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REVIEW ARTICLE
Acinetobacter infections: a growing threat for critically ill patients

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SUMMARY

There has been increasing concern regarding the rise of *Acinetobacter* infections in critically ill patients. We extracted information regarding the relative frequency of *Acinetobacter* pneumonia and bacteraemia in intensive-care-unit (ICU) patients and the antimicrobial resistance of *Acinetobacter* isolates from studies identified in electronic databases. *Acinetobacter* infections most frequently involve the respiratory tract of intubated patients and *Acinetobacter* pneumonia has been more common in critically ill patients in Asian (range 4–44%) and European (0–35%) hospitals than in United States hospitals (6–11%). There is also a gradient in Europe regarding the proportion of ICU-acquired pneumonias caused by *Acinetobacter* with low numbers in Scandinavia, and gradually rising in Central and Southern Europe. A higher proportion of *Acinetobacter* isolates were resistant to aminoglycosides and piperacillin/tazobactam in Asian and European countries than in the United States. The data suggest that *Acinetobacter* infections are a growing threat affecting a considerable proportion of critically ill patients, especially in Asia and Europe.

INTRODUCTION

A considerable proportion of critically ill patients acquire an infection during their stay in an intensive care unit (ICU) and the frequency of these infections varies considerably in different populations and clinical settings [1–3]. The development of ICU-acquired infections is strongly related to prolonged ICU stay and is associated with worse outcomes including increased morbidity and mortality [4, 5].

During the last two decades clinicians in various countries have witnessed a growing number of critically ill patients who suffer from infections due to microorganisms that belong to the *Acinetobacter* genus, mainly strains of the species *Acinetobacter baumannii*. *Acinetobacter* are a group of non-fermentative Gram-negative bacteria that have minimal nutritional requirements and can survive on a variety of surfaces and aqueous environments [3, 6]. Apart from ICU patients it has been shown to be a cause of community-acquired respiratory tract infections, including pneumonia, in immunocompetent people living in the tropics [7]. In addition, *Acinetobacter* has been identified as one of the most common causes of infection in soldiers who sustained trauma during the Vietnam, Afghanistan, and Iraq wars [8]. However, despite these important associations, they cannot be compared with the magnitude of the growing global epidemic of *Acinetobacter* ICU-acquired infections in critically ill patients. In this article, we undertook a review of surveillance and other prospective and retrospective studies of

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Table 1. Acinetobacter *intensive care unit-acquired infections* (*mainly pneumonia and/or bacteraemia*) *in patients reported in the reviewed studies*

Study period* (month/year)	First-named author [ref.]	Type of study†	City	Country	Type of ICU-acquired infection	No. of patients					Pneumonia		Bacteraemia	
						Admitted in the ICU		With ICU-acquired infections			Total isolates (*N*)	*Acinetobacter* isolates *n* (%)	Total isolates (*N*)	*Acinetobacter* isolates *n* (%)
						Total	>48 h ICU	*n*	%‡	%§				
Europe														
01/85–12/85	Costantini [12]	Surveillance	Padua	Italy	All types	1307	859 (stay)	231	18	27	285	38 (13)	179	18 (10)
04/86–12/86	Jimenez [13]	Prospective	Barcelona	Spain	VAP	—	77 (MV)	18	—	23	23	6 (26)	—	—
1/89–5/90	Fussle [14]	Prospective	Giessen	Germany	VAP	—	190 (MV)	32	—	17	40	0 (0)	—	—
01/85–12/96	Crowe [9]	Prospective	Notting-ham	UK	Bacteraemia	7161	—	n.a.	—	—	—	—	208	12 (6)
12/91–07/92	Garrouste-Orgeas [15]	Prospective	Paris	France	VAP	—	86 (MV)	30	—	35	42	11 (26)	—	—
01/90–12/95	Barsic [16]	Prospective	Zagreb	Croatia	Pneumonia, Bacteraemia, UTI	—	622 (stay)	n.a.	—	—	253	54 (21)	251	62 (25)
05/93–06/95	Trouillet [17]	Prospective	Paris	France	VAP	—	499 (stay)	135	—	27	245	22 (9)	—	—
01/94–12/95	Garcia-Garmendia [18]	Prospective	Seville	Spain	BSI	2709	2640 (stay)	233	9	9	—	—	250	42 (17)
11/95–10/96	Artigas [19]	Prospective	Saragossa	Spain	Pneumonia	103	—	23	22	—	35	10 (29)	—	—
01/96–09/96	Akca [20]	Prospective	Istanbul	Turkey	VAP	486	260 (MV)	81	17	31	101	9 (9)	—	—
01/95–12/98	Gruson [21]	Prospective	Bordeaux	France	VAP	3455	2033 (stay)	392	11	19	561	27 (5)	—	—
06/96–07/97	Cendrero [22]	Prospective	Grand Canaries	Spain	VAP	—	123 (MV)	19	—	16	25	2 (8)	—	—
1/97–12/97	Heckmann [23]	Prospective	Nierenberg	Germany	Pneumonia	—	217 (stay)	68	—	31	94	5 (5)	—	—
(9 months) Before 1999	Weist [24]	Surveillance	Potsdam	Germany	All types	262 (274 admissions)	—	59	23	—	71	3 (4)	20	2 (10)
02/98–01/00	Vosylius [25]	Prospective	Vilnius	Lithuania	All types	2261	812 (stay)	297	13	36	372	89 (24)	177	28 (16)
(12 months) Before 2000	Sofianou [26]	Prospective	Thessal-onica	Greece	VAP	448	198 (MV)	67	15	34	100	35 (35)	—	—
1999–2000	Hanberger [27]	Retrospective	(29 ICUs)	Sweden	All types	n.a.	—	n.a.	—	—	—	—	1398	0 (0)
12/99–05/01	Ertugrul [28]	Prospective	Istanbul	Turkey	VAP	—	100 (MV)	28	—	28	44	8 (18)	—	—
01/02–06/03	Piazza [29]	Retrospective	Naples	Italy	VAP	—	143 (MV > 72 h)	29	—	20	48	17 (35)	—	—
N. America														
01/92–07/97	Richards [30]	Surveillance	(112 ICUs, 97 hospitals)	USA	All types	181 993	—	n.a.	—	—	4389	263 (6)	2971	59 (2)

