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Derleme / *Review*

Prophylactic Use of Antibiotics in the Intensive Care Unit

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Yoğun Bakım Ünitesinde Profilaktik Antibiyotik Kullanımı

ABSTRACT

Infections during the intensive care treatment present a great continuous challenge to the physicians and to the patients. These infections can significantly increase the morbidity and mortality. One of the major issues to be addressed is the prophylactic use of antibiotics in intensive care units. The importance of infection prevention in critically ill patients is therefore based on its potential to reduce both morbidity and mortality. The relationship between this reduction and the prevention of the development of resistance remains unclear. The infections can also affect treatment costs, hospital stay, and patients' prognosis. This review tends to summarize all the topics regarding the prophylactic use of antibiotics, prevention of infections in intensive care units, and minimizing the resistance.

Keywords: *Intensive care unit, infections, antibiotics prophylaxis*

ÖZ

Yoğun bakım tedavisi sırasındaki enfeksiyonlar, hekimlere ve hastalara aşılması gereken bir sorun teşkil edegelmiştir. Bu enfeksiyonlar morbidite ve mortalite oranlarını önemli ölçüde artırabilir. Ele alınacak ana konulardan biri, yoğun bakım ünitelerinde antibiyotiklerin profilaktik kullanımıdır. Kritik hastalarda enfeksiyonun engellenmesinin önemi hem morbidite hem de mortaliteyi azaltma potansiyeline dayanmaktadır. Bu azalma ile direnç gelişiminin önlenmesi arasındaki ilişki net değildir. Enfeksiyonlar ayrıca tedavi masraflarını, hastanede kalış süresini ve hastaların prognozunu etkileyebilir. Bu derlemenin amacı, profilaktik antibiyotik kullanımı, yoğun bakım ünitelerinde enfeksiyonların önlenmesi ve antibiyotik direncini en aza indirgeme hususundaki konuları özetlemektir.

Anahtar kelimeler: *Yoğun bakım ünitesi, enfeksiyon, antibiyotik profilaksisi*

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INTRODUCTION

The development of infection during Intensive Care Unit (ICU) stay is associated with significant increases in morbidity and mortality. The administration of antibiotics in ICU is one of the major problems and subject of several controversies. Many efforts have been undertaken for a suitable "antibiotic stewardship", in order to optimize their utilization and minimize their side effects [1,2].

The appropriate use of antibiotics in ICU is important in ensuring an optimal clinical outcome, but in also controlling the emergence of resistance among pathogenic microorganisms and in containing costs [3,4].

Intensive care unit- acquired infections are frequently seen complications in the practice of critical care, with their cumulative incidence varying considerably among different patient populations.

The prevalence of antibiotic use among ICU patients is around 60%. It is reported that approximately 40% of all ICU patients, receive empiric antibiotic therapy [5]. Once initiated, empiric therapy is often continued for over 7 days, despite persistent negative microbiology results [6].

ICUs hospitalize heterogeneous group of patients under therapeutic treatment and prophylactic antibiotherapy, in order to minimize the infection.

The importance of prevention of infection in critically ill patients is therefore based on its potential to reduce both morbidity and mortality. The relationship between such reduction in both morbidity and mortality and the prevention of development of resistance remains unclear.

A clear distinction should be made between surgical and non-surgical patients. Interestingly, the proportion of surgical patients on antibiotherapy (26%) did not differ significantly from that of medical patients (24%). Various publications have reported the most frequent indications for antibiotherapy and the specific agents most frequently used [7,8].

It is known that approximately 500.000 surgical site infections (SSI) occur every year in the United States. Among patients who develop these infections, 60% of them will remain longer in the ICU, and they are 5 times more likely to be readmitted to the hospital and twice as likely to die compared to patients who had not developed infections. Moreover, the costs of these infections are high, and they are associated with other adverse events [9].

The antibiotic prophylaxis (ABP) in emergency surgery seems to be difficult compared to elective procedures. Sometimes it is difficult to differentiate between prophylaxis and early treatment.

The risk of acquiring an infection depends on the degree of the severity of the illness and the use of certain devices and procedures during ICU stay. These factors can cause a cumulative incidence of infections.

