Antibiotic Susceptibility Among Aerobic Gram-negative Bacilli in Intensive Care Units in 5 European Countries

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Context Surveillance of antibiotic resistance is especially important in intensive care units (ICUs) because the infection rates are much higher there than in other hospital wards and most epidemics with multiresistant bacteria originate in ICUs.

Objective To evaluate the incidence of decreased antibiotic susceptibility among aerobic gram-negative bacilli isolated from patients in ICUs.

Design Consecutive specimens collected on clinical indications from ICU patients were cultured and tested. Minimum inhibitory concentrations for amikacin, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, piperacillin, and piperacillin-tazobactam were determined using E test.

Setting Eighteen hospitals in Belgium, 40 in France, 20 in Portugal, 30 in Spain, and 10 in Sweden.

Subjects A total of 9166 gram-negative strains were initially isolated from 7308 patients between June 1994 and June 1995.

Main Outcome Measures The incidence of decreased susceptibility, defined as the sum of resistant and intermediate categories with use of the minimum inhibitory concentration break points recommended by the National Committee for Clinical Laboratory Standards.

Results The most frequently isolated organisms were Enterobacteriaceae (59%) followed by *Pseudomonas aeruginosa* (24%). The main sources were respiratory tract (42%), urine (26%), blood (14%), abdomen (11%), and skin and soft tissue (7%). Decreased antibiotic susceptibility across all species and drugs was highest in Portuguese ICUs followed by French, Spanish, Belgian, and Swedish ICUs. The highest incidence of resistance was seen in all countries among *P aeruginosa* (up to 37% resistant to ciprofloxacin in Portuguese ICUs and 46% resistant to gentamicin in French ICUs), *Enterobacter* species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*, and in Portugal and France among *Klebsiella* species.

Conclusion The high incidence of reduced antibiotic susceptibility among gram-negative bacteria in these ICUs suggests that more effective strategies are needed to control the selection and spread of resistant organisms.

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More than 20% of patients admitted to European intensive care units (ICUs) develop an ICU-acquired infection.[1] A high prevalence of decreased antibiotic susceptibility among gram-negative bacilli has been reported from ICU patients in France,[2,3] Belgium,[4] Germany,[5] and the Netherlands during 1990 and 1991,[6] the United States between 1990 and 1993,[7] and Belgium[8] and Sweden[9] during 1994 and 1995.

The National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention monitors secular trends of antibiotic resistance rates of nosocomial pathogens in US hospitals.[10,11] No corresponding international surveillance system is operational in Europe. The aim of this study was to conduct a cross-country comparison of the incidence of antibiotic resistance among aerobic gram-negative bacilli from patients in ICUs in Belgium, France, Portugal, Spain, and Sweden using determination of minimum inhibitory concentration.

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METHODS

Study Design and Bacterial Sampling

Multicenter susceptibility testing was performed using aerobic gram-negative bacilli isolated from patients admitted to ICUs between June 1994 and June 1995. The number of hospitals included was 18 in Belgium, 40 in France, 20 in Portugal, 30 in Spain, and 10 in Sweden, and these hospitals were chosen to represent different geographic areas of each country. Intensive care unit–acquired infections and ICU mortality have been the topic of a large, international, European epidemiological study.[1] Consecutive specimens collected on the basis of clinical indications were cultured and tested. A total of 11 249 gram-negative bacterial strains were isolated from 7308 ICU patients. Of these, 9166 were initial isolates (first recovered during ICU admission) and 2083 were repeat isolates of the same species from the same patients. Repeat isolates were not included in this analysis. The number of initial isolates and patients in the various countries were as follows: Belgium, 1435 isolates from 1029 patients; France, 2988 isolates from 2205 patients; Portugal, 2067 isolates from 1882 patients; Spain, 2174 isolates from 1845 patients; and Sweden, 502 isolates from 347 patients; for a total of 9166 isolates from 7308 patients in all countries. Decreased antibiotic susceptibility was analyzed for pathogens collected from all sites and for blood isolates alone.

Susceptibility Testing

Minimum inhibitory concentrations for amikacin (except in Sweden), ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, piperacillin, and piperacillin-tazobactam were determined using the E test (AB BIODISK, Solna, Sweden).[12] All laboratories performed quality control using reference strains of *Escherichia coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853 to confirm consistency of materials, methods, and results. Decreased susceptibility (ie, resistant and intermediate categories) was defined using the minimum inhibitory concentration break points recommended by the National Committee for Clinical Laboratory Standards.[13] The break points for susceptible and resistant categories were as follows: imipenem, 4 mg/L or less and 16 mg/L or more; ceftazidime, 8 mg/L or less and 32 mg/L or more; ceftriaxone, 8 mg/L or less and 64 mg/L or more; piperacillin, 16 mg/L or less and 128 mg/L or more (except *P aeruginosa*, ≤64 mg/L and ≥128 mg/L); piperacillin-tazobactam, 16/4 mg/L or less and 128/4 mg/L or more (except *P aeruginosa*, ≤64/4 mg/L and ≥128/4 mg/L); gentamicin, 4 mg/L or less and 16 mg/L or more; amikacin, 16 mg/L or less and 64 mg/L or more; and ciprofloxacin, 1 mg/L or less and 4 mg/L or more.[13]

RESULTS

Body Sites

The main sources of isolates were respiratory tract (42%), urine (26%), blood (14%), abdomen (11%), and skin and soft tissue (7%).