06/94–12/94	Kollef [31]	Prospective	Washington	USA	Late-onset VAP (MV > 4 days)	—	314 (MV > 120 h)	87	—	28	61	4 (7)	—	—
03/95–11/02	Wisplinghoff [11]	Surveillance	49 cities (SCOPE project)	USA	BSI	n.a.	—	n.a.	—	—	—	—	10 515	168 (2)
09/98–08/01	Wood [32]	Retrospective	Memphis, Tennessee	USA	VAP	n.a.	—	299	—	—	621	68 (11)	—	—
2003	Gaynes [33]	Surveillance	Nationwide	USA	All types	n.a.	—	n.a.	—	—	4365	301 (7)	2351	56 (2)
S. America														
1993–1999	Santucci [34]	Surveillance	Sao Paolo	Brazil	All types	320	—	175	55	—	33	8 (24)	233	31 (13)
(4 months) 1999	Bilevicius [35]	Retrospective	Sao Paolo	Brazil	Sepsis	249	—	54	22	—	—	—	23	3 (13)
Asia														
05/89–05/90	Chung [36]	Retrospective	Seoul	Korea	Pneumonia	920	—	63	7	—	109	9 (8)	—	—
06/92–05/96	Bang [10]	Retrospective	Ibn Sina	Kuwait	Septicaemia	280	—	79	28	—	—	—	103	12 (12)
4/96–10/97	Singh [37]	Prospective	Varanasi	India	RTI, bacteraemia, UTI	—	102 (stay)	56	—	55	98	10 (10)	12	0 (0)
01/96–10/99	Sun [38]	Retrospective	Beijing	China	VAP	—	58 (MV)	28	—	48	53	17 (32)	—	—
01/97–06/99	Mahmood [39]	Prospective	Karachi	Pakistan	BSI	n.a.	—	86	—	—	—	—	86	5 (6)
12/97–06/99	Wu [40]	Surveillance	Taipei	Taiwan	VAP	596	—	48	8	—	41	11 (25)	—	—
01/98–12/99	Rozaidi [41]	Surveillance	Kuala Lumpur	Malaysia	All types	988	—	228	23	—	28	12 (43)	156	40 (26)
(9 months) Before 2001	Hira [42]	Prospective	New Delhi	India	VAP	—	28 (MV)	23	—	82	28	1 (4)	—	—
01/00–12/01	Erbay [43]	Prospective	Denizli	Turkey	All types	—	434 (stay)	113	—	26	118	22 (19)	75	3 (4)
03/01–09/01	Kanafani [44]	Prospective	Beirut	Lebanon	VAP	—	70 (MV)	33	—	47	46	11 (24)	—	—
07/01–10/01	Pawar [45]	Prospective	New Delhi	India	VAP	952	—	25	3	—	42	2 (5)	—	—
02/01–08/01	Pawar [46]	Prospective	New Delhi	India	CVC related, BSI	1314	—	35	3	—	—	—	17	2 (12)
01/01–01/03	Namiduru [47]	Retrospective	Gaziantep	Turkey	VAP	n.a.	—	140	—	—	230	60 (26)	—	—
07/02–12/03	Agarwal [48]	Prospective	Chandigarh	India	All types	278	201 (stay)	67	24	33	34	15 (44)	—	—
10/02–08/03	Meric [49]	Prospective	Kocaeli	Turkey	All types	280	131 (stay)	52	19	40	38	11 (29)	15	0 (0)

