudomonas* AND multidrug resistance, *Acinetobacter* AND carbapenem resistance, antibiotic resistance AND (*Pseudomonas* OR *Acinetobacter* OR *Escherichia coli* OR *Klebsiella*) AND mortality, antibiotic resistance AND (*Pseudomonas* OR *Acinetobacter* OR *Escherichia coli* OR *Klebsiella*) AND length of stay, and antibiotic resistance AND (*Pseudomonas* OR *Acinetobacter* OR *Escherichia coli* OR *Klebsiella*) AND cost. The searches were performed to address the issues of prevalence, mortality, increased LOS, and increased hospital costs. Following the review of all abstracts, a total of 85 papers were considered relevant and were evaluated for the preparation of this report. All included papers on the clinical and economic impact of gram-negative bacilli included proper control groups. Only papers published in English were considered.

E. COLI AND *K. PNEUMONIAE* STRAINS RESISTANT TO EXTENDED-SPECTRUM CEPHALOSPORINS

Among the species *E. coli* and *K. pneumoniae*, a worrisome trend during the last two decades has been the development of resistance to extended-spectrum cephalosporins, e.g., cefotaxime, ceftazidime, and ceftriaxone (54). Such resistance is most often due to the breakdown of the extended-spectrum cephalosporin by extended-spectrum β-lactamases (ESBLs), but it may also be due to plasmid-mediated or chromosomally hyperproduced AmpC (46). Depending on the breakpoint system used, certain ESBLs may not always be detected and classified as resistant to all cephalosporins; however, with the current European Committee on Antimicrobial Susceptibility Testing breakpoints (www.eucast.org), ESBL-producing isolates are usually resistant to at least one extended-spectrum cephalosporin (72). The genes encoding the ESBLs are found on plasmids and have a great propensity to spread between bacteria (8).

Resistance to fluoroquinolones, co-trimoxazole, and tri-

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▽ Published ahead of print on 10 December 2007.

TABLE 1. Prevalence of resistance to extended-spectrum cephalosporins in *E. coli* and *K. pneumoniae* in various parts of the world

Region	Period	Setting	Resistance (%)		Reference
			K. pneumoniae	*E. coli*	
North America					
United States	2003	ICU	20.6	5.8	50
United States	2004	Intra-abdominal infections	5.3	2.8	63
United States (Brooklyn)	2006	All infections	59		40
Latin America					
Seven countries	2000	Urinary tract infections	22.3	3.1	25
Ten countries	2004	Intra-abdominal infections	27.6	12.0	63
Europe					
Northern Europe	2000–2001	Nosocomial infections	5.2	1.4	7
Southern Europe	2000–2001	Nosocomial infections	25.7	6.6	7
Nine countries	2004	Intra-abdominal infections	8.8	6.4	63
Asia					
China	1998–2002	Nosocomial infections	37.3	31.3	30
Japan	1998–2002	Nosocomial infections	11.0	6.5	30
Singapore	1998–2002	Nosocomial infections	36.4	12.3	30
Oceania (Australia)	1998–2002	Nosocomial infections	4.6	1.6	30
South Africa	1998–2002	Nosocomial infections	29.6	1.9	30

methoprim is frequently observed among ESBL producers (15, 69). Thus, the presence of an ESBL is a good marker of the MDR phenotype. The carbapenems, i.e., imipenem, meropenem, and ertapenem, are considered the drugs of choice for the treatment of infections caused by extended-spectrum cephalosporin-resistant *E. coli* and *K. pneumoniae*; however, carbapenem resistance is emerging in certain geographic areas (27, 43, 52, 54, 79). The tetracycline derivative tigecycline has promising in vitro activity against many of these MDR organisms; but the clinical experience with this agent is still limited (48), and low-grade tigecycline resistance in members of the family *Enterobacteriaceae* has been reported and has been attributed to efflux pump mechanisms (32, 58, 65).

Prevalence of resistance. The rates of resistance to extended-spectrum cephalosporins in *E. coli* and *K. pneumoniae* in various parts of the world are summarized in Table 1. Although statistics from many parts of the world are unavailable, accumulating evidence still suggests that resistance to extended-spectrum cephalosporins in *E. coli* and, in particular, *K. pneumoniae* has become a worldwide problem (55), with only certain areas in the United States and northern Europe being relatively spared. Also, the recently described dissemination of ESBL-producing *Enterobacteriaceae* in the community poses a new threat, since this may become a powerful reservoir for the continued influx of resistant strains into hospitals (3, 60).