Clinical and Research Consequences

Through the factors predisposing for ICU infection, the frequent device utilization in intensive care is responsible for most nosocomial ICU-acquired infections. Endotracheal intubation, mechanical ventilation, central venous catheter, and urinary catheterization are the most important procedures responsible for the infections of respiratory tract, bloodstream, and urinary tract in ICU patients. The first week of ICU admission is characterized by impaired host defense (especially neutropenic patients), contributing to increased infection rates during these procedures. The early use of antibiotics may prevent the infection in these situations.

• Device-Related Risks: Patients who suffer an episode of Ventilator Acquired Pneumonia (VAP) or nosocomial bloodstream infection have been shown to need prolonged hospital stay associated with increased mortality rates as well [10-13].

Endotracheal intubation and duration of mechanical ventilation more than 48 hours are considered as risk factors for infections. Patients who have altered protective airway reflexes prior to endotracheal intubation due to a decreased level of consciousness or other causes are at a particularly high risk of early onset VAP. Compared to a conscious patient with a natural airway and spontaneous breathing, the presence of an endotracheal tube and mechanical ventilation in patients under sedation and muscle relaxation carries a 6 to 21-fold increased risk for development of nosocomial pneumonia [14].

Several mechanisms contribute to the increased risk of respiratory tract infection. A decreased level of consciousness after head trauma, stroke or need for emergency endotracheal reintubation, are associated with aspiration of contaminated oral and/or gastric contents due to the absence of upper airway reflexes. Infections caused by microorganisms that colonize the digestive tract of the patient on admission to the ICU are called “primary endogenous diseases.” Pneumonias of primary endogenous development, for example, are caused by the flora present in the oropharynx of patients at intubation. These microorganisms have either been aspirated before admission by a comatose patient or are aspirated through or inoculated on insertion of an endotracheal tube during the procedure of intubation. In the absence of systemic antibiotherapy, intubated stroke and head trauma patients have a 36% incidence of pneumonia developing soon after intubation [15]. It is reported that at medical indications for ICU stay (intubation for acute pulmonary edema, for resuscitation after cardiac arrest, coma due to drug overdose, and stroke), the incidence of early onset pneumonia was 51.3% in patients not receiving antibiotic prophylaxis (ABP) [16]. The infusion of muscle relaxants and the absence of systemic antibiotic therapy are considered as risk factors for VAP

during prolonged intubation and mechanical ventilation [17]. ABP reduces bacteremia, ventilator associated pneumonia and mortality among patients in ICU [18-20].

The use of ABP when aspiration is suspected or in trauma and comatose patients, is still a matter of debate, as several authors reported that restrictive politics may be more advantageous in reduction of antibiotic use to minimize development of resistance against them in ICU [21]. However, based on the abovementioned evidence [15-20], we strongly support the use of ABP in these circumstances, regardless of the definitive lack of evidence and guidelines.

A central line-associated bloodstream infection (CLABSI) is considered as bloodstream infection in a patient with infected central line developing within the 48-hour period unless another source was verified before the insertion of central line catheter [22]. Annually, about 80.000 CRBSIs developing in ICUs have been recently reported with a total of 250.000 cases of BSIs [23,24]. The isolated pathogens are in majority coagulase-negative *staphylococci, Staphylococcus aureus, enterococci*, and *Candida* spp [25]. Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) database and CDC reported a Gram-negative bacilli incidence as 21% and 19% respectively [25]. The proposed mechanisms include: direct contamination (dirty hands, poor hygiene, septic insertion), colonization of catheter (from insertion site, defective surface of the carheter), blood-borne infection from another site, and contamination of administered liquids [26,27]. The material of catheter may play an important role, for example silastic or silicone lastomer catheters. Some microorganisms for example *S. aureus* can adhere to host proteins [26,28].