ICU, Intensive care unit; VAP, ventilator-associated pneumonia; RTI, respiratory tract infections; UTI, urinary tract infections; CVC, central venous catheter; BSI, bloodstream infections; MV, mechanically ventilated; n.a., not applicable, UK, United Kingdom; USA, United States of America.

* Chronological presentation of studies by the mean time of examined period.

† Studies describing outbreaks of *Acinetobacter* infection were excluded from this review.

‡ Percentage of infected patients out of the total number of patients admitted to the ICU.

§ Percentage of infected patients out of those that stayed >48 h in the ICU.

ICU-acquired infections to estimate the frequency and antimicrobial resistance patterns of *Acinetobacter* in critically ill patients in various areas of the world.

METHODS

Search strategy and study selection

We initially screened 565 studies that were retrieved by searches of the PubMed, Cochrane, and Current Contents databases (papers archived by April 2006) by using the key terms 'Acinetobacter' and '(intensive care *or* ICU *or* critically ill)'. Then, we focused on surveillance and other prospective and retrospective studies of ICU-acquired infections excluding randomized controlled trials and case-control studies. We further reviewed studies that reported the number of *Acinetobacter* isolates as well as the total number of bacterial isolates from specimens collected from ICU patients with pneumonia and/or bacteraemia. In addition, we included studies that provided data regarding the antimicrobial resistance of *Acinetobacter* isolates from critically ill patients receiving care in the ICU setting. We excluded studies that focused on paediatric patients, evaluated ICU infection outbreaks, or studied less than 11 patients or *Acinetobacter* isolates. Moreover, a study was not eligible for inclusion in our review if it evaluated isolates collected from the hospital environment (not clinical isolates). Data were collected from studies written in English, French, German or Italian.

Data extraction

We extracted data from the reviewed studies regarding the relative frequency of various pathogens causing ICU-acquired infections and the antimicrobial resistance of *Acinetobacter* from *in vitro* susceptibility tests. In order to present data regarding ICU-acquired *Acinetobacter* infections in hospitals in various countries through the years, studies were divided in subcategories, by the geographic area where the hospital-ICU was located (Europe, North America, South America, Asia, Africa, and Oceania).

Definitions

An infection was defined as ICU-acquired if the onset occurred at least 48 h after admission of the patient to the ICU. In studies that focused exclusively on patients with ICU-acquired pneumonia, isolates from cultures of sputum, tracheo-bronchial aspirates, bronchoalveolar lavage, protected brush specimens, and/or blood were included in our analysis. In three of the reviewed studies isolates from polymicrobial infections were excluded from the analysis [9–11].

RESULTS

ICU-acquired pneumonia and bacteraemia

Forty-one studies were identified that fulfilled the inclusion criteria for review and reported data on the relative frequency of isolation of *Acinetobacter* from infected adult patients with ICU-acquired pneumonia or bacteraemia [9–49]. Most of the *Acinetobacter* isolates were classified as *Acinetobacter baumannii*. Table 1 shows that 25 of the 41 studies were prospective; eight additional studies were characterized as surveillance studies, and so were considered to be prospective in design. The remaining eight studies were retrospective.

It is evident that the frequency of *Acinetobacter* infections among patients with ICU-acquired pneumonia and/or bacteraemia varies considerably between different countries, and even between different regions of the same country. However, *Acinetobacter* was a more common cause of ICU-acquired pneumonia in studies originating from Asian (range 4–44%) and European countries (0–35%) than in those originating from the United States (6–11%). A gradient in the proportion of ICU-acquired pneumonias caused by *Acinetobacter* in various European countries was apparent. Specifically, rates were very low in Scandinavia and became gradually higher in Germany and the United Kingdom, and highest rates were reported for France, Spain, Italy, and finally Greece and Turkey.

