

REVIEW

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Antimicrobial resistance in Europe and its potential impact on empirical therapy

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ABSTRACT

The problem of microbial drug resistance is a major public health concern, due to its global dimension and alarming magnitude, although the epidemiology of resistance can exhibit remarkable geographical variability and rapid temporal evolution. The major resistance issues overall are those related to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Enterobacteriaceae* producing extended-spectrum β -lactamases, and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Europe is not free from any of these issues, although their impact may be significantly different in different countries. MRSA rates are high in several European countries, but seem to have levelled off in some settings. Diffusion of VRE is still irregular. The most alarming resistance trends are those observed for *Enterobacteriaceae* and the Gram-negative non-fermenters, with a generalized increase in rates of resistance to the most important anti-Gram-negative agents (β -lactams and fluoroquinolones) and the circulation of strains showing multidrug resistance phenotypes.

Keywords antibiotic resistance, Europe, nosocomial pathogens, resistance epidemiology

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THE PROBLEM: RESISTANT PATHOGENS AT THE BEGINNING OF THE NEW CENTURY

Microbial drug resistance has steadily evolved in response to the selective pressure generated by antimicrobial chemotherapy, and the introduction of new antimicrobial agents has invariably been followed by the appearance of resistant strains among naturally susceptible bacterial species.

At the beginning of the new century, the problem of microbial drug resistance has achieved a global dimension and an alarming magnitude, being one of the leading unresolved problems in public health. The relentless evolution of resistance, in the face of a decrease in the development of new antimicrobial agents active against resistant pathogens, has led to an increasing number of cases in which the pathogen is resistant to most, or even all, drugs available for

clinical use (the so-called pandrug resistance phenotypes), i.e. a situation reminiscent of the pre-antibiotic era.

The epidemiology of drug resistance can exhibit remarkable geographical variability and rapid evolution over time, due to a complex interplay of factors involved in the selection and spread of different resistant 'bugs' and resistance genes, which are still only partially understood. The scope of this article is to briefly analyse the trends for major types of resistance in Europe, including those related to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Enterobacteriaceae* producing extended-spectrum β -lactamases (ESBLs), and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Differences within other settings and the potential impact on the selection of empirical therapy are also discussed.

MRSA: DIFFERENT EVOLVING TRENDS?

S. aureus remains one of the most important pathogens, both in the hospital setting and in the community [1], with MRSA being one of the

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most important resistant pathogens worldwide [2]. The most recent data from the European Antibiotic Resistance Surveillance System (EARSS) confirm the diffusion of MRSA in Europe, but with notable variability in the proportion of MRSA among invasive isolates from different European countries (EARSS Annual Report 2005 (2006); available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)). The highest rates are reported in western and southern Europe, and in the Balkan region, whereas rates are lower in continental Europe, and even lower in The Netherlands and in Scandinavia (Table 1). Analysis of trends concerning the proportion of MRSA observed in recent years (1999–2005) revealed a significantly increasing trend in some countries, overall stability in others, and a significantly decreasing trend in two cases (France and Slovenia, apparently after the enforcement of strict control measures for MRSA) (Table 1).

In Europe, an overall stable trend in MRSA rates has been reported for isolates from skin and soft tissue infections (SSTIs) during the period 1998–2004 [3] (Fig. 1). Interestingly, this situation was substantially different from that observed in North America, where, during the same period, a

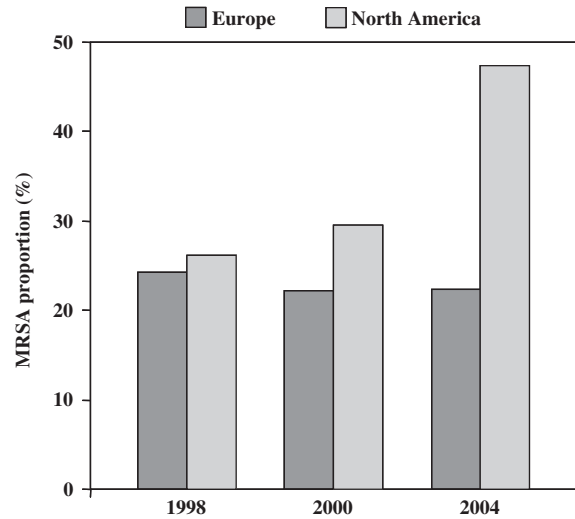


Fig. 1. Proportion (%) of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates from skin and soft tissue infections in Europe and in North America during the period 1998–2004. Data are from Moet *et al.*[3].

