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Distribution and antibiotic susceptibility of pathogens isolated from adults with hospital-acquired and ventilator-associated pneumonia in intensive care unit

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ABSTRACT

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common hospital infections with the highest prevalence in intensive care units (ICU). The aim of this study was to investigate prevalence of bacterial pathogens isolated from ICU patients with HAP/VAP and reveal their susceptibility rates in order to establish a basis for empirical antibiotic therapy. Prospective cohort study was conducted in central ICU of Clinical Centre Kragujevac, Serbia, from January 2009 to December 2015, enrolling 620 patients with documented HAP (38.2%) or VAP (61.8%).

Gram-negative agents were isolated in 95.2%. Generally, the most common pathogens were *Acinetobacter* spp. and *Pseudomonas aeruginosa,* accounting for over 60% of isolates. The isolates of *Acinetobacter* spp. in HAP and VAP had low susceptibility to the 3rd generation cephalosporins, aminoglycosides, fluoroquinolones (0–10%). The rate of susceptibility to piperacillin-tazobactam was below 15%, whereas for carbapenems and 4th generation cephalosporins it was about 15–20%. Isolates of *P. aeruginosa* from HAP and VAP showed low susceptibility to ciprofloxacin and gentamicin (below 10%), followed by amikacin (25%), while the rate of susceptibility to carbapenems and 4th generation cephalosporin was 30–35%. Furthermore, 86% of isolates of *P. aeruginosa* non-susceptible to carbapenems were also non-susceptible to ciprofloxacin. The highest level of susceptibility from both groups was retained toward piperacillin-tazobactam. In ICU within our settings, with predominance and high resistance rates of Gram-negative pathogens, patients with HAP or VAP should be initially treated with combination of carbapenem or piperacillin-tazobactam with an anti-pseudomonal fluoroquinolone or aminoglycoside. Colistin should be used instead if *Acinetobacter* spp. is suspected. Vancomycin, teicoplanin or linezolide should be added only in patients with risk factors for MRSA infections.

Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common infections acquired in the hospital with the highest prevalence in intensive care units (ICUs) [1,2]. Depending on the case definition and study population incidence of HAP is usually between 5 and 15 cases per 1000 hospital admissions but incidence of VAP in patents on mechanical ventilation is 6–20 fold greater [3–5].

These infections negatively impact important patient outcomes and the health-care system because HAP and VAP significantly prolong treatment, escalate health care costs and are leading cause of death attributed to hospital infections [6–8]. Physicians everywhere struggle to control these infections, but with varying success, despite wide-range of preventive measures and advances in antimicrobial therapy. Another problem is insufficiently precise definition of HAP and VAP in current guidelines (in 2016 guidelines it was stated that no "gold standard" for the diagnosis of HAP or VAP exists) [9], and clinicians are left without clear recommendations regarding treatment decisions which leads to variation in antibiotic use and potentially inappropriate use, resulting with worsening of resistance issues.

HAP/VAP are caused by an imbalance between normal host defenses and the ability of microorganisms to colonize and then invade the lower respiratory tract. Although a wide spectrum of bacterial pathogens can cause HAP/VAP the most frequent causative agents are aerobic Gram-negative bacilli, especially *Pseu-*

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domonas aeruginosa (*P. aeruginosa*), *Acinetobacter* spp ., *Klebsiella pneumoniae, Escherichia coli* as well as Gram-positive cocci like *Staphylococcus aureus* [10,11]. Bacteria which cause HAP/VAP are often resistant to various antibiotics, but exact susceptibility profile depends on hospital or ICU, patient population and previous exposure to antibiotics. It is not static, but changes over time. Many infections are polymicrobial and caused by multi-drug resistant (MDR) pathogens. Since early initiation of appropriate empiric antibiotic therapy is of vital importance for the patient, good knowledge of local prevalence of pathogens and their drug susceptibility patterns is essential. In some developing countries, the etiologic agents of HAP/VAP and their susceptibility to antibiotics are not systematically followed, making choice of empiric therapy difficult.

The aim of this study was to investigate prevalence of bacterial pathogens isolated from patients with HAP/VAP in an ICU and reveal their susceptibility rates in order to establish a basis for empirical antibiotic therapy.

Methods

Study design and setting

We conducted a prospective cohort study in central ICU of Clinical Centre Kragujevac, Kragujevac, Serbia from January 2009 to December 2015. This Medical-Surgical ICU has 18 beds and annually about 850 patients are treated. The study was approved by the Ethics Committee of Clinical Centre Kragujevac.