The available data from South America countries were limited and we did not identify a study originating from Africa or Oceania that fulfilled the criteria for inclusion in the review. Overall, the available data from the reviewed studies do not permit firm conclusions to be made regarding the secular trends of the relative frequency of *Acinetobacter* infections among patients with ICU-acquired pneumonia and/or bacteraemia during the last three decades.

Antimicrobial resistance of *Acinetobacter* clinical isolates

We identified 32 studies that fulfilled the criteria for inclusion in this part of the review [9, 16, 21, 26, 34, 44, 48, 50–74]. These studies reported data on the *in vitro*

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Table 2. *Antimicrobial resistance of* Acinetobacter *isolates from patients in the intensive care unit setting in various countries*

			Acinetobacter spp. [resistant/total number of isolates (%)]									
			Penicillins		Aminoglycosides			Cephalosporins		Quinolones	Carbapenems	
Time-period examined (month/year)	First-named author [ref.]	Country	Piperacillin/Tazobactam	Ampicillin/Sulbactam	Amikacin	Gentamicin	Tobramycin	Ceftazidime	Cefepime	Ciprofloxacin	Imipenem	Meropenem
Europe												
01/85–12/96	Crowe [9]	UK	n.a.	n.a.	n.a.	12/18 (67)	n.a.	n.a.	n.a.	12/18 (67)	n.a.	n.a.
01/90–12/95	Barsic [16]	Croatia	n.a.	n.a.	174/227 (77)	208/227 (92)	n.a.	211/227 (93)	n.a.	166/227 (73)	3/227 (1)	n.a.
06/93–12/93	Mulin [50]	France	n.a.	n.a.	51/56 (91)	56/56 (100)	56/56 (100)	n.a.	n.a.	n.a.	0/56 (0)	n.a.
06/94–06/95	Hanberger [51]	Belgium	10/28 (36)	n.a.	4/28 (15)	5/28 (18)	n.a.	5/28 (18)	n.a.	n.a.	3/28 (12)	n.a.
06/94–06/95	Hanberger [51]	France	132/299 (44)	n.a.	108/299 (36)	197/299 (66)	n.a.	209/299 (70)	n.a.	n.a.	27/299 (9)	n.a.
06/94–06/95	Hanberger [51]	Portugal	93/124 (75)	n.a.	12/124 (10)	79/124 (64)	n.a.	100/124 (81)	n.a.	n.a.	6/124 (5)	n.a.
06/94–06/95	Hanberger [51]	Spain	100/174 (58)	n.a.	n.a.	141/174 (81)	n.a.	132/174 (76)	n.a.	n.a.	28/174 (16)	n.a.