Table 1. Proportion (%) of methicillin-resistant *Staphylococcus aureus* (MRSA) among invasive isolates of *S. aureus* and of vancomycin-resistant enterococci (VRE) among invasive isolates of *Enterococcus faecium* in several European countries in 2005

Country	<i>S. aureus</i>		<i>E. faecium</i>	
	No. of isolates	% MRSA	No. of isolates	% VRE
Bulgaria	160	31	28	<1
Finland	790	3 ^a	94	<1
France	3483	27 ^b	194	2
Germany	874	21 ^a	256	10 ^a
Greece	681	42	227	37 ^a
Italy	1431	37	193	19
Ireland	1360	42	220	31 ^a
Israel	546	41	71	46 ^a
The Netherlands	1401	<1 ^a	188	<1
Poland	197	24	20	5
Portugal	1153	47 ^a	95	34 ^b
Romania	83	61 ^a	10	<1
Slovenia	349	10 ^b	30	<1
Spain	1337	27	141	3
Sweden	1774	1	253	<1
UK	3967	44 ^a	224	33

Data are from the EARSS 2005 annual report (EARSS Annual Report 2005 (2006), pp. 143–144; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)).

^aSignificant increasing trend observed during recent years.

^bSignificant decreasing trend observed during recent years.

consistent increase in MRSA rates was observed among isolates from SSTIs (Fig. 1). This phenomenon probably reflects the diffusion of MRSA at the community level in the USA [1], due to the emergence and spread of community-associated MRSA strains (which are known to be mostly responsible for SSTIs) and to the increasing leakage from hospitals of the classical hospital-associated MRSA strains. In Europe, the diffusion of MRSA into the community has apparently been delayed, although recent reports indicate that this phenomenon is now emerging in several European countries [4; 17th European Congress of Clinical Microbiology and Infectious Diseases, 2007; abstracts P1599, P1304 and P1324].

VRE: THE EUROPEAN SCENARIO

VRE, which are well-established resistant pathogens in the USA [5], remain a problem with an overall lower and inconsistent impact in Europe. In 2005, the proportion of VRE among invasive isolates of *Enterococcus faecium* was higher than 30% in only four European countries (Greece, Ireland, Portugal, and the UK) and in Israel, whereas the proportion remained consistently lower, or VRE were virtually absent, in others (Table 1). An increasing trend was observed in only some of the countries affected by the highest rates (Table 1), but with a worrisome revival of

vancomycin-resistant *E. faecium*, recently reported in England and Wales (available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1224142369573 (accessed 28 October 2008)).

The proportion of vancomycin-resistant strains remains much lower among *Enterococcus faecalis*, the enterococcal species most commonly isolated from clinical sources, with rates that have attained a maximum of 5% (in Portugal), but are lower than 1% in most countries (EARSS Annual Report 2005 (2006), pp. 49–51; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)).

ESBL PRODUCTION AND MULTIDRUG RESISTANCE IN ENTEROBACTERIACEAE: A RAPIDLY CHANGING EPIDEMIOLOGY

The emergence and dissemination of ESBL producers among the *Enterobacteriaceae* dates back to the mid-1980s, and is a consequence of the selective pressure generated by the introduction of oxyimino-cephalosporins into clinical practice. The evolution of ESBLs in *Enterobacteriaceae* has occurred through two major mechanisms: (i) selection for point mutants of the TEM- and SHV-type plasmid-mediated broad-spectrum β -lactamases (prevalent among *Enterobacteriaceae* circulating in the clinical setting since the 1970s), which have acquired the ability to degrade expanded-spectrum cephalosporins and monobactams; and (ii) capture of new ESBL genes from environmental bacteria (e.g. the genes encoding CTX-M-, VEB-, GES-, TLA-, SFO- and BES-type enzymes) through horizontal gene transfer [6].

