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REVIEW

INTENSIVE CARE UNIT-ACQUIRED INFECTIONS – PATHOGENS SUSCEPTIBILITY AND DRUG RESISTANCE – PROBLEMS AND SOLUTIONS

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Abstract. Hospital-acquired infections have an important impact on intensive care unit patients, since they significantly influence patients' outcome. Around 30% of the intensive care unit patients develop nosocomial infections. A major issue regarding the pathogens involved in this category of hospital-acquired conditions is the emergence of antibiotic resistance.
Several measures for improving infection control both in terms of prevention and therapy have been developed and recommended. Hand hygiene is the single most important procedure for preventing the spread of healthcare-associated infections. Device-related infections are the most common potentially preventable events. Onset timing, presence of risk factors for multi-drug resistant pathogens, as well as posttherapeutic course of patients govern the choice for initial empiric antibiotic therapy along with the duration of antimicrobial treatment.
Key words: nosocomial infection, intensive care unit, antibiotic resistance, prevention, hand hygiene

Exposing the problem

In order to understand the concepts of drug susceptibility and resistance it is important, firstly, to highlight the most frequent hospital-acquired infections, the prevailing involved pathogens and their impact on intensive care unit patients' survival.

According to Centers for Disease Control and Prevention (CDC) the nosocomial infections are localized or generalized infections that occur as a consequence of the presence of a pathogen or its toxin, which was neither present nor during the incubation interval at the moment of admission. The majority of hospital-acquired infections become clinically obvious after 48 hours (the standard incubation interval) after admission (although this interval differs from case to case). An infection is not considered hospital-acquired in two circumstances: when it was present at admission (except when a change of the pathogen or symptoms that are suggestive for another infection occurs) and a newborn infection which is proved to be vertically transmitted, which become obvious within 48 hours. Germs colonization (the presence of microorganisms that are not inducing clinical signs and symptoms) and aseptic inflammation (when there is tissue reaction to trauma or non-infectious agents) are not considered infections [1].

The three most frequent hospital-acquired infections (HAI) from Intensive Care Unit (ICU) are: Ventilator-Associated Pneumonia (VAP), Catheter-Related Infections (CRI) and Urinary Tract Infections (UTI).

Ventilator-Associated Pneumonia (VAP) is defined as a nosocomial pneumonia which occurs in patients who receive mechanical ventilation without signs or symptoms of pneumonia at admission. VAP represents almost 25% of ICU infections and accounts for over 50% of the antibiotics prescribed in the ICU patients. The incidence of VAP among intubated patients is between 9% and 27%, while almost 90% of hospital-acquired pneumonias occur during mechanical ventilation. The risk was evaluated to be of 3% per day in the first 5 days, 2% per day in the next 5 days and 1% per day afterwards [2]. The impact of VAP on survival in a trauma population of 15.492 patients was evaluated by Magnotti et al. The results were astonishing: 38% of the patients required admission in ICU (70% from those had an Injury Severity Score (ISS) <25 (indicative of severe injury); the overall mortality was 4%; the mortality of those with VAP was 16% (approximately five time greater than of those without VAP, which was 3%) [3].

Early onset of VAP (in the first 4 days) is correlated with a better prognosis since infection is usually secondary to an antibiotic-susceptible bacteria, whereas a late onset is more probably induced by multi-resistant organisms and is associated with a poorer outcome [2].

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The overall mortality for nosocomial pneumonia ranges between 30% and 70%.Attributable mortality rate for VAP varies from 33 to 50%. The pathogens involved in increasing mortality are Pseudomonas aeruginosa and Acinetobacter species. However, hospital-acquired pneumonia can be induced by a very large spectrum of organisms (including viruses, fungi and commensal flora of oropharynx in immunocompromised patients) or it can be polymicrobial. The most frequently encountered aerobic Gram-negative bacteria are: Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae and Acinetobacter species. Anaerobic organisms can also induce pneumonia in non-ventilated patients, occurring usually as a consequence of aspiration [2].

Catheter-Related Infections (CRI) include localized infections (usually at the needle insertion point), catheter-related bloodstream infections (CRBSI), septic thrombophlebitis, endocarditis and other metastatic infections (such as pulmonary and cerebral abscesses), osteomyelitis and endophthalmitis [4].