06/94–06/95	Hanberger [51]	Sweden	9/16 (56)	n.a.	n.a.	0/16 (0)	n.a.	0/16 (0)	n.a.	n.a.	3/16 (19)	n.a.
06/95–03/96	Siegrist [52]	Switzerland	5/11 (45)	n.a.	0/11 (0)	0/11 (0)	n.a.	2/11 (18)	5/11 (45)	n.a.	2/11 (18)	n.a.
01/90–12/01	Barsic [53]	Croatia	n.a.	n.a.	318/486 (65)	464/486 (95)	n.a.	455/486 (94)	n.a.	386/486 (79)	6/486 (1)	n.a.
01/90–12/93	Barsic [53]	Croatia	n.a.	n.a.	114/148 (77)	135/148 (91)	n.a.	138/148 (93)	n.a.	116/148 (78)	0/148 (0)	n.a.
01/94–12/97	Barsic [53]	Croatia	n.a.	n.a.	90/142 (63)	135/142 (95)	n.a.	131/142 (92)	n.a.	109/142 (77)	3/142 (0)	n.a.
01/98–12/01	Barsic [53]	Croatia	n.a.	n.a.	114/196 (58)	194/196 (99)	n.a.	186/196 (95)	n.a.	161/196 (82)	3/196 (2)	n.a.
01/95–12/98	Gruson [21]	France	10/27 (37)	n.a.	13/27 (48)	17/27 (63)	15/27 (56)	24/27 (89)	23/27 (85)	21/27 (78)	0/27 (0)	n.a.
11/96–05/97	Krause [54]	Austria	4/36 (11)	n.a.	n.a.	n.a.	n.a.	2/36 (6)	4/36 (11)	n.a.	3/36 (8)	4/36 (11)
01/97–12/97	Villari [55]	Italy	n.a.	n.a.	40/42 (95)	n.a.	n.a.	n.a.	n.a.	n.a.	0/42 (0)	n.a.
(12 months) Before 2000	Sofianou [26]	Greece	n.a.	n.a.	30/35 (85)	n.a.	n.a.	34/35 (97)	n.a.	16/35 (46)	0/35 (0)	n.a.
01/00–12/02	Jones [56]	Italy	197/425 (46)	n.a.	n.a.	556/768 (72)	n.a.	474/692 (69)	350/475 (74)	526/686 (77)	108/569 (19)	62/455 (14)
01/00–12/02	Jones [56]	Germany	92/1225 (8)	n.a.	n.a.	138/979 (14)	n.a.	143/988 (15)	67/623 (11)	258/1126 (23)	43/1253 (3)	35/1024 (3)
01/00–12/02	Jones [56]	France	92/878 (11)	n.a.	n.a.	407/936 (44)	n.a.	393/1106 (36)	345/857 (40)	635/1038 (61)	41/1088 (4)	42/147 (29)
07/98–12/03	Garnacho-Montero [57]	Spain	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	26/41 (63)	n.a.
11/01–02/04	Agodi [58]	Italy	17/19 (90)	4/19 (21)	18/19 (95)	17/19 (90)	16/19 (85)	18/19 (95)	18/19 (95)	18/19 (95)	1/19 (5)	1/19 (5)
N. America												
03/95–02/98	Wisplinghoff [59]	USA	n.a.	n.a.	3/96 (3)	16/96 (17)	6/96 (6)	29/96 (30)	22/96 (23)	33/96 (34)	0/96 (0)	n.a.
1995–2000	Friedland [60]	USA	527/2363 (22)	575/2573 (22)	363/2573 (14)	n.a.	715/2573 (28)	1003/2573 (40)	478/1,390 (34)	1,302/2,573 (51)	91/2,573 (4)	n.a.

