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Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011)☆,☆☆

Helio S. Sader *, David J. Farrell, Robert K. Flamm, Ronald N. Jones

JMI Laboratories, North Liberty, IA 52317, USA

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ABSTRACT

Treatment of infections in the intensive care unit (ICU) represents a great challenge, especially those caused by Gram-negative organisms. Rapid introduction of appropriate antimicrobial therapy is crucial to reduce mortality; resistance rates in the ICU can be elevated due to antimicrobial selection pressure. We evaluated the antimicrobial susceptibility patterns of Gram-negative bacteria isolated from patients hospitalized in ICUs (ICU patients). The isolates were consecutively collected as part of the SENTRY Antimicrobial Surveillance Program from January 2009 to December 2011 and tested for susceptibility to multiple antimicrobial agents at a central laboratory by reference broth microdilution methods. Antimicrobial susceptibility results for 5989 bacterial isolates from ICU patients (3445 from the United States [USA] and 2544 from Europe [EU]) were analyzed and compared to those of 17,244 organisms from non-ICU patients (9271 from USA and 7973 from EU). *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* were the most frequently isolated organisms from ICU patients, followed by *Enterobacter* spp., *Serratia* spp., *Haemophilus influenzae*, *Acinetobacter* spp., and *Proteus mirabilis*. Susceptibility rates were generally lower among ICU isolates compared to non-ICU organisms. *E. coli* isolates from ICU patients exhibited elevated extended-spectrum β-lactamase (ESBL)-phenotype rates (13.7% in USA and 16.6% in EU); furthermore, only amikacin (90.5–94.8% susceptibility), colistin (99.8–100.0% inhibited at ≤2 μg/mL), imipenem (95.5–96.0%), meropenem (95.4–95.8%), and tigecycline (96.3–98.0%) exhibited good activity against *Klebsiella* spp. ESBL-phenotype rates have increased among both *E. coli* and *Klebsiella* spp. from ICU patients in the USA and in Europe, with the most noticeable increase among *Klebsiella* spp. from Europe (from 27.5% in 2009 to 41.8% in 2011; $P = 0.015$ and odds ratio = 0.89 [95% confidence interval, 1.13–3.18]). Meropenem susceptibility among *Klebsiella* spp. improved slightly in the USA but decreased markedly in Europe from 100.0% in 2009 to 89.7% in 2011. Only colistin (99.4% susceptible) and amikacin (97.3% in USA and 84.9% in EU) exhibited good activity against *P. aeruginosa* strains from ICU patients. The greatest differences in susceptibility rates between *P. aeruginosa* strains from ICU and non-ICU patients were observed for the anti-pseudomonal β-lactams, such as ceftazidime, meropenem, and piperacillin/tazobactam. The results of this study (101 medical centers) highlight major antimicrobial coverage problems and trends in antimicrobial resistance for USA and EU ICU patient isolates.

1. Introduction

Infection is a common problem in intensive care units (ICUs) and has been associated with considerable morbidity, mortality, and costs (Martin and Yost, 2011; Vincent et al., 2009). Infections caused by Gram-negative bacteria have characteristics that are of particular concern. These organisms are highly efficient at up-regulating or acquiring genes that code for antimicrobial resistance, especially in the presence of antimicrobial selection pressure (Peleg and Hooper, 2010). Furthermore, the armamentarium of drugs for treatment of infections caused by multidrug-resistant (MDR) Gram-negative bacilli is very restricted. Although several drugs have been approved for treatment of Gram-positive infections in recent years, the pipeline of novel agents to meet the challenge of MDR Gram-negative organisms remains limited (Boucher et al., 2013).

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* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: helio-sader@jmilabs.com (H.S. Sader).

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MDR organisms pose considerable challenges to the health care system in relation to diagnosis, treatment, and infection control. These challenges are amplified in the ICU environment where selective pressure for the emergence of antimicrobial resistance and the risks for transmission of organisms among patients are greater. Moreover, broad-spectrum and/or multiple antimicrobial agents are more commonly used for empiric therapy in the ICU due to the higher probability of antimicrobial resistance and the increased severity of the infection (Fraimow and Tsigrelis, 2011; Hanberger et al., 2009).

It has been shown that delay in the initiation of appropriate antimicrobial therapy is associated with increased morbidity and mortality in patients with severe infections, particularly those caused by Gram-negative bacteria (Morata et al., 2012; Peralta et al., 2007; Retamar et al., 2012). Thus, there is a clear need for surveillance and early warning diagnostic systems that can detect signs of emerging and/or increasing antimicrobial resistance at the local, regional, and national levels. In this study, we evaluated the antimicrobial susceptibility patterns of Gram-negative bacteria isolated from hospitalized patients in ICUs and compared them with those from patients in other wards (non-ICU patients) of the same hospitals during the same time period across the United States (USA) and Europe (EU).

2. Materials and methods

2.1. Organism collection

The isolates were consecutively collected as part of the SENTRY Antimicrobial Surveillance Program (Kaiser et al., 2013) from January 2009 to December 2011. Only 1 isolate per patient infection episode was included in this surveillance study. During the study period, a total of 6848 Gram-negative organisms were isolated from ICU patients (3946 from the USA and 2902 from EU), and the antimicrobial susceptibility results for the eight most frequently isolated organisms were analyzed in the present study, comprising 5989 bacterial isolates, 3445 from USA, and 2544 from EU medical centers. Infections from ICU patients include infections acquired in the ICU as well as those acquired outside the ICU (other hospital ward or in the community). Furthermore, the antimicrobial susceptibility patterns of isolates from ICU patients were compared to those of isolates collected from non-ICU patients in the same medical centers during the same time period, which included 9271 isolates from the USA and 7973 isolates from EU medical centers.