Organisms

The distribution of bacterial species is shown in TABLE 1. The most frequently isolated organisms in all countries were Enterobacteriaceae (59%) followed by *P aeruginosa* (24%). The most frequent species of Enterobacteriaceae were *E coli*, *Enterobacter* species, *Klebsiella* species, *Serratia* species, *Proteus* species, *Morganella morganii*, and *Citrobacter* species. The species included in Table 1 constituted 97% of the total strains in Belgium, 96% in France, 98% in Portugal, 98% in Spain, and 95% in Sweden.

Decreased Antibiotic Susceptibility

The incidence of decreased antibiotic susceptibility by species and country is shown in TABLE 2, indicating significant differences for some drug-pathogen combinations between countries.

Table 1. Gram-negative Bacterial Isolates in Intensive Care Unit Patients*

Isolates	Belgium	France	Portugal	Spain	Sweden
Escherichia coli	20	24	24	30	26
Pseudomonas aeruginosa	20	25	25	25	12
Enterobacter species	16	10	9	8	13
Klebsiella species	11	10	13	9	14
Acinetobacter species	2	10	6	8	3
Proteus species	7	7	7	7	6
Serratia species	7	4	7	4	2
Citrobacter species	3	2	3	2	4
Stenotrophomonas maltophilia	4	2	2	2	6
Morganella morganii	5	2	2	2	1
Haemophilus species	2	0	0	1	8

*Data are the percentage of bacterial species isolated from intensive care unit patients in Belgium, France, Portugal, Spain, and Sweden.

COMMENT

In summary, we found that the percentage of decreased antibiotic susceptibility across all species and drugs was highest in Portuguese ICUs, followed by French, Spanish, Belgian, and Swedish ICUs. The highest incidence of resistance was seen in all countries among *P aeruginosa*, *Enterobacter* species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*. In Portugal and France, there also was a high (20%-34%) level of decreased susceptibility to ceftazidime among *Klebsiella* species. The most active agents were amikacin and imipenem (Table 2). This is similar to findings from a large North American ICU study conducted between 1990 and 1993 of antibiotic resistance among gram-negative isolates.[7]

The high incidence of decreased susceptibility among gram-negative bacteria seen in France (Table 2) was similar to the findings of a French study performed during 1991.[3] The overall resistance to most antibiotics found in Belgium[8] (Table 2) was similar to that found in 1990 in studies performed in Belgium,[4] Germany,[5] and the Netherlands.[6] However, because the methods

Table 2. Percentage of Decreased Antibiotic Susceptibility Among Gram-negative Isolates From ICU Patients*

	All Gram-negative Isolates	*Acinetobacter* Species	*Enterobacter* Species	*Escherichia coli*	*Klebsiella* Species	*Pseudomonas aeruginosa*	*Serratia* Species
Imipenem							
Belgium	10 (7)	12	3	1	0	16	1
France	10 (7)	9	2	0	0	24	0
Portugal	9 (7)	5	3	0	1	21	3
Spain	10 (5)	16	2	0	0	22	0
Sweden	10 (6)	19	0	0	0	19	0
Ceftazidime							
Belgium	13 (16)	18	43	4	3	11	5
France	18 (18)	70	36	1	20	14	2
Portugal	21 (16)	81	48	3	34	16	16
Spain	15 (11)	76	31	1	4	16	6
Sweden	7 (9)	0	26	3	3	2	0
Ceftriaxone							
Belgium	29 (28)	64	37	2	6	69	25
France	32 (27)	89	34	1	12	57	17
Portugal	35 (22)	91	42	2	6	64	13
Spain	25 (22)	87	30	2	4	49	6
Sweden	19 (15)	75	26	1	4	46	0
Piperacillin							
Belgium	31 (36)	42	49	40	27	14	41
France	39 (43)	85	41	39	43	26	37
Portugal	41 (39)	85	54	43	54	22	62
Spain	34 (35)	87	33	50	21	15	22
Sweden	20 (18)	62	26	17	21	5	0
Piperacillin-tazobactam							
Belgium	22 (27)	36	51	15	14	13	34
France	17 (18)	44	31	3	10	19	23
Portugal	25 (22)	75	43	11	28	20	48
Spain	11 (10)	58	23	4	3	8	9
Sweden	13 (18)	56	26	5	7	5	11
Gentamicin							
Belgium	10 (11)	18	3	4	2	23	6
France	26 (25)	66	17	4	11	46	20
Portugal	29 (19)	64	28	7	30	41	58
Spain	16 (15)	81	4	7	5	18	6
Sweden	6 (9)	0	0	1	1	7	11
Amikacin							
Belgium	4 (8)	15	4	1	2	4	11
France	11 (11)	36	8	1	9	13	6
Portugal	6 (7)	10	5	2	6	8	3
Spain	7 (4)	51	0	1	2	4	1
Sweden	ND	ND	ND	ND	ND	ND	ND
Ciprofloxacin							
Belgium	13 (12)	18	31	6	1	16	15
France	24 (23)	78	20	2	18	35	21
Portugal	25 (22)	75	21	11	7	37	35
Spain	17 (17)	81	4	14	2	14	19
Sweden	7 (3)	19	0	1	4	8	11