Urinary tract infections (UTIs) present a major problem among the ICU infections. Their reported incidence is approximately 14.3% [29]. The incidence of catheter-related UTI is evaluated around 4.2% in symptomatic cases and 14.0% as asymptomatic bacteriuria [30]. Catheter-associated urinary infection can be defined as the combination of an indwelling urinary catheter for at least 2 days, fever and bacteriuria. The incidence is reported from 2.5/1000-4.8/1000 catheter days based on International Infection Control Consortium data gathered from 50 ICUs [31].

UTIs can be classified as non-urologic (presented in diabetes, trauma, renal failure) and urologic which include neurogenic bladder, urogenital surgery, kidney transplantation, and urinary stones. Several conditions can predispose to UTI as diabetes, immunosuppressive diseases, different infectious sites (appendicitis, ileus, and diverticulitis), tissue hypoxia, and urogenital trauma. The main pathophysiologic mechanism is infection through urethra but it may be hematogenous or originated per continuity by closer organs. In ICU, hypoxia and impaired tissue perfusion are common complications and can induce UTI as well. Another mechanism is presented by biofilms which are pathogen colony accumulations in tissues surfaces. The isolated bacteria are in majority *E. Coli, Enterococcus* spp, and *Klebsiella* [32-35].

The prevention of catheter-induced urinary infection mainly includes taking some measures as insertion of catheter when needed, avoidance of unnecessary catheterization, use of aseptic technique during catheterization, and removal of the catheter as soon as possible. The shorter the period of catheterization, the lower the rate of infection [35].

• Immunosuppression-related risks: The host can be immunocompromised due to diseases and/or drugs that impair their immune system. Several diseases are treated with immunosuppressive drugs as organ transplants, gastrointestinal diseases (inflammatory bowel disease, autoimmune pancreatitis, and autoimmune hepatitis), and onco-hematological illnesses. The immune system can also be impaired in neutropenic patients, and HIV infections [36,37].

Concerning the way of the ABP application in ICU, different issues should be considered:

• Gastrointestinal decontamination: The presence of potentially pathogenic microorganisms (PPMs) in the digestive tract plays a central role in the pathogenesis of most nosocomial infections. Primary endogenous infections usually develop during the first few days after ICU admission but may develop even nine days later, during the second week of ICU stay, if primary colonization persists. Exceptions to this relatively sensitive bacterial etiology are pati-

ents who chronically carry hospital flora after recent discharge and patients admitted to the ICU from other wards after prolonged hospital stay where nosocomial flora induce primary endogenous infections. Previously healthy patients with trauma, acute liver, pancreatitis or burn may carry normal pathogens. Patients with chronic diseases may carry Aerobic Gram-Negative Bacilli (AGNB) and Methicillin-resistant *Staphylococcus Aureus* (MRSA). Patients referred to the ICU from wards or other hospitals are highly likely to be carriers of abnormal potential pathogens as well [38].

After ICU admission, alterations of the control mechanisms of the oropharynx and the gut occur concurrently with disease and/or its therapy, leading to significant changes of the normal colonization pattern. The prevalence of abnormal digestive tract colonization increases with the severity of illness. The antimicrobial agents administered orally also have a narrow antimicrobial spectrum, thus they don't decrease indigenous intestinal flora, thus preserving the resistance capacity of the gut against colonization, while being active against all aerobic gram-negative PPMs such as *Pseudomonas* and *Acinetobacter spp*.

The selection of antibiotics is based on their own characteristics: preservation of normal intestinal flora, limitation of the emergence of resistant microorganisms (using antimicrobials with the lowest resistance potential), and control of inflammation (using antimicrobials with endotoxin/anti-inflammatory properties) [39,40]. The decision to employ ABP should be based on the stratification of risk for infection, considering mainly the presence of endotracheal intubation and need for mechanical ventilation. Patients requiring prolonged intubation, defined as the need for endotracheal intubation and mechanical ventilation for more than 48 hours, constitute the principal target population for antibiotic prophylaxis. The complete regimen of Selective Decontamination of Digestive tract (SDD) antibiotic prophylaxis in intubated patients consists of a combination of a 3-to 5-day course of an intravenous antibiotic with a mixture of topical non-absorbable antibiotics administered both as a sticky paste to the oral cavity and as a suspension through the nasogastric tube [40-42]. Bos et al. [43] concluded in their study that selective decontamination was superior to oral decontamination regarding the incidence of mechanical ventilator-associated pneumonia. The authors found that SDD can reduce the incidence of ventilator- induced pneumonia up to 50 percent.