Impact of resistance on mortality, LOS, and hospital costs. A total of 14 papers were considered, and of these, 8 papers found an impact on resistance to extended-spectrum cephalosporins (in most cases caused by ESBL production) on one or several of the three outcome variables, mortality, LOS, and increased hospital cost. The findings from these papers are displayed in Table 2. Six of the papers describe the impact on resistance to extended-spectrum cephalosporins in patients with bloodstream infections, while the rest of the papers considered various types of nosocomial infections. All of the studies are retrospective cohort studies; nine of the studies used either matched controls or multivariate analysis, in order to minimize residual confounding; but only a few of them feature matched controls, an approach that is recommended when the source populations for resistant and susceptible cases are different (37). Lastly, all except two studies found in this collection were single-center studies, indicating that local epidemiological factors may be of importance for the reported findings.

The impact of ESBL production on mortality from bacteremia caused by *Enterobacteriaceae* has been studied in a recent meta-analysis by Schwaber et al. (67), and a significantly increased rate of mortality was found in the ESBL group (pooled relative risk [RR], 1.85; 95% confidence interval [CI], 1.39 to 2.47). The same study demonstrated an increased RR for delayed effective therapy (pooled RR, 5.36; 95% CI, 2.73 to 10.53). The increased mortality observed in patients with bloodstream infections (BSIs) can be contrasted with the findings of eight additional studies, all of which also included patients with types of infections other than BSIs. Among those studies, increased mortality was found in only one, although a tendency toward a higher rate of mortality in the ESBL group could be observed in some of the studies. Six of seven studies found increased LOSs for patients with extended-spectrum cephalosporin-resistant isolates, while increased cost was found in the three studies that considered this parameter.

MDR *P. AERUGINOSA*

MDR in *P. aeruginosa* is usually defined as resistance to three or more of the following antimicrobial agents: antipseudomonal penicillins (e.g., piperacillin), antipseudomonal cephalosporins (e.g., ceftazidime), fluoroquinolones (e.g., ciprofloxacin), carbapenems (imipenem, meropenem, and doripenem), and the aminoglycosides (gentamicin, tobramycin, or amikacin) (17). Resis-

TABLE 2. Impact of extended-spectrum cephalosporin resistance in *Enterobacteriaceae* on mortality, LOS, and hospital cost

Type of study	Setting	Type of infection	Bacteria	No. of cases/ no. of controls	Parameter	Main findings	Significance (P value or 95% CI)	Reference
Studies showing an impact of resistance								
Case-control	Tertiary care	Nosocomial	*E. coli* and *K. pneumoniae*	33/66[a]	LOS	Cases, 1.76 times greater duration	1.17–2.64	42
					Increased cost	Cases, 2.90 times higher cost	1.76–4.78	
Case-control	Tertiary care	BSI	*K. pneumoniae*	44/118[a]	LOS	Cases, 39.6 days; controls, 23.9 days	$P < 0.008$	38
Case-control	Multicenter	Nosocomial	*K. pneumoniae*	9/9	Mortality	Cases, 44%; controls, 33%	$P > 0.05$	9
					LOS	Cases, 37 ± 25 days; controls, 15 ± 10 days	$P = 0.04$	
Case-control	Tertiary care	Peritonitis (CAPD[b])	*E. coli*	11/77	Mortality	Cases, 27.3%; controls, 3.9%	$P = 0.02$	83
Retrospective cohort	Tertiary care	BSI	*Enterobacteriaceae*	99/99[a]	LOS	Cases, 1.56 greater duration	$P = 0.001$	68
					Increased cost	Cases, 1.57 times higher cost	$P = 0.003$	
Retrospective cohort	Tertiary care	Non-urinary tract	*E. coli* and *Klebsiella* spp.	21/21[a]	Mortality	Cases, 8%; controls, 14%	$P = 0.182$	44
					LOS	Cases, 21 days; controls, 11 days	$P = 0.006$	
					Increased cost	Attributable cost, $16,450	$965–31,937	
Retrospective cohort	Tertiary care	BSI	*K. pneumoniae*	46/82[a]	Mortality	OR[c] for death in cases, 2.66	1.07–6.59	76
					LOS	Cases, 22 days; controls, 16 days	$P = 0.03$	
Prospective cohort	Tertiary care	BSI	*E. coli*	46/308[a]	Mortality	OR for death in cases, 3.57	1.48–8.60	47
Studies showing no impact of resistance								
Case-control	Tertiary care	Nosocomial	*Enterobacteriaceae*	23/174	Mortality	Cases, 26%; controls, 16%	$P = 0.14$	18
Case-control	Tertiary care	Nosocomial	*K. pneumoniae*	60/60[a,d]	Mortality	Cases, 30%; controls, 28.3%	*P = 0.0841*	33
Case-control	Tertiary care	Nosocomial	Enterobacteriaceae	31/39	Mortality	Cases, 3.0%; controls, 2.4%	$P > 0.05$	13
Case-control	Tertiary care	BSI	*E. coli and Klebsiella* spp.	35/105[a]	LOS	Cases, 8.2 additional days	$P = 0.182$	84
Retrospective cohort	Tertiary care	Nosocomial	*K. pneumoniae*	68/75[a]	Mortality	RR[e], 0.94	0.45–1.97	28
Prospective cohort	Multicenter	BSI or pneumonia	*Enterobacteriaceae*	135/40	Mortality	Cases, 5.2%; controls, 12.5%	$P = 0.15$	4