Recent international surveillance data indicate an overall increasing trend in ESBL production rates in Europe, not only in *Klebsiella pneumoniae* (the species in which ESBLs are most widespread), but also in *Escherichia coli* [7]. In Europe, an increasing trend in ESBL production in *E. coli* has also been reported for isolates causing SSTIs [3]. These data are consistent with the reported increasing trends concerning resistance to third-generation cephalosporins (3GCs) in *E. coli* (which largely reflect ESBL production) in most European countries (EARSS Annual Report 2005 (2006); available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)) (Table 2), and in England and Wales (recent HPA surveillance data; available

Table 2. Rates (%) of resistance to third-generation cephalosporins (3GCs) and of multidrug resistance (MDR) among invasive isolates of *Escherichia coli* in different European countries

Country	3GC		MDR	
	No. of isolates	Resistance rate (%)	No. of isolates	Resistance rate (%)
Bulgaria	203	28 ^a	196	16
France	5835	1 ^a	5808	0
Germany	1012	2 ^a	1006	0
Greece	1139	7	1136	2
Italy	1191	8 ^a	1090	4
The Netherlands	1890	2 ^a	1182	1
Poland	176	5	175	3
Portugal	1076	12 ^a	1039	8
Romania	80	16	75	3
Spain	2997	8 ^a	2992	3
Sweden	3198	1 ^a	2991	0
UK	1692	6 ^a	1689	2

Data are from the EARSS 2005 annual report (EARSS Annual Report 2005 (2006), p. 145; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)). MDR was defined as resistance to fluoroquinolones, 3GCs and aminoglycosides, irrespective of susceptibility to aminopenicillins. ^aSignificant increasing trend observed during recent years.

at: http://www.hpa.org.uk/infections/topics_az/ecoli/ecoli07/amr.htm (accessed 28 April 2007)). The explosive diffusion of ESBL-producing *E. coli* strains, which are no longer restricted to the hospital setting but are also spreading within the community [8], is clearly a matter of serious concern that may have major implications for empirical therapy, as *E. coli* is the most common Gram-negative species isolated from clinical specimens in either setting [1].

The mechanisms underlying this recent epidemiological evolution are not fully understood; they seem, at least in part, to be related to the emergence and dissemination of the CTX-M-type ESBL genes. These genes, captured from *Kluyvera* spp., are carried on transferable plasmids that exhibit a notable propensity to spread among *E. coli* and other *Enterobacteriaceae* [9,10], and their acquisition can generate highly successful clones [11,12]. Indeed, rapid dissemination of CTX-M-type ESBLs has recently been documented in several European countries, where these enzymes are becoming the dominant type of ESBL and have outnumbered the classical TEM- and SHV-type ESBL variants [13]. ESBL production is a matter of clinical concern, not only because it impairs the activity of expanded-spectrum cephalosporins and most other β -lactams (except carbapenems), but also because it is often linked to multidrug resistance (MDR) concerning other anti-Gram-negative agents (e.g. aminoglycosides

and fluoroquinolones) [14]. Indeed, a worrisome and increasing trend in MDR (defined as resistance to fluoroquinolones, 3GCs, and aminoglycosides) has been reported for *E. coli* in many European countries (EARSS Annual Report 2005 (2006); available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)) (Table 2).

