Editorials

Increasing Multidrug Resistance and Limited Treatment Options: Situation and Initiatives in Europe

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Antimicrobial resistance due to the continuous selective pressure from widespread use of antimicrobials in humans, animals and agriculture has been a growing problem for decades. In 2001, European Union Ministers of Health adopted Council Recommendations on the prudent use of antimicrobial agents in human medicine with a number of specific measures aimed at containing the spread of antimicrobial resistance by prudent use of antimicrobial agents [1]. The first recommendation was that Member States should establish and strengthen surveillance systems on antimicrobial resistance and the use of antimicrobial agents. Since 1999, the European Antimicrobial Surveillance System (EARSS, http://www.rivm.nl/earss/) provides validated data on the prevalence and spread of major disease-causing bacteria with resistance to one or more antibiotics. It has since become one of the most successful dedicated infectious disease surveillance systems in Europe. In order to be able to compare resistance rates of individual countries, the study sample and methods must be comparable. In this respect the variety of susceptibility testing methods in Europe represents a challenge; however, the quality of antimicrobial susceptibility testing of EARSS participating laboratories is regularly checked through external quality assessment exercises. EARSS has so far only gathered information on antimicrobial resistance in seven bacteria of clinical relevance and isolated from invasive infections (blood and cerebrospinal fluid samples). In its recently published Annual Report 2007, the EARSS reiterated its previous conclusion that “the data that EARSS has gathered over the years bring an unpleasant, but important message: antimicrobial resistance is becoming a larger public health problem year after year and only a concerted effort might turn the tide” [2].

This issue of Eurosurveillance is the second one this month dedicated to antimicrobial resistance, in connection with the first-ever European Antibiotic Awareness Day - a European Union (EU) health initiative involving all key players to increase awareness of Europeans about antimicrobial resistance and prudent use of antibiotics. While the first issue reported on encouraging examples of countries that took corrective actions and show decreasing trends in resistance [3-8], this issue focuses on bacteria that are not among the classical human pathogens, yet are, due to resistance to multiple antibiotics, increasingly complicating patient management in hospitals and other healthcare institutions. These pathogens also contribute considerably to the morbidity and mortality of healthcare-associated infections in Europe.

Enterococci are frequently responsible for healthcare-associated infections. They show an increasing prevalence of acquired resistance to ampicillin, aminoglycosides and glycopeptides, leaving the therapeutic alternatives to few antibiotics that were recently introduced into clinical practice and have limited indications, i.e. quinupristin-dalfopristin, linezolid, tigecycline and daptomycin. In this issue, G. Werner et al. review the situation in Europe [9] where vancomycin-resistant enterococci appear to be a serious and growing problem in most countries with the highest rates being reported by Greece, Ireland, Portugal, Cyprus and the United Kingdom [2]. The highest resistance rates are seen in the species Enterococcus faecium of which defined clonal groups have shown an enhanced capacity to disseminate in the nosocomial setting. Despite this clonality, the population of hospital-acquired, vancomycin-resistant E. faecium isolates tends to be polyclonal with highly mobile resistance determinants. The control of vancomycin-resistant enterococci remains a formidable task for hospital infection control practitioners. Both prudent use of antibiotics and compliance with hand hygiene and other infection control measures are essential to reduce selection and spread of multidrug-resistant enterococci.

Multidrug resistance is also increasing in Gram-negative bacilli [2]. In this issue, T.M. Coque et al. highlight the growing threat posed by increasing prevalence of extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae all over Europe, even in countries traditionally showing low prevalence rates of resistance [10]. The highest prevalence rates are being reported by eastern and south-eastern European countries. Although originally, ESBLs were mainly found in bacteria responsible for healthcare-associated infections, their prevalence is now increasing in the community. In particular, emergence and spread of the CTX-M-15 ESBL enzyme is reported in most European countries, both in hospitals and the community. The patient risk factors for colonisation and/or infection are not only prior use of third-generation cephalosporins, but also of other antibiotics, and the ESBL reservoir is not limited to humans as ESBLs have been isolated from animals, food and environmental samples.

The relentless increase in resistance to third-generation cephalosporins and fluoroquinolones in Enterobacteriaceae such as Escherichia coli and Klebsiella pneumoniae in Europe [2] has led to increasing use of carbapenems in hospitals, one of the most potent class of antibiotics against Gram-negative bacilli infections. Outbreaks due to metallo-beta-lactamase (MBL) producing, thus carbapenem-resistant, K. pneumoniae is therefore of great concern [11]. Isolates of Gram-negative bacilli simultaneously containing plasmids encoding various ESBLs, MBLs or AmpC beta-lactamases are now increasingly being reported in Europe. The acronym
Multidrug-resistant bacteria, which was originally coined for extensively drug-resistant Mycobacterium tuberculosis, is now used, though with various definitions, to describe such multidrug-resistant Gram-negative bacilli isolates for which only one or two antibiotic alternatives are available for therapy [12,13]. This increasing number of reports of XDR Gram-negative bacilli is particularly worrisome, especially because it has not been paralleled by development and availability of alternative therapeutic options. There are very few new antibiotics with a novel mechanism of action in the pharmaceutical industry research and development pipeline.

