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Global antimicrobial resistance in Gram-negative pathogens and clinical need

Ursula Theuretzbacher



Resistance in Gram-negative bacteria has become a serious problem in many regions of the world as it may reduce the treatment options substantially. Carbapenem-resistance is a good marker for such situations and is most prevalent in *Acinetobacter*, *Pseudomonas* but also increasingly in *Enterobacteriaceae*, especially *Klebsiella*. This review gives a rough global picture highlighting the epicentres of resistance. The medical need for novel treatment options globally is undeniable even if many countries with good stewardship and infection control conditions are not highly affected. Antibiotic pipelines are encouraging, as new drugs in development reduce the resistance rate to individual pathogens. Despite some progress, efforts to discover and develop novel drugs that are not prone to cross-resistance to existing antibiotic classes should be intensified.

Address

Center for Anti-Infective Agents, Eckpergasse 13, 1180 Vienna, Austria

Corresponding author: Theuretzbacher, Ursula
(utheuretzbacher@cefaia.com)

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Introduction

The percentage of resistant strains in many Gram-negative pathogens has been rising globally for the last 10 years. Antibiotic pipelines have not kept up with this trend. No novel antibiotic with a new chemical structure, an unexploited target or new mode of action has been developed and marketed for several decades. Substantial improvements in the ability of known antibiotic classes to respond to emerging resistance have not been seen since the first carbapenem became available in 1985.

As highlighted in the WHO Global Priority List of antibiotic-resistant bacteria developed to guide research, discovery and development of new antibiotics, carbapenem-resistant (CR) *Enterobacteriaceae*, *Pseudomonas*

aeruginosa (PA) and *Acinetobacter baumannii* (AB) complex are critical priority targets for new antibiotics to fill the gap of urgently needed treatment options [1**]. This article focuses on hospital-associated CR *Enterobacteriaceae* with *Klebsiella pneumoniae* (KP) as the predominant CR species among *Enterobacteriaceae*, as well as CR PA and CR AB. All three pathogens frequently show an extensively drug resistance phenotype.

About one-third of acute-care hospital-acquired infections, and more than 40% in intensive care units, are caused by these three WHO priority pathogens [2,3]. These infections are difficult to treat and are associated with higher morbidity and mortality than infections due to susceptible strains [4]. A meta-analysis has described the increased mortality associated with CR Gram-negative pathogens; the pooled crude mortality in patients with CR *Enterobacteriaceae* (CRE) infections is about 40% [5]. Urinary tract infections cause lower mortality than bloodstream infections. Similarly, a meta-analysis showed that patients infected with CR PA had significantly higher pooled mortality than those infected with carbapenem-susceptible PA [6]. Increased mortality in CR AB-infected patients compared to those infected with susceptible bacteria confirm similar results to patients infected with PA [7*]. Though a higher likelihood of inappropriate therapy may be a major reason for the increased mortality, other factors such as more severe co-morbidity or increased virulence may contribute to this finding [8].