Carbapenems are the only β -lactams that retain potent activity against multidrug-resistant *Enterobacteriaceae* producing ESBLs, and clinical data indicate that they are the drugs of choice for the treatment of serious infections caused by similar strains [14,15]. Acquired carbapenem resistance, however, can emerge among *Enterobacteriaceae* through at least two different mechanisms: (i) loss of porins in strains of *Klebsiella* spp. producing ESBLs or in strains of *Enterobacter* spp. overproducing AmpC-type β -lactamases; or (ii) production of an acquired carbapenemase [16]. The former mechanism involves mutation, and can emerge during carbapenem therapy [17]. A recent report from the UK suggests that *Klebsiella* and *Enterobacter* isolates with this resistance mechanism are increasing in frequency [18].

Concerning acquired carbapenemases, with very few exceptions the enzymes found in *Enterobacteriaceae* are either serine carbapenemases of molecular class A (e.g. KPC-, SME- and NMC/IMI-type enzymes) or metallo- β -lactamases (MBLs) of molecular class B (e.g. IMP- and VIM-type enzymes) [16,19]. The class A serine β -lactamases (especially the KPC-type enzymes) are currently emerging on the east coast of the USA [20], and do not yet appear to have had a significant impact in Europe, although a recent report describing a multiclonal outbreak of KPC-producing *E. coli* in Israel [21] could be a harbinger of the emergence of these enzymes in Europe and in the Mediterranean region. Acquired MBLs are still uncommon among *Enterobacteriaceae* [20,22,23], except in Greece, where a remarkable spread of acquired MBLs has recently been observed among *Enterobacteriaceae* [24–27], and this is apparently the major cause of the unusually high rates of carbapenem resistance (27.8% in 2005 and 27.9% in 2006) reported by the EARSS surveillance system among invasive isolates of *K. pneumoniae* from Greece (<http://www.earss-rivm.nl>). MBL-producing strains can exhibit very complex MDR phenotypes, due to the acquisition of multiple resistance determinants. Indeed,

K. pneumoniae strains producing the VIM-1 MBL and the SHV-5 ESBL, showing a virtually pan-drug-resistant phenotype, have recently been described in intensive-care units (ICUs) of Greek hospitals [28].

P. AERUGINOSA AND A. BAUMANNII: TOWARDS COMPLEX MULTIDRUG AND PANDRUG RESISTANCE

Antibiotic resistance is even more serious among the Gram-negative non-fermenters (GNNFs) *P. aeruginosa* and *A. baumannii*, which are important nosocomial pathogens, especially in ICUs. The EARSS surveillance data, which have been extended to include *P. aeruginosa* since 2005, reveal that acquired resistance to major antipseudomonal agents is a sizeable problem in several countries, although with remarkable geographical differences (EARSS Annual Report 2005 (2006), pp. 66–71; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)). Overall, the most serious problems are encountered in the countries of eastern Europe, with rates of resistance to piperacillin, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides that in some cases (e.g. Romania) can exceed 50% (Table 3).

P. aeruginosa can acquire resistance to any antipseudomonal drug through a broad repertoire of resistance mechanisms, and exhibits a remarkable propensity to acquire MDR phenotypes [29–31]. Overall, 7.4% of invasive *P. aeruginosa* isolates from Europe were found to be resistant to the five classes of drugs (piperacillin and tazobactam, 3GCs, carbapenems, aminoglycosides, and fluoroquinolones) surveyed by the EARSS in 2005 (EARSS Annual Report 2005 (2006), pp. 70; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)), whereas the isolation of strains resistant to most or all the available antipseudomonal drugs, except colistin, is no longer exceptional and is highly alarming in the clinical setting [32,33].

Concerning *Acinetobacter* spp., the most recent European data from the SENTRY surveillance system (referring to the period 2001–2004) revealed that, except for colistin, which was active against 97.3% of isolates, only carbapenems retained substantial activity (rates of susceptibility to imipenem and meropenem were 73.7% and

Country	Piperacillin	Ceftazidime	Carbapenems	Fluoroquinolones	Aminoglycosides
Bulgaria	50	45	38	47	53
France	15	9	14	27	22
Germany	17	11	24	19	13
Greece	30	27	39	39	40
Ireland	7	10	11	14	7
The Netherlands	4	5	5	9	7
Poland	50	31	27	31	56
Romania	61	52	61	64	64
Spain	4	6	17	14	4
Sweden	9	5	18	6	<1
UK	2	3	9	8	3

Data are from the 2005 EARSS report (EARSS Annual Report 2005 (2006), p. 147; available at: http://www.rivm.nl/earss/Images/EARSS%202005_tcm61-34899.pdf (accessed 28 April 2007)).

