

COMMENTARY

Think (Gram) negative!

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See related research by Meyer *et al.*, <http://ccforum.com/content/14/3/R113>

Abstract

The increasing prevalence of multiresistant Gram-negative bacteria of the Enterobacteriaceae family in Europe is a worrisome phenomenon. Extended-spectrum betalactamase-producing *Escherichia coli* strains are widespread in the community and are frequently imported into the hospital. Of even more concern is the spread of carbapenem-resistant strains of *Klebsiella* spp. from regions where they are already endemic. Antibiotic use is a main driver of antibiotic resistance, which again increases broad spectrum antibiotic use, resulting in a vicious circle that is difficult to interrupt. The present commentary highlights important findings of a surveillance study of antimicrobial use and resistance in German ICUs over 8 years with a focus on Gram-negative resistance.

In a recent issue of *Critical Care*, Meyer and colleagues [1] report interesting surveillance data from ICUs in 30 German hospitals, based on a large amount of microbiology and pharmacy data gathered between 2001 and 2008. One of the main study findings is a decreasing rate of methicillin-resistant *Staphylococcus aureus* (MRSA) and a dramatic increase of third generation cephalosporin (3GC) resistant Enterobacteriaceae over the study period. In recent years, most European countries have succeeded in reducing the burden of disease caused by MRSA [2,3]. This progress has, however, been partly offset by the increase across Europe in the prevalence of multiresistant Gram-negative pathogens producing extended-spectrum betalactamases (ESBLs) or carbapenemases [4].

The current study confirms this worrisome finding and also shows an increase in carbapenem, 3GC and fluoroquinolone use in German ICUs with a stable volume of overall antibiotic use. The latter two antibiotic classes have been repeatedly identified as risk factors for carriage

of multidrug resistant Gram-negatives [5,6]. Carbapenems on the other hand are first-line drugs for the treatment of infections due to ESBL-producing bacteria. It is tempting to assume that overuse of fluoroquinolones and 3GC antibiotics contributed to the observed increase in ESBL producers, which subsequently increased carbapenem use.

The ecological nature of the data, however, makes it difficult to infer clear cause-and-effect relationships [7], as does the failure to differentiate between hospital- and community-acquired isolates and clinical versus surveillance cultures [8]. In addition, the analysis of trends is hampered by variation in the number of participating ICUs over time. Nevertheless, the increased burden of multidrug-resistant Gram-negative bacteria is a real phenomenon.

In contrast to MRSA, ESBL producers - notably strains of *Escherichia coli* carrying plasmids of the CTX-M family - are mostly imported from the community into the hospital. Assuming a relationship with antibiotic use in animals and subsequent transmission of antibiotic resistant *E. coli* via the food chain is alluring, but strong epidemiological evidence is still lacking [9,10]. Transmission of ESBL-producing organisms within families might also contribute to the spread [11]. The recently started European Union-funded SATURN project (Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria) will gather more information on these risk factors.

As mentioned above, antibiotic overuse in humans probably plays a central role in the spread of ESBL producers. In the context of this study it is noteworthy that Germany has a relatively high level of fluoroquinolone use in the community [12]. As to antibiotic use in hospitals, the overall quantity of antibiotic use in German ICUs is comparable to that of other countries [13]. What about the quality of antibiotic prescribing? Although there is important heterogeneity between ICUs, inappropriate antibiotic use is still common in Germany (as in many other countries), where infectious diseases as a stand-alone speciality and antibiotic stewardship programmes are still underdeveloped [14].

Compared to other European countries or highly publicised health threats, such as bioterrorism and swine

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flu, public awareness and political commitment to control multidrug-resistant microorganisms has been slow to rise in Germany. Only recently (2009) has a German reference centre for surveillance of Gram-negative bacteria been established [15], which focuses, among other things, on detection of carbapenemase-producing bacteria. A first outbreak of carbapenemase-producing *Klebsiella pneumoniae* in Germany has recently been reported, probably linked to an index patient with previous healthcare contact in Greece [16]. The fact that two ICUs in 2008 reported carbapenem-resistant *K. pneumoniae* in the current study raises the concern that these strains might already be more common in Central Europe than previously assumed since detection of these strains may be difficult with routine laboratory techniques [17].

How can we control the rise of multidrug-resistant Gram-negatives? With regard to ESBL-producers the growing community reservoir makes it unlikely that we will be able to control the spread by conventional measures targeted at nosocomial infection control. The promotion of prudent antibiotic use in the community and animal husbandry should therefore be a key priority. As to carbapenemase-producing Enterobacteriaceae, early identification of these strains and aggressive infection control measures seem essential [18]. Examining novel decolonization strategies for Gram-negative Enterobacteriaceae might be a further strategy worth evaluating. If we manage to enforce all these measures, we will hopefully be able to think positive again - even with regard to Gram-negatives.

Abbreviations

3GC = third generation cephalosporin; ESBL = extended-spectrum betalactamase; MRSA = methicillin-resistant *Staphylococcus aureus*.

Competing interests

SH has received consulting fees from DaVolterra (France). BH declares that he has no competing interests.

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