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Increasing burden of urinary tract infections due to intrinsic colistin-resistant bacteria in hospitals in Marseille, France

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ABSTRACT

The emergence of multidrug-resistant (MDR) Gram-negative bacteria has become a major public health problem, eliciting renewed interest in colistin, an old antibiotic that is now routinely used to treat MDR bacterial infections. Here we investigated whether colistin use has affected the prevalence of infections due to intrinsic colistin-resistant bacteria (CRB) in university hospitals in Marseille (France) over a 5-year period. All data from patients infected by intrinsic CRB were compiled from January 2009 to December 2013. *Escherichia coli* infections were used for comparison. Colistin consumption data were also collected from pharmacy records from 2008 to 2013. A total of 4847 intrinsic CRB infections, including 3150 *Proteus* spp., 847 *Morganella* spp., 704 *Serratia* spp. and 146 *Providencia* spp., were collected between 2009 and 2013. During this period, the annual incidence rate of hospital-acquired CRB infections increased from 220 per 1000 patients to 230 per 1000 patients and that of community-acquired CRB infections increased from 100 per 1000 patients to 140 per 1000 patients. In parallel, colistin consumption increased 2.2-fold from 2008 to 2013, mainly because of an increase in the use of colistin aerosol forms (from 50 unitary doses to 2926 unitary doses; $P < 10^{-5}$) that was significantly correlated with an increase in the number of patients positive for CRB admitted to ICUs and units of long-term care between 2009 and 2013 ($r = 0.91$; $P = 0.03$). The global rise in infections due to intrinsic CRB is worrying and surveillance is warranted to better characterise this intriguing epidemiological change.

1. Introduction

Antimicrobial resistance represents a major public health concern worldwide. Following the appearance in the 1980s of extended-spectrum β-lactamase-producing Gram-negative bacteria, which threaten both hospital settings and the community [1], carbapenems have been considered as the last-resource drugs and have been widely used in healthcare units [2]. However, since the early 2000s, various acquired carbapenemases, primarily *Klebsiella pneumoniae* carbapenemase (KPC) type [2] or, more recently, the New Delhi metallo-β-lactamase (NDM) [3], have emerged and spread worldwide [4], further limiting therapeutic options. These limits have forced clinicians and researchers to develop new treatment strategies and practices, including the use of alternative treatment options. The polymyxins are cationic cyclic polypeptide antibiotics composed of five chemical compounds (polymyxins A–E) [5,6]. Polymyxins are bactericidal antibiotics effective against most Gram-negative bacteria except bacteria of the genera *Proteus*, *Providencia*, *Serratia*, *Morganella* and *Burkholderia* that are intrinsically resistant [5]. Colistin (polymyxin E) was extensively used between the 1960s and 1980s to treat patients infected by Gram-negative bacteria but was gradually abandoned in the 1980s owing to nephrotoxicity and neurotoxicity [5,6]. In this context, colistin has recently been reconsidered as a treatment of last resort to treat patients with ventilator-associated pneumonia and bacteraemia due to carbapenemase-producing bacteria, mainly *K. pneumoniae*, *Acinetobacter* spp. and *Pseudomonas* spp. [5–7]. Unfortunately, the increased use of colistin as a 'last-line' therapeutic drug for the treatment of patients infected with these multidrug-resistant (MDR) Gram-negative bacteria has led to the recent emergence

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of colistin-resistant bacteria (CRB) among these bacterial species [5,8–12].

This increasing public health concern led us to investigate whether the use of colistin currently affects the biodiversity of bacterial pathogens isolated from hospitals towards an increase of intrinsic CRB. A 5-year (January 2009 to December 2013) retrospective analysis of data on intrinsic CRB from the four university hospitals of Marseille was performed, using *Escherichia coli* infections as a control, and these data were correlated with colistin consumption in the four hospitals during the same period.

2. Materials and methods

2.1. Study setting

The Assistance Publique–Hôpitaux de Marseille (AP-HM) comprises the four university hospitals (North, South, Conception and Timone Hospitals) of Marseille, which is the second largest city in France (2010 estimated city population, 850 726). Cumulatively, these hospitals include 4000 beds (ca. 1500 beds in Timone Hospital, 900 in the North Hospital, 700 in Conception Hospital and 600 in the South Hospital [13]).