CRI incidence varies between 3% and 9% when compared with all percutaneously inserted catheters in ICU (central venous catheter related infections account for an average of 90% of events), that equates with 2 to 8 infectious episodes at 1,000 days of central venous catheterization. In USA almost 5 million central venous catheters are inserted annually, accounting for an average of 15 million days of central venous catheterization and almost 450,000 episodes of CRI each year. Approximately 70% of CRBSI occur in patients with central venous catheters [5].

The characteristic skin flora that migrates on the surface of the catheters include coagulase-negative staphylococci (Staphylococcus epidermidis is most frequently encountered and involved in CRI) and Staphylococcus aureus, whereas pathogens such as Stenotrophomonas, Pseudomonas, Enterococci and Candida can colonize catheters through healthcare personnel hands. Many of the infections are induced by methicillin-resistant Staphylococcus aureus (MRSA) [5, 6].

Urinary Tract Infections (UTI) are the most common hospital-acquired infections (incidence – 30% from all HAI), and most frequently occur secondary to catheterization. Catheter-associated urinary tract infection (CAUTI) have been correlated with increased mortality, prolonged hospital stay and increased costs. The drainage urinary systems usually represent reservoirs for multiple drug resistance bacteria [7]. The daily risk of bacteriuria after catheterization varies between 3% and 10% and approaches 100% after 30 days. The prevailing pathogens resulting in CAUTI (including both symptomatic and asymptomatic bacteriuria), according to CDC's National Healthcare Safety Network (NHSN), assessed during 2006-2007 are: Escherichia coli (21.4%), Candida species (21.0%), Enterococcus species (14.9%), Pseudomonas aeruginosa (10.0%), Klebsiella pneumoniae (7.7%) and Enterobacter species (4.1%). Almost one quarter of cases with Escherichia coli and one third of cases with Pseudomonas aeruginosa are fluoroquinolone-resistant [7].

Taking into consideration the impact of HAI on ICU patients in terms of increasing morbidity and mortality, understanding pathogens' sensitivity pattern and drug resistance are mandatory in order to establish adequate therapeutic regimes to reduce these parameters.

Mechanisms of developing antibiotic resistance

Antibiotic resistance can occur through several mechanisms. In the battle between pathogens and antimicrobial agents, pathogens make use of several solutions for counteracting such as: genetic alterations – deoxyribonucleic acid (DNA) mutations, drug inactivation with enzymes such as beta-lactamases, acetylases, adenylases and phosphorylases, or alteration of membrane structure and characteristics in order to reduce drugs' binding capacity or leading to changes in cell's permeability capacity, thus influencing intracellular antibiotic storage [8].

In general, the pathway through which pathogens gain resistance comprises two directions (a vertical evolution – which basically consists in mutating existing genes [9] and a horizontal gene transfer – which signifies acquisition of novel genes from other pathogens strains or species) [10, 11]. The occurrence of new mutants is influenced by many factors such as: a dystrophic bacteria phenotype (such as a mutator phenotype – this means a dysfunction gene – for example one who plays a role in repairing deoxyribonucleic acid, or unstable sequences in the bases responsible for the resistance phenotype) or other circumstances such as low antibiotic concentrations, brief exposure time, slow antibiotic antimicrobial capacity and any other factors related to the number, size and location of genes responsible for mutations [9].

The horizontal gene transfer is currently recognized as an important pathway for gaining drug resistance. The transfer is mediated by genetic elements such as plasmids (segments of DNA independent of the chromosomes with the ability of replication), transposons (segments of DNA endowed with the capacity of inserting copies of itself in other DNA sites within the same cell) and bacteriophages (viruses that infect certain bacteria, thus introducing their genetic information) [10, 11].

The new pathogen mutants represent a permanent threat due to their aggressiveness and resistance, thus posing a perpetual challenge for the discovery of new therapeutic agents or of new treatment approaches.

Current status of ICU drug resistance – problems and debates

Almost 30% of the ICU patients develop nosocomial infections usually induced by the interconnection between several factors such as: illness severity, underlying disease, use of invasive devices and procedures (such as catheterizations, percutaneous punctures or endotracheal intubations) and also by close repeated contacts between the medical staff and patients [12]. In addition to the above mentioned elements, there are some other important, well-known supplementary factors that contribute not only to

the occurrence of hospital-acquired infections, but also to the emergence of antibiotic resistance. These are: use of antibiotics in animal and plant industry, lack of compliance to infection control policy, large number of patients with low resources and medical staff availability, failure to supervise microbiological pathogens course, long ICU stay and inappropriate antimicrobial choice and length of treatment [13].