In this issue, M. Souli et al. review the emergence of such XDR, or even pandrug-resistant, i.e. resistant to all available antibiotics, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae in Europe [14]. Unfortunately, common official definitions and recommendations on how to detect and report such isolates are still being developed and surveillance systems such as the EARSS do not specifically report such data. As a consequence, we presently do not fully know the prevalence of such isolates in all European countries. It looks like the highest, hospital-specific prevalence rates of XDR and pandrug-resistant isolates have been reported from centres in southern and eastern European countries. However, patients are regularly transferred between hospitals from different European countries and the issue is relevant for all Member States. M. Souli et al. [14] quote two recent studies where mortality attributable to XDR and pandrug-resistant Enterobacteriaceae was 19% and 33%, respectively. The antibiotics that usually remain active against XDR isolates are colistin and tigecycline, yet resistance to these last-line drugs is increasingly being reported [15,16].

Prompt treatment with appropriate antibiotics is essential in serious bacterial infections to prevent complications and death. Multidrug resistance has serious consequences on the outcome of serious infections because it usually delays administration of appropriate antibiotic therapy. Several studies have demonstrated an increased mortality for infections due to multidrug-resistant and XDR bacteria in high-income countries [17-20]. This is also true in many low-income countries where the surge in antimicrobial resistance is seen as disastrous because of the lack of resources for purchasing expensive second-line drugs. This was recently documented in a paediatric ward of a tertiary care hospital in Tanzania where the mortality rate in patients with septicaemia due to ESBL-producing Gram-negative bacteria was significantly higher than in those with non-ESBL isolates [21].

European physicians are increasingly being faced with infections caused by bacteria for which limited or no adequate therapeutic options exists. Although Europe appears to have relatively good information about prevalence of resistance compared to other parts of the world, coverage could be improved and should include surveillance of XDR and pandrug-resistant bacteria. European laboratories and hospitals should be able to rapidly detect such strains to adjust patient therapy and put in place adequate local control measures. Additionally, similar to other communicable diseases, multidrug-resistant bacteria do not respect borders. Physicians and laboratories should be aware of the risk posed by transfer of patients from hospitals in other countries [22]. In this context, rapid and effective international communication is important to prevent further spread of emerging, multidrug resistant microorganisms.

Interventions are urgently needed to control and prevent further spread of multidrug-resistant bacteria through improvement of antimicrobial prescribing and infection control practices in Europe. But so far these interventions, though quite successful, have been few and far between, and limited to community prescribing or to the control of specific hospital bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) [3-8]. Member States have taken various actions following Council Recommendation of November 2001 [1] and the Council Conclusions on antimicrobial resistance recently adopted by EU health ministers during the Slovenian Presidency of the EU [23]. The European Commission has put considerable attention on this issue at the EU level. Based on EARSS data and articles in this issue of Eurosurveillance, control programmes could consider including other multidrug-resistant microorganism targets in addition to MRSA. The European Commission is finalising its proposal for a Council Recommendation on patient safety and quality of health services, including the prevention and control of healthcare associated infections [24]. Once this proposal is discussed and adopted, this will contribute to strengthening national infection control programmes, including actions aimed at preventing spread of multidrug-resistant bacteria. Finally, the successive EU presidencies of Slovenia, France, the Czech Republic and Sweden have decided to make antimicrobial resistance a health priority. On 15 and 16 April 2009, a conference on “The Microbial Threat to Patient Safety in Europe” will be organised by the Czech Presidency of the EU. This European conference will cover standards and indicators for antibiotic stewardship in European hospitals, the influence of healthcare systems characteristics on antimicrobial resistance and healthcare-associated infections, as well as the importance of leadership and accountability to reduce patient risks linked to these infections, and will contribute to containing antimicrobial resistance in European hospitals. During the second part of 2009, the Swedish Presidency of the EU will organise a follow-up conference focusing more specifically on the gap between increasing multidrug resistance, the need for new antibiotics with a novel mechanism of action and incentives for research and development of such antibiotics. These partnership approaches between all the relevant stakeholders are expected to bring further positive progress in the containment of antimicrobial resistance at the EU level.

References

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