[a] Studies with either matched controls or multivariate analysis, in order to minimize confounding.
[b] CAPD, continuous ambulatory peritoneal dialysis.
[c] OR, odds ratio.
[d] Matched controls.
[e] RR, risk ratio.

tance is often caused by the interplay of various resistance mechanisms, including β-lactamases, aminoglycoside-modifying enzymes, topoisomerase mutations, decreased permeability, and the activities of efflux pumps (6). The presence of the emerging transmissible metallo-β-lactamases (MBLs) can in itself confer an MDR phenotype, since these β-lactamases can hydrolyze all β-lactams except aztreonam (80). Also, due to the collocation of genes encoding MBLs and aminoglycoside-mod-

TABLE 3. Prevalence of MDR among *P. aeruginosa* strains in various parts of the world

Region	Period	Setting	Resistance (%)	Reference
North America				
United States	2001	ICU/non-ICU	9.1/7.0	35
United States	2002	ICU	14	35
United States	2003	Nosocomial infections	9.9	36
South America, 10 sites	1997–1999	Nosocomial infections	8.2	24
Europe				
12 to 23 sites	1997–1999	Nosocomial infections	4.7	24
33 ICUs	1997–2000	ICU	3–50	29
Asia/Pacific				
17 sites	1997–1999	Nosocomial infections	1.6	24
Japan	2001	Nosocomial infections	2.8	74
Malaysia	2005	Nosocomial infections	6.9	62

ifying enzymes on mobile genetic elements, such isolates are also frequently resistant to aminoglycosides (80).

Prevalence of resistance. Although an abundance of studies have covered susceptibility to various antibiotics in *P. aeruginosa*, relatively few studies have examined the prevalence of MDR, defined as resistance to three or more antipseudomonal agents. One possible explanation for this could be the absence of an international consensus regarding the definition of MDR in *P. aeruginosa* (22). The resistance rates in various parts of the world are displayed in Table 3.

Impact of resistance on mortality, LOS, and hospital costs. Due to the different definitions of the MDR phenotype in *P. aeruginosa*, the data on the clinical and economic impact of resistance (Table 4) cannot easily be directly compared. Six studies found an impact on mortality and one found an impact on LOS, but in all of these studies the isolates were resistant to four or more antipseudomonal drugs. One study found no impact of the MDR phenotype on the outcome, but the isolates in that study were resistant to only two or more antipseudomonal antibiotics. Two of the studies showing an impact of the MDR phenotype on the outcome did not apply matched controls or multivariate analysis (37), and in one of the studies the impact detected in the univariate analysis disappeared in the multivariate analysis, indicating that factors other than the resistance phenotype were important for the outcome (85). Also, three of the studies showing an impact of the MDR phenotype on the outcome compared MBL-producing isolates with MBL-negative isolates, and MDR isolates were also present in the control groups. None of the studies were multicenter studies.