Table 2 (*cont.*)

Time-period examined (month/year)	First-named author [ref.]	Country	*Acinetobacter* spp. [resistant/total number of isolates (%)]									
			Penicillins		Aminoglycosides			Cephalosporins		Quinolones	Carbapenems	
			Piperacillin/Tazobactam	Ampicillin/Sulbactam	Amikacin	Gentamicin	Tobramycin	Ceftazidime	Cefepime	Ciprofloxacin	Imipenem	Meropenem
1995	Friedland [60]	USA	n.a.	29/210 (14)	9/210 (4)	n.a.	26/210 (12)	49/210 (23)	n.a.	65/210 (31)	4/210 (2)	n.a.
1996	Friedland [60]	USA	33/372 (9)	60/372 (16)	22/372 (6)	n.a.	53/372 (14)	99/372 (27)	n.a.	145/372 (39)	11/372 (3)	n.a.
1997	Friedland [60]	USA	167/601 (28)	174/601 (29)	99/601 (17)	n.a.	167/601 (28)	284/601 (47)	n.a.	357/601 (59)	10/601 (2)	n.a.
1998	Friedland [60]	USA	90/495 (18)	97/495 (20)	74/495 (15)	n.a.	144/495 (29)	186/495 (38)	153/495 (31)	251/495 (51)	10/495 (2)	n.a.
1999	Friedland [60]	USA	158/520 (30)	134/520 (26)	109/520 (21)	n.a.	184/520 (35)	216/520 (42)	197/520 (38)	270/520 (52)	37/520 (7)	n.a.
2000	Friedland [60]	USA	79/375 (21)	81/375 (22)	50/375 (13)	n.a.	94/375 (25)	169/375 (45)	128/375 (34)	214/375 (57)	19/375 (5)	n.a.
04/99–06/99	Namias [61]	USA	n.a.	n.a.	45/55 (82)	46/55 (84)	47/55 (85)	46/55 (84)	47/55 (85)	46/55 (84)	9/55 (16)	n.a.
1998–2001	Karlowsky [62]	USA	n.a.	n.a.	129/1144 (11)	833/1875 (44)	n.a.	357/1648 (22)	241/850 (28)	741/1507 (49)	41/1380 (3)	5/57 (9)
1998	Karlowsky [62]	USA	n.a.	n.a.	30/273 (11)	179/452 (40)	n.a.	55/389 (14)	40/134 (30)	188/407 (46)	10/352 (2)	n.a.
1999	Karlowsky [62]	USA	n.a.	n.a.	34/233 (15)	207/428 (48)	n.a.	68/365 (19)	57/141 (40)	148/330 (45)	13/315 (4)	n.a.
2000	Karlowsky [62]	USA	n.a.	n.a.	30/252 (12)	208/449 (46)	n.a.	110/405 (27)	58/190 (31)	187/365 (51)	4/340 (1)	n.a.
2001	Karlowsky [62]	USA	n.a.	n.a.	35/386 (9)	239/546 (44)	n.a.	124/489 (25)	86/385 (22)	218/405 (54)	14/373 (4)	5/57 (9)
01/00–12/02	Jones [56]	USA	977/3429 (29)	n.a.	n.a.	3124/6618 (47)	n.a.	2429/5954 (41)	2075/5162 (40)	3369/5808 (58)	451/6006 (8)	571/2154 (27)
01/00–12/02	Jones [56]	Canada	209/903 (23)	n.a.	n.a.	270/1185 (23)	n.a.	266/1162 (23)	23/97 (24)	299/1156 (26)	17/918 (2)	17/348 (5)
S. America												
1993–1999	Santucci [34]	Brazil	n.a.	n.a.	43/48 (90)	35/50 (70)	n.a.	41/47 (87)	4/6 (66)	33/44 (75)	12/49 (25)	n.a.
1997–2001	Tognim [63]	7 countries	606/826 (73)	n.a.	545/826 (66)	554/826 (67)	405/706 (57)	565/826 (68)	541/826 (66)	574/826 (70)	108/826 (130)	110/826 (13)
1997	Tognim [63]	7 countries	145/193 (75)	n.a.	124/193 (64)	128/193 (66)	124/193 (64)	137/193 (71)	128/193 (66)	140/193 (73)	17/193 (9)	17/193 (9)
1998	Tognim [63]	7 countries	173/215 (80)	n.a.	157/215 (73)	150/215 (70)	128/218 (60)	177/215 (82)	156/215 (72)	152/215 (71)	28/215 (13)	28/215 (13)
1999	Tognim [63]	7 countries	82/129 (64)	n.a.	81/129 (63)	77/129 (60)	63/129 (49)	81/129 (68)	66/129 (51)	84/129 (65)	15/129 (12)	14/129 (11)
2000	Tognim [63]	7 countries	86/123 (70)	n.a.	80/123 (65)	84/123 (68)	n.a.	80/123 (65)	76/123 (62)	79/123 (64)	21/123 (17)	21/123 (17)
2001	Tognim [63]	7 countries	120/166 (72)	n.a.	103/166 (62)	115/166 (69)	90/166 (54)	90/166 (54)	115/166 (69)	119/166 (72)	27/166 (16)	30/166 (18)
Asia												
01/96–11/96	Gulati [64]	India	n.a.	n.a.	67/107 (63)	90/107 (84)	n.a.	n.a.	n.a.	78/107 (73)	n.a.	n.a.
1996	Gunseren [65]	Turkey	75/80 (94)	n.a.	57/80 (71)	73/80 (91)	n.a.	74/80 (93)	71/80 (89)	59/80 (74)	23/80 (29)	n.a.