All ICU and non-ICU isolates were deemed clinically significant by algorithms in place in participant medical centers. ICU isolates were mainly from pneumonia (46.4%), bacteremia (42.8%), and skin and skin structure infections (SSSI; 7.6%), whereas, non-ICU isolates were more frequently isolated from bacteremia, (54.9%), followed by pneumonia (17.6%) and SSSI (17.6%; data not shown).

Isolates were collected from 65 medical centers in the USA and 36 medical centers from 9 EU countries (Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, and United Kingdom). Species identification was performed at the participant medical center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using the VITEK 2 System (bioMerieux, Hazelwood, Missouri, USA) or matrix-assisted laser desorption/ionization time-of-flight (Bruker Daltonics, Bellerica, MA, USA), as necessary.

2.2. Susceptibility testing

Isolates were tested for susceptibility to multiple antimicrobial agents at a central laboratory (JMI Laboratories) by reference broth microdilution methods as described by the CLSI M07-A9 document (CLSI, 2012). MIC results of USA isolates were interpreted according to CLSI criteria in M100-S23 (CLSI, 2013), whereas MIC results of EU isolates were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 3.0, January 2013) (EUCAST, 2013). *Escherichia coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" based on the CLSI screening criteria for extended-spectrum β-lactamase (ESBL) production, i.e., MIC of ≥2 μg/mL for ceftazidime or ceftriaxone or aztreonam (CLSI, 2013). Although an ESBL confirmation test was not performed and other β-lactamases, such as AmpC and *Klebsiella pneumoniae* carbapenemases (KPC), may also produce an "ESBL-phenotype", these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds.

3. Results

The frequency of occurrence of Gram-negative organisms isolated from ICU and non-ICU patients in the USA and EU is listed in Table 1. *E. coli* was the most frequently isolated Gram-negative organism from both ICU (1441 isolates; 21.0%) and non-ICU patients overall (6693; 33.8%); however, *E. coli* was less frequently isolated in the USA compared to EU. Among ICU patients, *E. coli* ranked second in the USA (732; 18.6%) and first in EU (709; 24.4%), whereas among non-ICU patients, *E. coli* was the most common organism in both regions, but with a higher prevalence in the EU (42.0 versus 27.1%; Table 1).

Klebsiella spp. ranked second overall among ICU (1320; 19.3%) and non-ICU patients (3571; 18.0%) patients, but it was more commonly isolated in the USA compared to EU. Among ICU patients, *Klebsiella* spp. ranked first in the USA (865; 21.9%) and third in EU (455; 15.7%: Table 1). *Pseudomonas aeruginosa*, the third most commonly isolated overall in both ICU (1,207; 17.6%) and non-ICU patients (2,383; 12.0%), showed similar frequency in the USA and EU but ranked third among isolates from ICU patients in the USA (678; 17.2%) and second in EU (529; 18.2%). Furthermore, *P. aeruginosa* was more commonly isolated from ICU patients (17.2–18.2%) compared to non-ICU patients (12.0–12.1%; Table 1). *Enterobacter* spp. ranked fourth among isolates from ICU and non-ICU patients from the USA and EU, with similar frequency in both regions, e.g., 7.9–10.9% (Table 1).

Serratia spp., *Haemophilus influenzae*, *Acinetobacter* spp., and *Proteus mirabilis* ranked fifth, sixth, seventh, and eighth, respectively, among isolates from ICU patients from the USA and EU with similar frequencies in both regions. *Serratia* spp. and *Acinetobacter* spp. were relatively more common among ICU compared to non-ICU patients. Conversely, *P. mirabilis* was more frequently isolated from non-ICU compared to ICU patients (Table 1). Other less frequently isolated organisms (combined) accounted for 12.7 and 12.3% of Gram-negative organisms cultured from ICU patients in the USA and EU, respectively. Among non-ICU patients, the top 8 pathogens accounted

Table 1
Frequency of Gram-negative organisms isolated from ICU and non-ICU patients (SENTRY Program, 2009–2011).

Organisms	Rank order (no. of isolates/frequency [% of total])			
	ICU		Non-ICU	
	USA	Europe	USA	Europe
E. coli	2 (732/18.6)	1 (709/24.4)	1 (2926/27.1)	1 (3767/42.0)
Klebsiella spp.	1 (865/21.9)	3 (455/15.7)	2 (2279/21.1)	2 (1292/14.4)
P. aeruginosa	3 (678/17.2)	2 (529/18.2)	3 (1306/12.1)	3 (1077/12.0)
Enterobacter spp.	4 (430/10.9)	4 (278/9.6)	4 (944/8.7)	4 (706/7.9)
Serratia spp.	5 (238/6.0)	5 (198/6.8)	7 (435/4.0)	6 (270/3.0)
H. influenzae	6 (224/5.7)	6 (145/5.0)	5 (599/5.5)	8 (231/2.6)
Acinetobacter spp.	7 (166/4.2)	7 (139/4.8)	8 (318/2.9)	7 (257/2.9)
P. mirabilis	8 (112/2.8)	8 (91/3.1)	6 (464/4.3)	5 (373/4.2)
Subtotal (top 8)	(3445/87.3)	(2544/87.7)	(9271/85.7)	(7973/88.9)
Grand total	(3946/100.0)	(2902/100.0)	(10,817/100.0)	(8967/100.0)

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