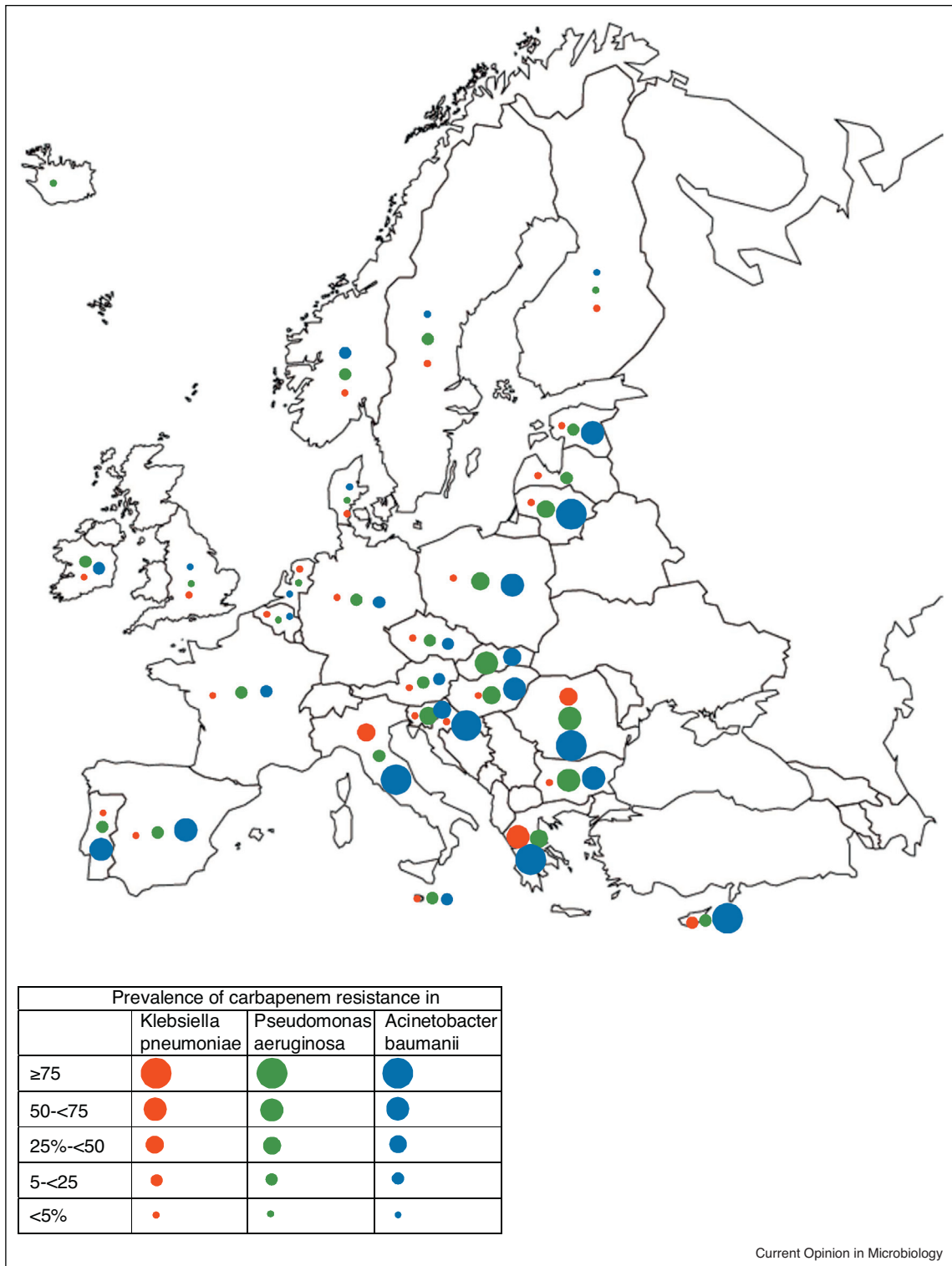
Resistance

Carbapenem resistance is usually a good surrogate for extensively drug resistance (XDR), especially in KP and AB, less so in PA.

Klebsiella pneumoniae

KP is a common Gram-negative pathogen in healthcare facilities. In Europe, the rate of resistance to third generation cephalosporins with co-resistance to fluoroquinolones and aminoglycosides, the most common multi-drug resistance (MDR) phenotype, ranges from 0 to 60% (EARS-net report 2015). A similar wide range is seen with the rate of resistance to carbapenems, which are important antibiotics for the treatment of such MDR strains (Figure 1). If CR is part of a combined resistance pattern, XDR may result where the therapeutic options are severely limited [9]. Similar to the variation seen across Europe, wide inter-country variations are also seen globally (Figure 1). India reports high CR in KP (about

Figure 1



Resistance rates of carbapenem-resistant Gram-negative pathogens in Europe.

Sources: Latest available data, mostly 2012–2016.

EARS-Net, WHO, CDC National Healthcare Safety Network, KARMS Korea, SENTRY, INFORM, CANWARD, AURA 2016, MARATHON Russia.

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