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Five-year trends for ventilator-associated pneumonia: Correlation between microbiological findings and antimicrobial drug consumption

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ABSTRACT

The epidemiology of multidrug-resistant bacteria (MDRB) has changed significantly in European healthcare settings, with a decrease in frequency of meticillin-resistant *Staphylococcus aureus* and an increase in extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. Little is known about the effects of these changes on ventilator-associated pneumonia (VAP). A retrospective 5-year trend analysis of ICU antibiotic consumption and resistance in bacteria causing VAP was undertaken. Poisson regression analysis between complete microbiological data and antibiotic consumption was performed. In total, 252 episodes of VAP in 184 patients were identified between 2007 and 2011, from which 364 causal bacteria were isolated. Enterobacteriaceae isolation rates increased significantly over this period [from 6.64 to 10.52 isolates/1000 patient-days; $P = 0.006$], mostly due to an increase in AmpC-producing Enterobacteriaceae (APE) (2.85–4.51 isolates/1000 patient-days; $P = 0.013$), whereas the number of episodes due to *S. aureus* and *Pseudomonas aeruginosa* remained stable. A positive association was found between the increase in APE infections and an increase in past-year antibiotic consumption: amoxicillin/clavulanic acid ($P = 0.003$), ceftazidime and cefepime ($P = 0.007$), carbapenems ($P = 0.002$), fluoroquinolones ($P = 0.012$), macrolides ($P = 0.002$) and imidazoles ($P = 0.004$). No such association was found for the emergence of resistance in *P. aeruginosa*. These results indicate a change in the epidemiology of VAP, with Enterobacteriaceae exceeding *P. aeruginosa* and *S. aureus*. Moreover, a positive correlation was observed between antibiotic consumption and the incidence of potentially MDRB such as APE. No such correlation was found for ESBL-producing *Escherichia coli* and antibiotic-resistant *P. aeruginosa*.

1. Introduction

Ventilator-associated pneumonia (VAP), defined as pneumonia occurring >48 h after the initiation of mechanical ventilation, is the most common life-threatening hospital-acquired infection in the intensive care unit (ICU). This complication affects 8–28% of

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patients receiving mechanical ventilation [1] and accounts for up to 50% of all antimicrobials prescribed in the ICU. It is associated with increased morbidity, increased costs and increased length of stay in the ICU [2,3]. In older series, the principal pathogens recovered in bronchoscopy samples were *Pseudomonas aeruginosa* (24.4%), *Staphylococcus aureus* (20.4%), Enterobacteriaceae (14.1%) and *Haemophilus* sp. (9.8%) [1]. Several studies have shown that initial treatment of VAP with inappropriate antimicrobial drugs is associated with a poorer outcome [4]. Knowledge of the epidemiology and resistance trends of the bacteria concerned is therefore of particular importance.

Over the last decade there has been a considerable change in the epidemiology of multidrug-resistant bacteria (MDRB) in Europe [5,6], particularly in French healthcare settings [7]. In the Assistance Publique–Hôpitaux de Paris (AP-HP), a consortium of Parisian hospitals, the incidence of meticillin-resistant *S. aureus* (MRSA) was found to have decreased by 43% over a period of 9 years with the implementation of a bundle programme to control cross-transmission [8]. Over the same period, the incidence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae increased by 182%, mostly due to the emergence of *Escherichia coli* clones producing CTX-M type ESBL both in the community and in healthcare settings [9].

The relationships between antibiotic use and the emergence of MDRB are complex. Possible or confirmed MDRB infection leads to an increase in antibiotic consumption, which itself increases the selective pressure favouring the most resistant bacteria. Several recent studies have reported an effect of antibiotic use on MDRB emergence both at the national [10] and hospital levels [11,12]. However, it was not possible to control for differences in prescription habits, the infections treated, infection control measures and epidemic phenomena between participating hospital wards in these studies.

We avoided such biases in this study by focusing on changes in the epidemiological characteristics of bacterial VAP, a typical hospital-acquired infection, within a single ICU department. We also investigated the correlation between ICU antibiotic consumption and antimicrobial resistance of the pathogens recovered in the ICU between 2007 and 2011.

2. Methods

2.1. Setting and case definition

Louis Mourier Hospital is a 460-bed, university-affiliated tertiary care institution in Colombes (France), with 600 ICU admissions per year.