A recent report from the National Healthcare Safety Network published in 2013 highlighted current status of pathogens drug resistance. The study included 2,039 hospitals, who reported 69,475 hospital-acquired infections and 81,139 pathogens; approximately 80% from those are included in 8 pathogen entities: Staphylococcus aureus (16%), Enterococcus species (14%), Escherichia coli (12%), coagulase-negative staphylococci (11%), Candida species (9%), Klebsiella pneumoniae and Klebsiella oxytoca (8%), Pseudomonas aeruginosa (8%) and Enterobacter species (5%). An average of 20% of the pathogens belong to multidrug-resistant group: methicillin-resistant Staphylococcus aureus (MRSA; 8.5%), vancomycin-resistant Enterococcus (3%), extended-spectrum cephalosporin-resistant Klebsiella pneumoniae and Klebsiella oxytoca (2%), Escherichia coli (2%) and Enterobacter species (2%); carbapenem-resistant Pseudomonas aeruginosa (2%), Klebsiella pneumoniae/oxytoca (<1%), Escherichia coli (<1%) and Enterobacter species (<1%) [14].

Concerning antimicrobial resistance, depending on the type of hospital-acquired infection, several data have been obtained: for blood-stream infections – 1,637 facilities reported CRBSI; 76% reported the presence of MRSA, 89% of Enterococcus faecium and only 4% and 7% of Escherichia coli, respectively Enterobacter species resistant to carbapenems; 20% of facilities reported CRI with carbapenem-resistant Klebsiella species; for urinary tract infections – 871 facilities reported CAUTI; 86% reported the presence of vancomycin-resistant Enterocccus faecium, 67% of fluoroquinolone-resistant Escherichia coli and only 8% carbapenem-resistant Escherichia coli; 20% of facilities also reported CAUTI with carbapenem-resistant Klebsiella species; for nosocomial pneumonia – 570 facilities reported VAP; 77% - MRSA, 56% - carbapenem-resistant Acinetobacter baumannii and 16% - carbapenem-resistant Klebsiella species [14].

Therefore antibiotic resistance of pathogens to powerful antimicrobial agents such as carbapenems is currently well recognized. There are several pathogens that have been labeled by Infectious Diseases Society of America as "ESKAPE" pathogens due to their ability of bypassing antimicrobial drugs' effect. These are: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species [15].

Nowadays, carbapenem (imipenem, ertapenem, meropenem, doripenem – beta-lactam antibiotics with antimicrobial properties against gram-positive and negative, and against anaerobic bacteria) resistance represents a major problem, considering that these antimicrobial agents are reserved for severe infections. Acinetobacter baumanii is one of the pathogens which, in the past few years increased its resistance to carbapenems (12). Enterobacteriaceae species gained the ability of producing carbapenemase enzymes, such as New Delhi metallo-beta-lactamases (NDM), first described in 2008 and isolated from patients who were healthcare provided in India or Pakistan. These enzymes basically are endowed with the capacity of hydrolyzation of all beta-lactams, with the exception of aztreonam, and lately, many pathogens were discovered to have this ability (Klebsiella pneumoniae, Escherichia coli, Citrobacter freundii, Enterobacter cloacae, Morganella morganii, Pseudomonas aeruginosa and Acinetobacter baumannii) [16].

Concerning gram-positive pathogens in ICU – the most important are methicillin/oxacillin-resistant staphylococcus aureus and vancomycin-resistant enterococci. One major problem in the treatment of MRSA is its increasing vancomycin-resistance. The underlying cause for this phenomenon is transmission of resistance via plasmids from enterococci to staphylococci, as enterococci are known to have a great adaptability, thus determining a multitude of resistance phenotypes to ampicillin, aminoglycosides and other beta-lactam antibiotics [18].

Antimicrobial resistance in Pseudomonas aeruginosa is also a concern because this pathogen develops resistance in certain conditions, imposed by antimicrobial pressure, through many pathways related to enzymes production and changes of cellular membrane permeability. Resistance problems occur also in fungal infections. More and more non-Candida albicans species are incriminated in invasive fungal infections (for example, fluconazole-resistant Candida krusei and Candida glabrata). However, further studies are needed in order to establish risk factors for fungal selection [18].