*Blood isolates are reported in parentheses. ICU indicates intensive care unit; ND, not done.

of this and previous studies were different, a direct comparison of the findings is difficult. The high bacterial inoculum (10^8 colony-forming units [CFUs] per milliliter) provided by E test that was used in this study is a sensitive tool for detecting resistant subpopulations that may cause development of resistance during therapy. In previous studies, a microdilution method with a lower inoculum (10^4 CFUs/mL)[3-6] was used that may not detect resistant subpopulations as easily as the E test.

The lower resistance levels found in Swedish ICUs compared with Belgium, France, Portugal, and Spain (Table 2) may be due to several different factors. These include prudent use of antibiotics, lower total antibiotic administration, and better compliance with infection control measures, such as hand disinfection and barrier precautions by health care workers.

Because our data represent all consecutive gram-negative isolates initially recovered from patients in the participating ICUs, they include pathogens isolated from patients with community- and hospital-acquired infections. No analysis was done to determine whether the isolates tested caused infection or only colonized these critically ill patients. The isolates from specimens other than blood may reflect colonization; however, colonization is often a prerequisite for infection. We found similarly high levels of decreased susceptibility among blood isolates compared with isolates from all sites (Table 2).

Bacterial resistance to ceftazidime is a serious emerging problem. Approximately 40% of *Enterobacter cloacae* were resistant to ceftazidime, according to studies of ICU isolates in the United States between 1987 and 1991[10] and between 1994 and 1995,[14] which corresponds to the findings in our study (Table 2). This is probably related to production of stably derepressed chromosomal class-1 β-lactamase, which hydrolyzes β-lactam antibiotics other than carbapenems.[15] Previous use of third-generation cephalosporins is more likely to cause the selection of resistance to β-lactams in blood isolates of *Enterobacter* species, which is associated with higher mortality.[16] An increased ciprofloxacin resistance among *Enterobacter* species was seen in Belgium and France (Table 2) compared with previous studies performed in 1990[4] and 1991.[3]

In Portugal and France, 36% and 26%, respectively, of *Klebsiella pneumoniae* showed decreased susceptibility to ceftazidime (data not shown). This was probably caused by the production of extended-spectrum β-lactamases[15,17] and is concordant with a study by Livermore and Yuan.[18] According to Jarlier et al,[3] decreased susceptibility to ceftazidime among *K pneumoniae* in French ICUs was 36% in 1991. In the United States, resistance to ceftazidime among *K pneumoniae* in ICU isolates increased from 3.6% in 1990 to 14.4% in 1993.[7] Markedly lower resistance rates of *Klebsiella* species to all β-lactam antibiotics was observed in this study in Belgium compared with a previous study performed in 1990 (Table 2).

The lower susceptibility of *P aeruginosa* to imipenem compared with ceftazidime was consistent across all 5 countries in this study. The mechanism of resistance to imipenem among *P aeruginosa* (mainly decreased penetration through outer membrane) is well investigated and may occur more readily than development of resistance to ceftazidime (mainly related to hyperproduction of class 1 β-lactamases).[15]

Acinetobacter species (Table 2) and *S maltophilia* (data not shown) were the most resistant pathogens to all investigated drugs. Although not the most virulent gram-negative pathogen, *Acinetobacter* is an increasingly infectious threat, especially for patients receiving broad-spectrum antimicrobial therapy and requiring life support.[19-21] A Spanish study[20] has shown that *Acinetobacter* isolates, usually acquired in the ICU, are multiresistant and may cause severe infections associated with a high mortality rate. Riley et al[21] recently described the failure to stop the spread of gentamicin-resistant *Acinetobacter baumannii* in an Australian ICU despite infection control measures.

The high levels of decreased susceptibility among most species of gram-negative bacilli to ceftazidime, ceftriaxone, piperacillin, piperacillin-tazobactam, gentamicin, and ciprofloxacin in Belgium, Portugal, France, and Spain (Table 2) further limits use of these drugs for empirical monotherapy. Spread of multiresistant bacteria in the ICU can be minimized with infection control measures such as rigorous hand disinfection between patient contacts, barrier precautions, and isolation of patients infected with resistant isolates. We suggest that hospitals should have an active program for online antibiotic resistance surveillance of common drugs, using quantitatively accurate minimum inhibitory concentration methods, to constantly evaluate antibiotic administration and pharmacy formulary options. These measures have the potential to minimize morbidity and mortality associated with infections caused by multiresistant bacteria in critically ill patients.[18,22-25] However, studies to develop and evaluate the most effective strategies to minimize selection and spread of resistant organisms in the ICU are sorely needed, as are investigations to better quantify their clinical and economic consequences.

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