01/96–12/97	Jang [66]	Taiwan	n.a.	n.a.	n.a.	n.a.	n.a.	11/24 (46)	n.a.	3/22 (14)	6/22 (27)	n.a.
1998	Yucesoy [67]	Turkey	223/255 (87)	n.a.	190/255 (75)	211/255 (83)	n.a.	229/255 (90)	218/255 (86)	185/255 (73)	117/255 (46)	n.a.
1996–2002	Wang [68]	China	637/1538 (41)	n.a.	454/1538 (30)	n.a.	n.a.	676/1538 (50)	380/963 (40)	646/1538 (41)	84/1538 (6)	n.a.
1996	Wang [68]	China	82/164 (50)	n.a.	33/164 (21)	n.a.	n.a.	82/164 (49)	n.a.	72/164 (44)	12/164 (7)	n.a.
1998	Wang [68]	China	85/206 (41)	n.a.	45/206 (22)	n.a.	n.a.	87/206 (42)	n.a.	82/206 (40)	6/206 (3)	n.a.
1999	Wang [68]	China	97/205 (47)	n.a.	55/205 (27)	n.a.	n.a.	98/205 (48)	n.a.	105/205 (51)	14/205 (7)	n.a.
2000	Wang [68]	China	131/272 (48)	n.a.	117/272 (43)	n.a.	n.a.	133/272 (49)	131/272 (48)	128/272 (47)	11/272 (4)	n.a.
2001	Wang [68]	China	139/347 (40)	n.a.	118/347 (34)	n.a.	n.a.	156/347 (45)	153/347 (44)	149/347 (43)	17/347 (5)	n.a.
2002	Wang [68]	China	103/344 (30)	n.a.	86/344 (25)	n.a.	n.a.	120/344 (35)	96/344 (28)	110/344 (32)	24/344 (7)	n.a.
03/00–06/00	Hsueh [69]	Taiwan	67/155 (43)	72/155 (47)	67/155 (43)	80/155 (52)	n.a.	75/155 (48)	44/155 (28)	74/155 (48)	8/115 (7)	21/155 (14)
06/00–05/02	Thongpiya-poom [70]	Thailland	n.a.	n.a.	n.a.	n.a.	n.a.	289/422 (69)	n.a.	227/422 (54)	n.a.	n.a.
03/01–09/01	Kanafani [44]	Lebanon	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0/11 (0)	n.a.
05/01–11/03	Yildirim [71]	Turkey	37/73 (51)	n.a.	49/64 (77)	63/69 (91)	n.a.	55/75 (73)	n.a.	57/76 (75)	17/77 (22)	10/77 (13)
07/02–12/03	Agarwal [48]	India	7/16 (44)	n.a.	12/16 (75)	n.a.	n.a.	15/16 (94)	n.a.	8/16 (50)	1/12 (8)	n.a.
01/03–01/04	Akcam [72]	Turkey	4/38 (11)	n.a.	23/38 (61)	n.a.	n.a.	6/38 (16)	7/38 (18)	14/38 (37)	25/38 (66)	n.a.
Africa												
01/84–09/84	Potgieter [73]	S. Africa	n.a.	n.a.	5/32 (15)	17/32 (54)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
01/88–12/88	Hammond [74]	S. Africa	n.a.	n.a.	13/20 (60)	19/20 (95)	19/20 (95)	n.a.	n.a.	n.a.	n.a.	n.a.

n.a., Not applicable; USA, United States of America; UK, United Kingdom.

susceptibility testing of *Acinetobacter* isolates from patients with ICU-acquired infections; seven also reported data on the relative frequency of *Acinetobacter* infection among patients with ICU-acquired pneumonia and/or bacteraemia [9, 16, 21, 26, 34, 44, 48]. The data on the antimicrobial resistance of *Acinetobacter* isolates are summarized in Table 2. Some studies included not only *Acinetobacter* isolates that were thought to be the cause of infection but also isolates thought to represent colonization.

Most studies gave information on the *in vitro* susceptibility of *Acinetobacter* isolates to piperacillin/tazobactam, aminoglycosides, third-generation cephalosporins, quinolones, and imipenem. In contrast, only a few studies reported the susceptibility of isolates to sulbactam, meropenem, and polymyxins. Two studies, one from Brazil and the other from seven countries in South America found that 0/19 and 6/166 (4%) of *Acinetobacter* isolates were resistant to polymyxin B [34, 63].

A careful review of the data presented in Table 2 suggests that the proportions of *Acinetobacter* isolates that were resistant to various antimicrobial agents were higher in the studies originating from Asian and European countries than the United States. It is evident that most *Acinetobacter* isolates were susceptible to imipenem (as well as meropenem in the few studies that included testing for this antibiotic). Further, the majority of *Acinetobacter* clinical isolates from critically ill patients originating from the developed world were susceptible to piperacillin/tazobactam, but again it appears that a higher proportion of isolates from the United States than from European countries were susceptible to this agent.

It is noteworthy that several studies reported approximately 90% of *Acinetobacter* isolates from critically ill patients were resistant to aminoglycosides in European countries, while less than 50% of such isolates were resistant to aminoglycosides in all but one study from the United States. A broad range of the proportion of clinical isolates with resistance to third-generation cephalosporins (6–95%) was observed. Finally, about 50% of *Acinetobacter* isolates were resistant to ciprofloxacin, even in the United States.