In addition to the studies presented in Table 4, a recent case-control study showed an impact of fluoroquinolone-resistant *P. aeruginosa* on mortality and hospital costs (26). The fluoroquinolone-resistant isolates in that study were also resistant to one to two other classes of drugs; i.e., some of them had an MDR phenotype. In the multivariate analysis performed in the same study, only imipenem resistance was associated with increased mortality. The imipenem-resistant isolates in the study were also resistant to a median of three other classes of drugs, implying that all of the isolates in this group were in fact MDR isolates.

CARBAPENEM-RESISTANT *ACINETOBACTER* SPP.

Acinetobacter spp. are frequently resistant to fluoroquinolones, aminoglycosides, and all β-lactams, with the exception of the carbapenems; and carbapenems are therefore often increasingly considered the drugs of choice for the treatment of infections due to *Acinetobacter* spp. (51). However, carbapenem resistance in *Acinetobacter* spp. is emerging in many parts

TABLE 4. Impact of the MDR phenotype in *P. aeruginosa* on mortality, LOS, and hospital cost

Type of study	Setting	Infection	No. of cases/ no. of controls	Parameter	Main findings	Significance (*P* value or 95% CI)	Reference
Studies showing an impact of resistance							
Case-control	Tertiary care	Nosocomial	69/247	Mortality	OR,[a] 5.0	1.1–22.9	31
Retrospective cohort	Tertiary care	Nosocomial	44/68[b,c]	Mortality	Cases, 54.5%; controls, 16.2%	$P < 0.05$	11
Case-control	Tertiary care	BSI	6/184[b,c]	Mortality	Cases, 83.3%; controls, 36.4%	$P = 0.03$	34
Prospective	Tertiary care	Nosocomial/	98/103	Mortality	RR, 1.98	1.0–3.9	41
Prospective	Tertiary care	Nosocomial	86/212[c]	Mortality	RR, 1.60	1.2–2.1[d]	85
Retrospective matched cohort	Tertiary care	Nosocomial	82/82[b,c,e]	Mortality	OR, 4.4	$P = 0.04$	1
Retrospective cohort study showing no impact of resistance	Tertiary care	Noscomial	18/35[c,f]	Mortality	Cases, 22%; controls, 23%	$P > 0.05$	53

[a] OR, odds ratio.
[b] MDR was defined as resistance to four or more antibiotics.
[c] Studies with either matched controls or multivariate analysis, in order to minimize confounding.
[d] Not significant in multivariate analysis.
[e] Matched controls.
[f] MDR was defined as resistance to two or more antibiotics.

TABLE 5. Prevalence of carbapenem resistance in *Acinetobacter* spp. in various parts of the world

Region	Period	Setting	Resistance (%)		Reference
			Imipenem	Meropenem	
North America					
15 centers	2002–2004	Nonduplicate clinical isolates	8.3	6.5	78
24 centers	2001	Non-ICU isolates	6.1	10.4	35
15 centers	2006	All isolates	33	53	40
South America					
25 centers	2002–2004	Nonduplicate clinical isolates	28.1	28.5	78
7 countries	2001	Nonduplicate clinical isolates	16.3	18.1	73
Europe					
48 centers	2002–2004	Nonduplicate clinical isolates	30.2	26.9	78
37 centers	1997–2000	Nonduplicate clinical isolates	16	14	77
Asia/Pacific, 2 centers	2002–2004	Nonduplicate clinical isolates	1.2	6.0	78
Australia	1999–2004	Nonduplicate clinical isolates	11	11	78

of the world (10), mainly due to carbapenemases and, possibly, other mechanisms, such as alterations of outer membrane proteins (6). Although these multiresistant *Acinetobacter* spp. may still retain susceptibility to the polymyxins (i.e., colistin and polymyxin B), sulbactam, and possibly tigecycline, panresistant isolates that are resistant to all available drugs are now being reported (20).

Prevalence of resistance. Although *Acinetobacter* spp. are the causative agents of BSIs, as well as other infections, less often than *E. coli*, *Klebsiella* spp., and *P. aeruginosa* are (5), their occurrence is increasing dramatically (57). The frequently observed multiresistance of *Acinetobacter* sp. isolates complicates antibiotic therapy. A recent study has reported an average rate of carbapenem resistance of 27% among *Acinetobacter* spp. in European countries (78). Another study covering three continents, including Europe, reported an average rate of carbapenem resistance of 16% among *Acinetobacter* spp. (23). These high levels of resistance make polymyxins the drugs of last resort for the treatment of infections due to multiresistant *Acinetobacter* spp. (21). The resistance rates in various parts of the world are summarized in Table 5.