All adult patients (≥15 years) presenting at least one episode of VAP at this hospital between January 2007 and December 2011 were included in this observational historical cohort study. The completeness of episode counts was ensured by cross-referencing data from two different and completely independent registries: the files of the microbiology department and the nosocomial infection registry of the ICU.

VAP was defined according to widely accepted criteria [13]. Lung samples were obtained for each patient by invasive techniques, namely protected telescopic catheter (PTC) specimens [1] or bronchoalveolar lavage (BAL). Samples were immediately dispatched at room temperature to the microbiology department for analysis. VAP episodes were classified as 'early' if they occurred on or before Day 5 of mechanical ventilation and as 'late' if they occurred after Day 5 [1,14]. A new episode was defined as the occurrence of a new VAP due to bacterial species different than those responsible for the previous episode; hence, patients with more than one VAP were included as long as the pathogen was different.

2.2. Microbiological study

Lung specimens were processed according to standard procedures [15]: (i) direct examination following May–Grünwald–Giemsa and Gram staining; (ii) quantitative cultures on blood agar plates were incubated for 2 days in aerobic and anaerobic atmospheres, while cultures on chocolate agar plates were incubated for the same duration in a CO_2-enriched atmosphere; and (iii) specific, prolonged cultures for *Legionella* spp. and *Nocardia* spp., as appropriate.

The usual thresholds were applied for the interpretation of quantitative cultures, i.e. $\geq 10^3$ CFU/mL and $\geq 10^4$ CFU/mL for PTC and BAL specimens, respectively. All bacteria present in numbers exceeding the threshold were identified on the basis of their biochemical characteristics using an API® System (bioMérieux, Marcy-l'Étoile, France). Antibiotic susceptibility was determined by the disc diffusion method or with Etest strips (bioMérieux). Isolates were classified as susceptible, intermediate or resistant to the antibiotics concerned according to the guidelines of the Comité de l'antibiogramme de la Société française de microbiologie (CA-SFM) (http://www.sfm-microbiologie.org) [16].

2.3. Data collection and antibiotic policy

Prospectively collected data (clinical, biological, radiological and microbiological) were retrieved retrospectively from the microbiology department and from the patients' records for analysis. As stated above, the completeness of episode counts was ensured by cross-referencing the data from the microbiology department with those noted in the ICU nosocomial infection registry.

Patients with suspected VAP were given first-line empirical treatment with aminopenicillins ± β-lactamase inhibitors or cefotaxime for early episodes, or ceftazidime or imipenem, in combination with an aminoglycoside for late episodes. Selective digestive decontamination is not performed in our ICU. VAP prevention measures include strict hand hygiene policy with alcohol-based rubs, a 30–45° semi-recumbent position, cuff pressure monitoring but without subglottic secretion drainage, no ventilatory circuit changes unless specifically indicated, and chlorhexidine oral care.

During the study period, all patients admitted to the ICU were screened for multidrug-resistant organisms (MDROs) (MRSA and ESBL-producing Enterobacteriaceae) at admission and then once a week. Monitoring was conducted by the infection control unit to detect MDRO outbreaks.

Data regarding the activity [number of patient-days (PD) in full hospitalisation] from hospital administration and the annual consumption [defined daily doses (DDDs) per 1000 PD] of all antibiotics in the ICU over the study period were obtained from the hospital pharmacy department. These data were analysed according to the Anatomic Therapeutic Chemical (ATC) Classification System of the World Health Organization (WHO) (http://www.whocc.no/atc_ddd_publications/guidelines): groups G, V, M and A narrow-spectrum penicillins (J01CE + J01CF + J01CA04); aminopenicillins ± β-lactamase inhibitors (J01CR01 + J01CR02); penicillins active against *P. aeruginosa* (J01CA13 + J01CR03 + J01CA12 + J01CR05); third-generation cephalosporins (3GCs) ineffective against *P. aeruginosa* (i.e. cefotaxime J01DD01 + ceftriaxone J01DD04); 3GCs active against *P. aeruginosa* (ceftazidime J01DD02 + cefepime J01DE01 + monobactams J01DF); carbapenems (J01DH); aminoglycosides (J01GB); macrolides (J01FA); fluoroquinolones (J01MA); vancomycin (J01XA01); imidazoles (J01XD + P01AB); and trimethoprim plus sulfamethoxazole (J01EE01).