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Themed Issue: Resurrection of old antibiotics

Why new antibiotics are not obviously useful now

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ABSTRACT

For several years, the threat of antibiotic resistance and its health cost has dramatically risen and various alarming figures have been proposed to illustrate the mortality due to antibiotic resistance. However, predictions concerning different living beings are doomed to failure, as theorised in Alice's 'living croquet' theory. Actors of antibiotic resistance are the doctors, the patient and the bacteria. Considering that animals and the environment are involved, future disasters are unpredictable. Here we evaluate in a rational manner the reliability of scientific sources showing increasing resistance to antibiotics or increasing mortality related to antibiotic resistance, and we finally consider antibiotic resources to face the situation.

1. Introduction

For several years, the threat of antibiotic resistance and its health cost has dramatically risen. Various figures have been proposed regarding annual mortality due to antibiotic resistance, with 22,000 extra deaths in the USA [1] and 25,000 in Europe, while a French report claimed 12,500 extra deaths in France [2].

This appeared surprising to us considering the fact that we have monitored resistance and mortality related to antibiotic resistance in Marseille (France) since 2013 [3] and have not observed any excess mortality related to antibiotic resistance. We struggled to find cases of death linked to therapeutic impasses with antibiotics. From this point of view, the literature is extremely modest and only a few cases have been reported. In the current review, we evaluated the reliability of scientific sources showing increasing resistance to antibiotics as well as those showing an increase in mortality related to antibiotic resistance, and finally consider the current antibiotic resources to deal with emerging resistance.

2. Sources showing an increase in antibiotic resistance

Reports on antibiotic resistance only focus on bad news, namely the development of resistance, which mainly or exclusively concerns Gram-negative bacteria. However, the greatest fears regarding antibiotic resistance, i.e. methicillin-resistant *Staphylococcus aureus* (MRSA) [4] and vancomycin-resistant enterococci [5], have dramatically decreased with no clear explanations. As an example, in Europe and worldwide, the number of *S. aureus* isolated in sepsis situations has reduced two- or three-fold [6,7], but this trend is not observed in Marseille hospitals. In addition, mortality due to *S. aureus* in France is a leading cause of mortality among bacterial infections [8], and the number of serious infections with resistant isolates has decreased in recent years for *S. aureus*. Indeed, only 12.8% of invasive strains were resistant to methicillin in 2015 in Marseille hospitals [4]. At the same time, we currently observe the emergence of penicillin-susceptible strains, which has also been reported elsewhere [9].

Another major threat is *Escherichia coli*, for which there is, in France, extremely little resistance to carbapenems, like for all other members of the Enterobacteriaceae [10]. In parallel, we currently observe increasing healthcare-associated resistance to third-generation cephalosporins (3GCs) in Marseille (Fig. 1) but also in France through acquisition of extended spectrum β-lactamases (ESBLs) [11]. This can be easily circumvented by the use of the carbapenems, colimycin or aminoglycosides. It has to be noted that the prevalence of ESBLs is dramatically lower in community-acquired urinary tract infections [12]. Moreover, the level of resistance of invasive *Klebsiella pneumoniae* has been decreasing in our hospitals since 2012 [13]. However, although sporadic resistance to imipenem has also recently emerged in hospitals in France, these strains have not taken hold sustainably in our city up to now (Fig. 1). However, we know that the incidence of carbapenemase-producing *K. pneumoniae* is increasing in the south of Europe, especially in Italy and Greece [14,15]. In North Africa, there is a considerable increase in resistance to imipenem [16,17], which poses a problem, but many isolates remain sensitive to older antibiotics, including colistin. The third bacterial fear is *Pseudomonas aeruginosa*, whose resistance level has not particularly evolved over the last 15 years [18], although an increased rate of extensively drug-resistant (XDR) strains along with a decrease of multidrug-resistant (MDR)

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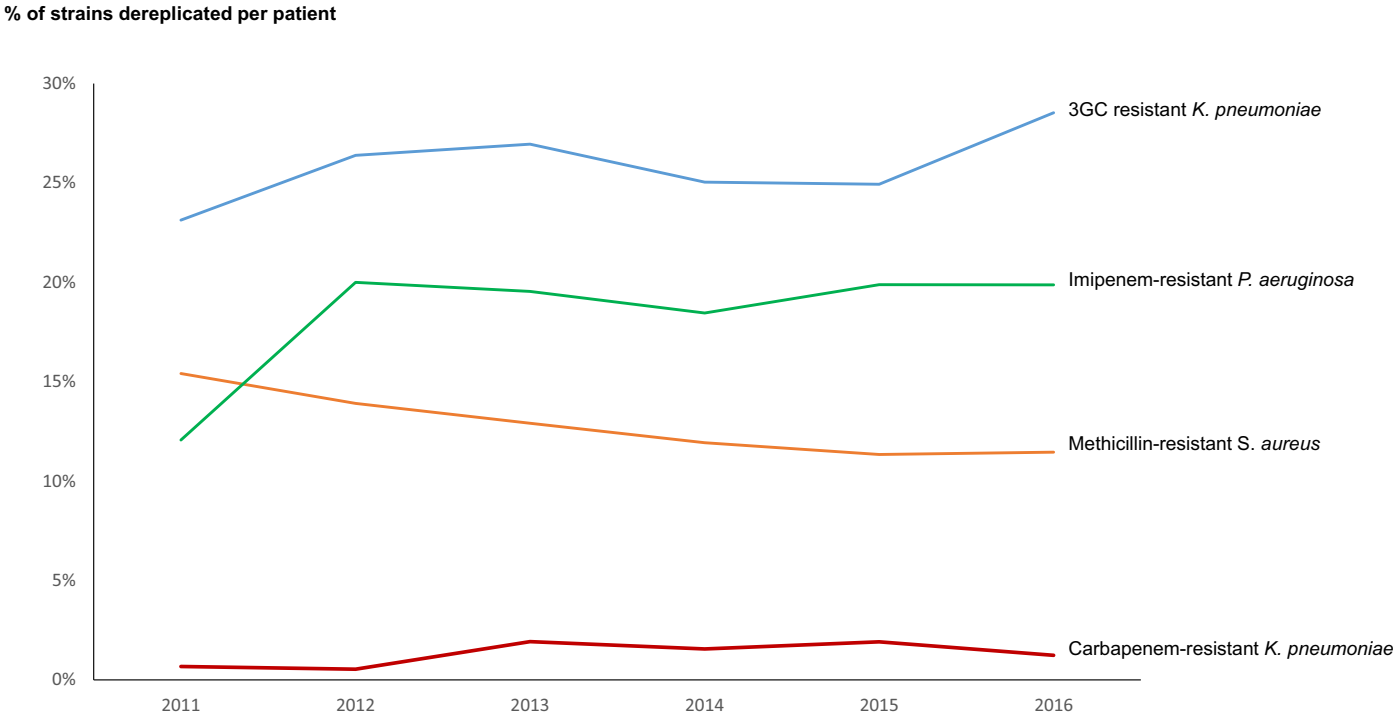