Impact of resistance on mortality, LOS, and hospital costs. Six studies were considered relevant for inclusion in this report on the clinical impact of carbapenem-resistant *Acinetobacter* spp., and two of these studies were conducted with burn patients (Table 6). The only study performed with patients with BSIs found significantly increased rates of mortality in the group of patients infected with carbapenem-resistant *Acineto-*

TABLE 6. Impact of carbapenem resistance in *Acinetobacter* spp. on mortality, LOS, and hospital costs

Type of study showing an impact of resistance	Setting	Infection	No. of cases/ no. of controls	Parameter	Main findings	Significance (P value or 95% CI)	Reference
Case-control	Tertiary care	Nosocomial	10/10	Mortality	Cases, 34%; controls, 27%	$P > 0.05$	9
				LOS	Cases, 31.5 days; controls, 13 days	$P = 0.02$	
Case-control	Tertiary care	Burn patients	34/43	Mortality	Cases, 26.5%; controls, 0%	$P < 0.01$	82
				LOS	Cases, 32.5 days; controls 21 days	$P < 0.01$	
Case-control	Tertiary care	Burn patients	34/183	LOS	Cases, 36.8 days; controls, 25.6 days	$P = 0.06$	81
				Cost	Cases, $98,575 higher	$P < 0.01$	
Case-control	Tertiary care	BSI	40/40[a]	Mortality	Cases, 57.5%; controls, 25.7%	$P = 0.007$	39
Case-control	ICU	Nosocomial infections	34/68[a]	Mortality	OR,[b] 3.9	1.4–10.7	61
				LOS	Cases, 30 days longer	11–38 days	
Case-control	ICU	Colonization	32/63[a]	LOS (ICU)	Cases, 19 days longer	5–28 days	61

[a] Studies with either matched controls or multivariate analysis, in order to minimize confounding.
[b] OR, odds ratio.

bacter spp. (39). Also, a study of nosocomial intensive care unit (ICU) infections found a significantly higher rate of mortality among patients infected with carbapenem-resistant *Acinetobacter* spp., and the same study also showed a significantly increased LOS (61). One case-control study of nosocomial infections found no significant differences in the rates of mortality between patients infected with carbapenem-resistant and -susceptible isolates but a more than twofold increase in hospital LOS (9). Among the two studies of burn patients, one found increased rates of mortality and LOSs (82), while one study detected only increased costs (81). One case-control study of nosocomial infections caused by multiresistant *Acinetobacter* spp., *P. aeruginosa*, and *S. aureus* did not meet the criteria for inclusion in this report. MDR *Acinetobacter* spp. were defined as being resistant to aminoglycosides, quinolones, and extended-spectrum cephalosporins; and *Acinetobacter* spp. were the dominant MDR pathogens among the case patients. The mortality rate was significantly higher for the cases than for the controls (27% and 12.7%, respectively; $P < 0.01$), although susceptibility to carbapenems was allowed in the case group (16).

GENERAL COMMENTS

For the members of the family *Enterobacteriaceae*, a recent meta-analysis has found increased rates of mortality among patients with BSIs caused by ESBL-producing organisms (67), while a majority of studies of other types of infections found no significant differences attributable to resistance to extended-spectrum cephalosporins. This finding is not surprising, partly since the presence of *Enterobacteriaceae* in other specimens may represent colonization rather than infection and partly because the overall rate of mortality among patients with non-BSIs caused by *Enterobacteriaceae* is generally low. The reason for the increased rate of mortality among patients with BSIs caused by ESBL-producing organisms seems to be a delay in effective treatment (2, 47, 75). With respect to the other parameters considered in this review, the currently available literature shows both increased LOSs and increased costs attributable to resistance to extended-spectrum cephalosporins in the *Enterobacteriaceae*. The trend toward the development of carbapenem resistance in the *Enterobacteriaceae* is of major concern, but the clinical and economic impact remains to be studied.