Solutions

ICU infection can have devastating consequences in critically ill patients. To a lesser or a greater extent, some infections can be prevented. Nevertheless, no prophylactic measure is universally effective and each patient poses a unique challenge. Infection control is extremely important and represents both an individual and a collective responsibility. Infection control includes a wide ensemble of measures, starting with hand hygiene.

Hand hygiene is the most efficacious way of reducing infection spread. In order to be effective, hands must be washed with soap and water for at least 30 to 45 seconds before and after each patient contact. Alcohol cleaning solutions have the same efficacy [19]. As a matter of fact, very simple prophylactic actions, such as hand washing with alcohol solutions or gels can save, annually, between 1000 and 2000 lives. Strict compliance to antiseptic techniques and hand washing remain the most important elements for CRBSI prevention [5].

Another significant aspect for infection control is catheters' management. The anatomic level for insertion plays a role in increasing the risk for CRI and this risk depends on skin flora density. Thus, catheters inserted in the lower extremity have a greater infection risk than

those located in the upper extremity Likewise, those inserted in the skin folds from the wrist and the elbow have a greater risk of CRI. For central venous catheters the recommendation is insertion in the subclavian instead of jugular or femoral vein [4]. Some health-care centers have the policy of central venous catheter (CVC) elective replacement after an established time frame (usually one week or less) even when there are no signs of infection. However, the myth that CVC routine replacement reduces risk infection finds no evidence to support this theory [20].

The choice for the appropriate catheter can bring a major benefit in decreasing infection risk. Endotracheal tubes with subglottic suction line can halve the VAP risk [21]. Silver-impregnated endotracheal tubes can reduce airways colonization, but it is not known yet if their use can diminish VAP incidence [22]. Similarly, CVC treated with antibiotics (minocycline/rifampin) or with antiseptics (clorhexidine/silver) can reduce CRBSI; in this regard it seems that antibiotic-coated catheters are most efficient [23].

Concerning multi-drug resistant (MDR) pathogens, barrier precautions such as gloves and gowns did not proved to be efficient in terms of reducing the incidence of MRSA or vancomycin-resistant enterococcus (VRE) colonization or infection, even when these measures were joined under meticulous supervision [24, 25]. Thus, these methods are insufficient for preventing MDR transmission. Other proposed solutions include universal decolonization (meaning decolonization of all patients without prior screening) and targeted decolonization (meaning screening, isolation and decolonization of carriers). These methods proved some benefits for MRSA infections [26]. Besides these, appropriate antibiotherapy strategies (in terms of best choice, best starting moment for antibiotic, duration of administration and adequate change of antimicrobial substance when needed) should be implemented. In order to achieve these aims, researchers are analyzing antibiotic stewardship programmes (such as "de-escalation strategies") to reduce MDR burden [13].

A very promising field for MDR infections treatment is represented by nanotechnology; through that researchers are trying to create nanoparticles (materials with nitric oxide-releasing nanoparticles properties – NONPs, chitosan-containing nanoparticles – chitosan NPs, metal-containing nanoparticles) with antimicrobial capacity [27, 28]. However, studies are ongoing in this field.

The choice for initial empiric antibiotic therapy for ICU-aquired infections depends on their time of onset and the risk factors for MDR pathogens (2). When late onset and/or risk factors for MDR microorganisms are present, a broad spectrum antibiotic therapy (late generation cephalosporin / carbepenem / β-lactam with β-lactamase plus fluoroquinolone/aminoglycoside plus linezolid/vancomycin) is initiated with subsequent de-escalation according to the clinical and microbiologic data, in order to minimize the emergence of resistance. In terms of duration, even though there is no universal consensus, antimicrobial treatment is recommended to be administered as a 7-day regimen, unless manifestations consistent with active infection persist (pyrexia > 38.3°C, white cells blood count over 10,000/mm^3).

Last, in search for solutions, researchers have employed old therapeutic agents such as Colistin (but with its drawback of high toxicity) or new antimicrobial agents, such as Tigecyclin (a tetracycline-class antimicrobial drug) which is usually reserved for MDR cases (this drug promises important benefits in patients with severe sepsis or septic shock, including cases induced by MRSA and VRE) [12, 17].

Conclusions

Hospital-acquired diseases have a significant impact upon ICU patients survival. Irrational use of antibiotics increases the risk of MDR infections. Several measures for improving infection control both in terms of prevention and therapy have been advocated. New studies are ongoing in order to establish novel ways of reducing MDR pathogens colonization and transmission and to improve or discover new therapeutic agents for the treatment of MDR infections.

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