The patients

The study included patients older than 18 years with HAP/VAP according to standard definition established by *American Thoracic Society (ATS)* and *Infectious Diseases Society of America (IDSA)* Guidelines from 2005 [4] and updated in 2016 [11]. The patients with isolation of causative agents within the first 48 h from admission to hospital were excluded. Only the first isolate from each patient was taken into account. Every patient was evaluated by the independent expert group composed of infectious diseases specialist, epidemiologist, specialist of intensive medicine and clinical pharmacologist. The patients were followed to the final outcome, either cure and discharge from the hospital or to the death.

Definition of pneumonia

Pneumonia was defined as the presence of new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, including new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. HAP is defined as a pneumonia which was not present at the time of hospital admission and occurring 48 h or more after the admission. HAP is also called "episode of pneumonia not associated with mechanical ventilation". VAP is defined as a pneumonia occurring >48 h after endotracheal intubation [4]. The patients which require intubation after developing severe HAP are treated like patients with VAP.

Thus, HAP and VAP belong to 2 mutually exclusive groups. Diagnosing HAP/VAP requires high clinical suspicion combined with bedside examination, radiographic studies, and microbiologic analysis.

Microbiological analysis

Bacteriological evidence of pulmonary infection was sought in accordance to the guidelines. Clinically significant values for quantitative culture were considered $\geq 10^4$ colony forming units (cfu)/ml for bronchoalveolar lavage (BAL), 10^3–10^4 cfu/ml for mini BAL, $\geq 10^5$ cfu/ml for undiluted tracheal secretions and $\geq 10^5$ cfu/ml for sputum [12]. Growth below the threshold concentration was assumed to be caused by colonization or contamination.

Isolation and identification of causative agents of HAP/VAP was performed in the hospital microbiology laboratory, using conventional biochemical methods [13]. The Antimicrobial susceptibility test was made by disk-diffusion method on Mueller-Hinton Agar (Biomerieux, France), by measuring the diameter of the zones of inhibition. The tested isolates were classified as susceptible or resistant (including intermediate) strains in accordance with guidelines of The Clinical and Laboratory Standards Institute (CLSI)[14].

Susceptibility to the following antibiotics was analyzed: amoxicillin + clavulanic acid (30 μg/mL), piperacillin-tazobactam (110 μg/mL), ceftriaxone (30 μg/mL), ceftazidime (30 μg/mL), cefepime (30 μg/mL), imipenem (10 μg/mL), meropenem (10 μg/mL), gentamicin (10 μg/mL), amikacin (30 μg/mL) and ciprofloxacin (5 μg/mL). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, by criteria proposed Magiorakos et al. [15].

Statistical analysis

The collected data were described by measures of central tendency (mean, median) and variability (standard deviation) if their nature was continuous, and by percentages, if the variables are categorical. Difference in values of a categorical variable among the study groups was tested for significance by Chi-square test (e.g. difference in resistance rates of isolates). The hypotheses were tested at 0.05 level of statistical significance. All calculations were performed using the statistical software SPSS version 18 for Windows (IBM SPSS, Inc, Chicago, Illinois, USA).

Results

In the observed period 620 patients admitted to the ICU developed HAP/VAP according to pre-defined criteria. HAP accounted for 38.2% and VAP for 61.8% patients. The rate of HAP and VAP was 10.3 cases per 100 patient-days. Mean patient age was 59.65 ± 16.02 years (range 19–91) and 69.0% of the patients (n = 428) were males.

In the majority of patients infection was caused by single pathogen (n = 354; 56.9%), whereas in other patients it was caused by two or three. Frequency of pathogens isolated from patients with HAP and VAP is shown in Table 1. From the total of 983 positive microbiological cultures Gram-negative agents were isolated in 95.2%. Generally the most common pathogens were *Acinetobacter* spp. and *P. aeruginosa* accounting for over 60% of isolates.

A statistically significant difference in the frequency of HAP and VAP isolates was found only for the *S. aureus* which was more frequent in the HAP group ($p < 0.001$) (the data not shown).

The results of susceptibility testing for the seven Gram-negative bacteria that most frequently caused HAP are shown in Table 2 and for causative agents of VAP in Table 3. According to these results, the isolates of *Acinetobacter* spp. in both groups were poorly susceptible to the third generation cephalosporins, aminoglycosides and fluoroquinolones (0–10%). The susceptibility rate to piperacillin-tazobactam was below15% whereas for carbapenems and 4th generation cephalosporin (cefepime) was somewhat higher (15–20%). Most isolates of *Acinetobacter* spp. from patients with HAP and VAP were MDR (91.6% and 94.2%, respectively). Although there was a difference in the rates of susceptibility to antimicrobial drugs between the two groups, it has not reached level of statistical significance.

Isolates of *P. aeruginosa* from HAP and VAP showed low degree of susceptibility to ciprofloxacin and gentamicin (below 10%), followed by amikacin (25%), while the rate of susceptibility to

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