The metanalysis of Oostdijk et al. [44] reviewed the current literature comparing selective gastric decontamination, oral decontamination, and their combinations. This metanalysis demonstrated the advantage of selective decontamination versus oral decontamination in reducing the likelihood of ventilator-associated pneumonia in 28-days follow up [45].

Prophylaxis in non-surgical patients is not supported by any randomized clinical trial and is not recommended by any scientific society. It is probably nourished by the idea that low bacterial growth could protect against infections. This policy increases antibiotic resistance and induces false confidence among physicians who consequently pay less attention to the possibility of occult infections [46].

• Systemic Prophylaxis: Antibiotic combinations are widely accepted if used appropriately in certain surgical procedures or patients. Concerning prophylaxis in non-surgical patients, after excluding a few specific conditions like neutropenia, the only two approaches for which there is evidence are SDD and VAP prophylaxis but still limited to certain situations. Intravenous antibiotic prophylaxis after endotracheal intubation for patients in whom no infection-specific antibiotherapy is indicated may be viewed in analogy to short-term surgical infection prophylaxis. Hence, systemic cefotaxime is an integral part of the digestive tract selective decontamination prophylactic protocol concept [47]. The comatose patients (stroke, liver failure, drug overdose), and those with primary respiratory disorders (pulmonary embolism, acute pulmonary edema and status asthmaticus) may benefit from short-term systemic antibiotic prophylaxis.

• Preoperative Antimicrobial Prophylaxis: ABP is used to reduce the incidence of postoperative surgical site infections. Patients undergoing procedures associated with high infection rates, those involving implantation of prosthetic material, and those in whom the consequences of infection are serious

should receive perioperative antibiotics. The antibiotic(s) should cover the most likely organisms and be present in the tissues before the surgical incision is performed, also maintaining the serum concentrations during the surgery. A single dose of a cephalosporin (cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures. This approach targets the most likely organisms (i.e., skin flora), while avoiding unnecessary broad-spectrum antimicrobial therapy. Duration of prophylaxis for surgical site infection should not exceed 24 hours in most cases [48,49].

Besides antibiotic prophylaxis, measures to prevent bloodstream infections or to reduce their incidence include training of healthcare personnel (careful manipulation and hand washing), proper selection of catheters and insertion sites (preferably upper-extremity site), and careful examination of the site (phlebitis and infiltration).

Data reported from a study also showed that antibiotics are inappropriately used because 993 (99%) out of 1000 patients included in the study received at least one antibiotic. Antibiotics were given to 85 (98%) of 87 patients for whom such treatment was not indicated, costing an average of 100 US Dollars per surgical procedure [50].

Antiseptics could be a cheaper alternative to antibiotics. Even though use of antiseptic solutions, such as chlorhexidine mouth washing, have been associated with reduction in respiratory tract infections in ICU patients, their effects on more objective outcomes need to be further established [51]. It remains unknown whether resistance to chlorhexidine will occur during its widespread prophylactic use [52,53].

CONCLUSIONS

In conclusion, use of antibiotics for prophylactic purpose in ICU is an important maneuver, which needs to take into consideration strict indications, patient category, type of prophylaxis, application modality, duration of use, possible complications and economic factors (costs). In order to apply ABP in ICU, apart from the clinical policies used for specific procedures, we consider it relevant to consider all the above-mentioned factors, while always applying strict aseptic and antiseptic procedures. Furthermore, we propose that systemic use of antibiotics needs to be combined with application of topical antiseptics on a case by case logic and evidence-based specific protocols.

The efficacy and success of ABP use in ICU depends on the right understanding and their rigorous application from all the ICU personnel, including physicians, nurses, microbiologists, and pharmacists. The correct administration policies need to be structured in the institution's general strategy framework of prevention and control of infections, including the implementation of locally developed guidelines.

Antibiotic use needs to be considered as a partial instrument of a multimodal strategy.

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