Fig. 1. Yearly evolution of the proportion of third-generation cephalosporin (3GC)-resistant *Klebsiella pneumoniae* (total, 8144 strains), imipenem-resistant *Pseudomonas aeruginosa* (total, 6824 strains), methicillin-resistant *Staphylococcus aureus* (total, 16 029 strains) and carbapenem-resistant *K. pneumoniae* (total, 8144 strains) from January 2011 to August 2016, Assistance Publique-Hôpitaux de Marseille, France. Strains were dereplicated per patient.

strains is reported [19]. In our experience, we observed an increase of imipenem-resistant strains (Fig. 1).

Finally, carbapenem-resistant *Acinetobacter baumannii* represents a significant threat due to its ability to acquire resistance to colimycin through mutations [20]. However, the pathogenicity of *A. baumannii* remains relatively moderate and it is rarely associated with excess mortality. Altogether, there is therefore a major reversal of resistance in Gram-positive bacteria, which is decreasing, while Gram-negative bacteria have an increasing resistance level. It is likely that over the next 20 years, the evolution of the proportion of infections with resistant bacteria in Europe will become stable, unlike current predictions.

3. Increase in mortality related to antibiotic resistance

Mortality related to antibiotic resistance has been the subject of several reports that are commonly and extensively cited and relied upon in the literature. Among them is the 2014 World Health Organization (WHO) report dealing with antibiotic resistance [21]. In this report, the WHO tried to determine the human and economic costs of infections due to MDR bacteria, focusing on MRSA, 3GC- and fluoroquinolone-resistant *E. coli*, and 3GC- and carbapenem-resistant *K. pneumoniae*. To do so, a systematic review of the literature was initiated, completed by a meta-analysis involving 221 studies that finally met the WHO eligibility criteria. Such a methodology is definitively not appropriate to effectively determine the true impact of antibiotic resistance on humanity. First, an important part of the studies included in the meta-analysis used models to draw their conclusions, making conclusions that do not reflect reality. Second, the WHO did not look for studies describing bacterial infections with true therapeutic impasses.

A number of these articles were published in journals of low impact and with poor peer-reviews, and others have no connection with the subject. In any case, a causation analysis was not performed by eliminating confounding factors, particularly inappropriate prescription of antibiotics. Thus, in most of these studies, what is tested is the inappropriate prescription of antibiotics: if a 3GC is prescribed in patients with bacteria resistant to this antibiotic, they are more likely to die than if the bacteria are susceptible.

This does not mean that mortality is higher with these bacteria but simply that the prescription of antibiotics was inappropriate, which is indeed more likely to occur in the case of MDR bacteria. Overall, a review of various studies regarding antibiotic resistance including a French report [2], an alarming report claiming 12,500 extra deaths annually in France, showed that no work could significantly yield the existence of therapeutic impasse wherein there is no solution with available antibiotics for treating patients. Such cases in the literature are exceptional even if we are aware that they may not have been reported in literature. We also do not have the opportunity to report the existence of a case of infection due to *A. baumannii* with a pandrug resistance profile, i.e. resistant to all antibiotics tested in first-line, including imipenem and colimycin. The patient recovered spontaneously and without antibiotics [22]. In total, there is very little evidence of deaths related to therapeutic impasses in Gram-negative bacteria and tuberculosis (TB). In our experience with *S. aureus*, mortality between wild-type and MDR strains does not differ significantly.

Again, studies overlook the fact that *S. aureus* clones have very different virulence; some are associated with extremely high mortality and others have a lower mortality. Indeed, virulence traits of *S. aureus* play a much more important role in the survival of the affected patient than their sensitivity or resistance to methicillin [23]. Paradoxically, as oxacillin or methicillin are toxin-inducers [24], infection with toxigenic methicillin-susceptible *S. aureus* treated with oxacillin is more likely to have a less favourable prognosis that MDR *S. aureus* of the same clone treated with vancomycin. In total, there is extremely little evidence of a direct link between antibiotic resistance and mortality, excluding situations in which the clinician has failed to use an active molecule or the laboratory has not extended the search for effective antibiotics in vitro.