70.4%, respectively). For other β -lactams (ceftazidime and cefepime) and ciprofloxacin, the susceptibility rates were lower than 50% [34]. Data for *Acinetobacter* spp. isolates from ICUs in North America and in some European countries (France, Germany, and Italy), reported by The Surveillance Network Database (Focus Technologies, Inc., Herndon, VA), referring to the years 2000–2002, are consistent with the finding that carbapenems are the only anti-*Acinetobacter* drugs that retain substantial activity [35] (Table 4). These data also revealed remarkable geographical variability in the susceptibility to various drugs (Table 4), which is probably related to the dissemination of *Acinetobacter* clones with different resistance phenotypes in different settings [36].

Under these circumstances, the dissemination of multidrug-resistant *Acinetobacter* clones that have also acquired resistance to carbapenems is a most worrisome aspect of the evolution of microbial drug resistance [37]. A recent paradigmatic example of this phenomenon has been observed in England, where a carbapenem-resistant *A. baumannii* clone that produces the OXA-23 carbapenemase and is susceptible only to colistin and tigecycline has started spreading in London and Southeast England [38]. In fact, acinetobacters

have evolved several mechanisms to acquire carbapenem resistance; the acquisition of OXA-type carbapenemases, e.g. OXA-23, OXA-24, and OXA-58, appears to be one of the most important emerging mechanisms [39].

CONCLUDING REMARKS

Antibiotic resistance issues concerning all major nosocomial pathogens exist in the European setting, although with significantly different impacts in different countries.

With regard to Gram-positive pathogens, MRSA rates are high overall in many European countries, but seem to have levelled off in some settings, whereas VRE diffusion is still irregular, with an important and growing impact in some countries but not in others.

On the other hand, remarkable increasing trends in resistance of *Enterobacteriaceae* and GNNFs have recently been observed in most European countries. In *Enterobacteriaceae*, the major problems are: (i) increasing resistance to expanded-spectrum cephalosporins (mostly mediated by ESBL production) and fluoroquinolones; (ii) increasing prevalence of strains with MDR phenotypes; (iii) and progressive extension of the

Antimicrobial agent	Susceptibility rates (%) in:				
	USA	Canada	France	Germany	Italy
Cefepime	44	67	28	74	18
Cefotaxime	23	37	15	35	11
Ceftazidime	42	71	35	67	26
Ciprofloxacin	40	72	38	75	21
Gentamicin	47	73	49	82	23
Imipenem	87	96	94	96	78
Levofloxacin	44	61	NR	82	14
Meropenem	66	94	68	96	75
Piperacillin-tazobactam	54	71	75	82	35

Data are from Jones *et al.* [35].
NR, not reported.

Table 4. Rates (%) of susceptibility among intensive-care unit isolates of *Acinetobacter* spp. from France, Germany, Italy and North America during the period 2000–2002

corresponding resistance determinants and the associated clinical problems to *E. coli*. Carbapenems retain overall potent activity against multi-drug-resistant *enterobacteriaceae*, but acquired carbapenem resistance has been reported in some settings and can be mediated by several mechanisms. In GNNFs, resistance to major anti-Gram-negative agents tends to be even more serious and prevalent, with complex MDR phenotypes increasing in frequency, and pandrug resistance phenotypes no longer being an exceptional finding.

TRANSPARENCY DECLARATION

G. M. Rossolini is on the speaker's bureau for Wyeth Pharmaceuticals. E. Mantengoli declares no conflict of interest.

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