DISCUSSION

Limitations

We must acknowledge several limitations of our review. First, we elected to review only a subset of the

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available studies on ICU-acquired infections that may have included data on *Acinetobacter* infections. However, studies using another design including randomized controlled trials, case-control studies, and case reports would not be helpful in our attempt to summarize the available data regarding the relative frequency of isolation of *Acinetobacter* from infected adult patients with ICU-acquired pneumonia or bacteraemia.

Second, we excluded studies focusing on outbreaks of *Acinetobacter* nosocomial infections. It should be emphasized that outbreaks of such infections have become relatively common in hospitals in several parts of the world, especially in the ICU setting, contributing significantly to the overall morbidity and mortality attributable to this pathogen [3]. Moreover, the distinction between endemic *Acinetobacter* infections in an ICU or hospital and an outbreak of such infections is usually not obvious. Thus, it is likely that a proportion of *Acinetobacter* infections that occurred in critically ill patients in the reviewed studies were part of an unrecognized outbreak. The differences that are noted between studies in the same country (e.g. the United States) or areas of a specific continent (e.g. Central Europe) may reflect the presence of such outbreaks.

Third, different methods were used among the studies for determination of antimicrobial resistance and thus observed differences in susceptibility may be a consequence of methodology. In addition, results from poorly standardized methods such as agar diffusion tests may have lead to false interpretations. Another limitation of our literature search for relevant studies on *Acinetobacter* infections is related to the changes in taxonomic classification of *Acinetobacter* spp. The majority of studies used methods that were not able to unambiguously identify *A. baumannii* and therefore it can not be excluded that *Acinetobacter* genomic species 3 or 13 or even *Acinetobacter* spp. outside the *A. calcoaceticus–A. baumannii* complex were misidentified.

We did not adopt a mathematical approach to the synthesis of extracted data on the secular trends of the relative frequency of *Acinetobacter* infections among patients with ICU-acquired pneumonia and/or bacteraemia. This was done for several reasons. Among them, the most important was that the studies were conducted in hospitals in several different cities/areas of different countries. No single centre provided a second report with relevant data from different (non-consecutive) time periods. However, several of the studies were conducted over a long period of time permitting a limited evaluation of the trends of *Acinetobacter* infections in critically ill patients within a specific setting.

Critical evaluation of the reviewed studies

The data suggest that *Acinetobacter* is indeed a growing public health threat affecting a considerable proportion of critically ill patients in several parts of the world. The increasing number of published studies regarding *Acinetobacter* ICU-acquired infections during the last decade represents a growing concern among clinicians and researchers for this emerging pathogen. These infections most frequently involve the respiratory tract of intubated patients. However, *Acinetobacter* is also a common cause of urinary tract and wound infections in ICU patients and on occasion local infections can progress to bacteraemia [62]. The data also support the view that infections caused by *Acinetobacter* are more common in critically ill patients receiving care in the ICU setting in hospitals in Asian and European countries and are considerably lower in the United States. Furthermore, the proportions of *Acinetobacter* isolates that were resistant to various antimicrobial agents in the studies from Asia and Europe were also higher than their counterparts from the United States. A notable exception was the low incidence of resistance from The Netherlands and Scandinavia [27] which is in keeping with the relatively few problems of resistance of other pathogens such as *Staphylococcus aureus*, *Enterococcus* spp. *Pseudomonas aeruginosa*, and Enterobacteriaceae found in these countries compared to other parts of the world.

The data also suggest that there are several noteworthy differences in the antimicrobial resistance patterns between *Acinetobacter* isolates from critically ill patients in European and United States hospitals, chief of the higher rates of resistance in Europe for piperacillin/tazobactam and aminoglycosides. These differences probably mirror the relative frequency of ICU-acquired infections due to *Acinetobacter* in patients in these two geographical areas. Although several assumptions can be made, including differences in antibiotic prescribing policies and infection control practices between countries, no firm conclusions can be made regarding the reasons for the observed differences.

Finally, it should be emphasized that data for the *in vitro* susceptibility testing of *Acinetobacter* clinical

isolates were not available in most of the studies included in our review for three important antibiotics with proven activity against this organism. Indeed, only a few studies reported results of isolates to meropenem [54, 56, 62, 63, 68, 69, 71], sulbactam [58, 60, 69], and polymyxins B and E. In addition, the data confirm that *Acinetobacter* spp. are frequently resistant to aminoglycosides and third-generation cephalosporins, which means that these antibiotics should be avoided for the treatment of these infections.

DECLARATION OF INTEREST

None.

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