2.2. Retrospective analysis of intrinsic colistin-resistant bacteria in the database

To perform this study, a 5-year retrospective Microsoft Excel database (January 2009 to December 2013) that only included samples from which intrinsic CRB were isolated was implemented. In this study, intrinsic CRB included *Morganella* spp., *Serratia* spp., *Proteus* spp. and *Providencia* spp. All of the data were collected from an 11-year historical bacterial database that included previously published data [14]. Duplicates were deleted, and only one bacterial identification per sample and patient was considered. To ensure that the observed trends were not due to a rise in the number of samples that were processed in the laboratory during the study period, the annual number of patients who were infected by *E. coli* was used as a control to calculate annual ratios. EPIMIC, which is a simple Microsoft Excel tool that is based on clinical microbiology data from the four university hospitals [15], was also used to retrospectively plot the weekly number of patients who were infected by intrinsic CRB and to set up a threshold to detect an increase in CRB, i.e. a number above the mean weekly number plus 2 standard deviations. Data from 2002 to 2008 were not included in this study because some gaps in these data were observed. Indeed, before 2009, two laboratories performed clinical microbiology analysis (one in Timone Hospital and the other in the North Hospital). Since 2009, only one laboratory performs all the analysis.

2.3. AP-HM colistin consumption

Annual AP-HM colistin consumption data were retrospectively collected from pharmacy records of all medical units from 2008 to 2013, according to prescriptive unitary doses and form (spray or fluid injection).

2.4. Hospital-acquired infections, community-acquired infections and others

The data analysed in the present study did not contain the date of hospitalisation. Therefore, based on the category of each healthcare unit where CRB were isolated, hospital-acquired CRB infections were defined as CRB infections observed in patients admitted to intensive care units (ICUs) or hospitalised in units of long-term healthcare. Community-acquired CRB infections were defined as infections observed in patients admitted to emergency units or units of short-term healthcare. Finally, other units were included in another group not included in the analysis of colistin consumption evolution.

2.5. Statistical analysis

Statistical analyses were performed using Pearson's χ^2 test and Pearson's coefficient correlation test. Finally, linear models were defined to analyse historical trends (the annual trend in the mean number of patients infected by CRB strains or the annual trend in the mean number of colistin units used). All of the tests were two-sided, and *P*-values of <0.05 were considered statistically significant. Data were analysed using the Epi Info v.3.01 (http://www.openepi.com/Menu/OE_Menu.htm) and R software (The R Project, Auckland, New Zealand).

3. Results

3.1. Total number of patients infected by intrinsic colistin-resistant strains, genus distribution and global trends

During this 5-year study, 4847 patients in the different units of the university hospitals of Marseille were identified to be infected by at least one CRB. Among the genera of interest, *Proteus* spp. were the most common pathogens (3150 isolates), followed by *Morganella* spp. (847 isolates), *Serratia* spp. (704 isolates) and *Providencia* spp. (146 isolates) (Table 1). During the same period, 23 436 patients were infected by *E. coli* (Table 1). The increase in the number of patients infected by CRB strains was predominantly due to *Proteus* spp., with a 1.7-fold increase between 2009 and 2013, and more precisely to an increase in hospital- and community-acquired urinary tract infections due to *Proteus* spp. (the annual trends in the number of patients infected by CRB were 33.8 patients and 38.9 patients, respectively) (Table 1). The number of CRB strains isolated from hospital-acquired infections increased 1.4-fold (584 vs. 799) throughout the study period, leading to an increase in the annual incidence rate of hospital-acquired infections caused by CRB strains from 220 per 1000 patients to 230 per 1000 patients (Table 2). Comparison between the annual number of patients infected by *E. coli* and CRB isolated from hospital-acquired infections revealed that this increase was not significant between 2009 and 2013 ($P = 0.19$) (Table 2) but was significant between 2010 and 2013 ($P = 0.01$) and between 2011 and 2013 ($P = 0.001$). Community-acquired CRB infections also increased over the study period (2.4-fold, from 198 to 476 between 2009 and 2013; annual incidence rate increase from 100 per 1000 patients to 140 per 1000 patients). Comparison between the annual number of patients infected by *E. coli* and CRB isolated from community-acquired infections revealed that this increase was significant over the study period ($P < 10^{-3}$) (Table 2). The ratio of the annual rate of CRB hospital-acquired infections to community-acquired CRB infections decreased over time from 2.1 to 1.7 (Table 2). Evolution of the number of CRB strains isolated per hospital, sample and year is presented in Table 3. CRB infections significantly increased for three of the four studied hospitals, with annual trends in the number of patients infected by CRB equal to 55.3 patients for Conception Hospital ($P = 0.03$), 63.8 patients for the North Hospital ($P = 0.005$) and 63.6 patients for Timone Hospital ($P = 0.04$) (Table 3). For these three hospitals, this increase was mainly due to rises in the number of urine samples positive for CRB (the annual trends in the number of patients infected were 34.8, 40.9 and 38.5 patients for Conception Hospital, the North Hospital and Timone Hospital, respectively), which were significant ($P = 0.06$, 0.01 and 0.048, respectively) (Table 3). Finally, retrospective analysis of the data per week (using EPIMIC) is presented in Fig. 1. The automated comparison between the weekly numbers of