The absence of an accepted international definition of MDR *P. aeruginosa* poses a problem when the impact of such resistance is estimated. Most of the studies considered in this report defined MDR as resistance to four or more antipseudomonal agents. If this criterion is applied, six studies indicate that increased mortality and one study indicated that increased LOSs were attributable to MDR *P. aeruginosa*. No studies addressing attributable costs could be identified. Three of the studies showing an impact of MDR *P. aeruginosa* on mortality featured isolates producing MBL in the case groups. Hence, it could be debated whether the observed effect was due to the MDR phenotype or whether it was related to other features of the MBL-producing isolates. For MDR *P. aeruginosa* strains, the polymyxins are still possible treatment alternatives, but resistance to these agents has also been described (20).

Six studies regarding the clinical impact of carbapenem-resistant *Acinetobacter* spp. were identified. One study of BSIs caused by *Acinetobacter* spp. identified carbapenem resistance as a risk factor for mortality (39). A similar observation was done in a study of ICU patients, in which increased rates of mortality and increased hospital LOSs were seen (61). One additional study of mixed infections found an impact on mortality, but generally, the number of patients in that study was low and the question of infection versus colonization was not properly addressed (82). Apart from the study of ICU patients, two other studies found an impact of MDR on hospital LOSs, and one study of burn patients found a substantial attributable cost. For carbapenem-resistant *Acinetobacter* spp., the polymyxins are the drugs of choice, although sulbactam and tigecycline have been proposed as possible treatment alternatives (45, 49). Regarding tigecycline, a cautionary report on two cases of the emergence of bloodstream infections caused by tigecycline-resistant *A. baumannii* during monotherapy with tigecycline was recently published; in both cases the patients were started on tigecycline for other indications (59). By taking into account the low serum concentration obtained with tigecycline (with an area under the concentration-time curve of approximately 5 mg · h/liter and a suggested pharmacodynamic target free area under the concentration-time curve/MIC of 12.5), one would reach the pharmacodynamic target only with tigecycline MICs of ≤0.25 mg/liter (19). Since wild-type isolates have MICs up to 1 mg/liter, therapeutic failures are likely to occur, at least if the drug is administered as monotherapy.

Considering the absence of an internationally accepted definition of the term MDR gram-negative bacilli, the development of an international standard for the terminology could be useful. Two adjectives have previously been used to define gram-negative bacilli that are resistant to several agents: MDR and pandrug resistant (PDR). Recently, Paterson and Doi have suggested the use of the term "extreme drug resistance" and the abbreviation "XDR" to complement the two previous terms (56). The same paper suggests that PDR should be used to designate gram-negative bacilli that are resistant to all authorized antimicrobial agents except tigecycline and the polymyxins and that the use of XDR should be restricted to bacteria that are also resistant to the latter two drugs. Although a standardized terminology is needed, it could be debated whether this use of PDR and XDR is optimal. Semantically, PDR would be an appropriate term for bacteria that are resistant to all authorized agents, a point that has also been made by Falagas et al. (22). Additionally, XDR is already defined internationally as "extensively drug resistant" and introduction of the term "extreme drug resistance" may create confusion (12). An alternative option would therefore be to use the term "extensively drug-resistant" (XDR) for gram-negative bacilli resistant to all authorized agents except tigecycline and the polymyxins, whereas PDR would be restricted to application to truly PDR bacteria. Attempts to reach an international consensus on definitions should be made, since this will greatly enhance the comparabilities of future studies of resistant gram-negative bacilli and thereby also facilitate future meta-analyses within this field.

CONCLUSIONS

Current evidence suggests that infections caused by ESBL-producing *Enterobacteriaceae* are associated with increased hospital LOSs and costs. Also, BSIs caused by ESBL-producing *Enterobacteriaceae* are associated with increased rates of mortality. MDR *P. aeruginosa* (resistance to four or more antipseudomonal agents) is associated with increased mortality and increased hospital LOSs. For *Acinetobacter* spp., BSIs and nosocomial ICU infections caused by carbapenem-resistant isolates are associated with increased rates of mortality. Other types of infections have not clearly been shown to be associated with higher rates of mortality but are associated with increased LOSs and hospital costs. The clinical and economic impact of MDR gram-negative bacilli is substantial and greatly worrisome. An international agreement on the definitions of such bacteria could potentially facilitate an orchestrated response against these pathogens.

ACKNOWLEDGMENT

The work related to this paper was supported financially by ReAct (Action on Antibiotic Resistance; www.reactgroup.org), an international coalition supported by the Swedish International Development Cooperation Agency.

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