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Hospital-acquired infections caused by antibiotic resistant bacteria

Zakażenia szpitalne wywołane przez lekooporne bakterie

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S u m m a r y

Hospital acquired infections (HAIs) caused by antibiotic resistant bacteria are a significant cause of morbidity and mortality worldwide. In recent decades the incidence of HAI with antibiotic resistant bacteria has increased remarkably. The percentages of antimicrobial resistance continued to increase in Europe leading to mounting healthcare costs, failed treatment and deaths. Approximately 4 100 000 patients are estimated to acquire a healthcare-associated infection in the European Union (EU) every year. The number of deaths occurring as a direct consequence of these infections is estimated to be at least 37 000. More than 70% of the bacteria that causes HAIs are resistant to at least one antibiotic. Antimicrobial resistance (AMR) is a serious threat to public health. Among Gram-positive bacteria vancomycin-resistant enterococci (VRE), pneumococcal infections, and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most important. Multidrug-resistant Gram-negative bacteria pose a serious and rapidly emerging threat to patients in healthcare settings, and are especially prevalent in intensive therapy units (ITUs).

This review details the main aspects of drug-resistant bacteria being a serious threat to patients in healthcare settings.

S t r e s z c z e n i e

Na świecie zakażenia szpitalne stanowią istotną przyczynę zachorowalności i śmiertelności, zwłaszcza jeżeli czynnikiem etiologicznym są lekooporne drobnoustroje. W Europie w ostatnich dekadach odnotowuje się stały wzrost częstości zakażeń szpitalnych wywołanych przez bakterie oporne na antybiotyki, co powoduje wzrost kosztów leczenia, niepowodzeń terapeutycznych i zgonów. Szacuje się, że rocznie w krajach Unii Europejskiej u około 4 100 000 hospitalizowanych pacjentów występują zakażenia szpitalne. Liczba zgonów będących bezpośrednim następstwem tych zakażeń wynosi około 37 000. Ponad 70% bakterii będących przyczyną zakażeń szpitalnych wykazuje oporność na co najmniej jeden antybiotyk. Lekooporność drobnoustrojów stanowi zatem poważny problem w aspekcie zdrowia publicznego. Spośród bakterii Gram-dodatnich głównymi patogenami są oporne na wankomycynę enterokoki (VRE), pneumokoki i metycylinooporne szczepy *Staphylococcus aureus* (MRSA). Zjawisko wielolekooporności występujące wśród bakterii Gram-ujemnych stanowi poważne i rosnące zagrożenie dla hospitalizowanych pacjentów, zwłaszcza w oddziałach intensywnej terapii.

W tym artykule omówiono zagadnienia dotyczące problematyki lekooporności wśród drobnoustrojów szpitalnych stanowiących istotne zagrożenie dla pacjentów placówek służby zdrowia.

INTRODUCTION

Hospital acquired infections (HAIs) also known as a nosocomial infections are a significant cause of morbidity and mortality worldwide, especially if the causative organism has developed resistance to a number of antimicrobial agents (1).

Approximately 4 100 000 patients are estimated to acquire a healthcare-associated infection in the European Union (EU) every year. The number of deaths occurring as a direct consequence of these infections is estimated to be at least 37 000. About 5-10% of patients admitted to acute care hospitals and long-term

care facilities in the United States develop a hospital-acquired infection, with an annual total of more than one million people (2).

Antimicrobial resistance (AMR) is a serious threat to public health. More than 70% of the bacteria that causes HAIs are resistant to at least one antibiotic. In recent decades the incidence of HAI with antibiotic resistant bacteria has increased remarkably and the fight against HAI has become of critical concern to clinicians worldwide. Antibiotic resistance is a critical challenge for infective disease management. The percentages of AMR, especially multidrug resistance (MDR), continued to increase in Europe leading to mounting healthcare costs, failed treatments, and deaths. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) indicate that the proportion of strains of major pathogens isolated from blood or cerebrospinal fluid (CSF) with resistance to important antimicrobial agents exceeds 10% or even 25% in several countries, with the highest figures seen in southern and eastern Europe (3, 4).

Multidrug-resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug-resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pandrug-resistance (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories (3).

Gram-positive and Gram-negative bacteria are both affected by the emergence and rise of antimicrobial resistance and this problem continues to grow (3).

Gram-positive resistance

Vancomycin-resistant enterococci (VRE) were first described in Europe in 1988 and have rapidly spread worldwide. Enterococci are a part of the normal human faecal flora. The main sites of colonization in the hospitalized patients are soft tissue wounds, ulcers, and the gastrointestinal tract. Enterococci were reported as the second most common cause of nosocomial infection in the US. Infections with these pathogens have been associated with poor outcomes (5).

There are six recognized phenotypes of vancomycin resistance: VanA, VanB, VanC, VanD, VanE, and VanG. Human enterococcal infections are mainly caused by 2 species: *Enterococcus faecalis* and *Enterococcus faecium*, which express the VanA or VanB phenotype. The most common nosocomial infections produced by these pathogens are urinary tract infections (associated with instrumentation and antimicrobial resistance) followed by intra-abdominal and pelvic infections. They also cause surgical wound infections, bacteriemia, endocarditis, neonatal sepsis, and rarely meningitis (6, 7).

The data from multicentre study from Poland revealed that among urinary tract pathogens Gram-positive cocci were isolated more frequently from a hospital setting (14.1%) and the most common were *Enterococcus* spp. (8.5%). Three strains of *E. faecalis* from

hospital expressed high-level aminoglycoside resistance (HLAR) (8). The incidence of human VRE infections in European countries is low (1-3%) compared with the high and rising rate in the US (9). An important feature in the emergence of the enterococci as a cause of nosocomial infections is their increasing resistance to a wide range of antibiotics both instrinsic and acquired resistance. Recommendations for controlling vancomycin resistance include reducing the use of drugs known to increase the risk of enterococcal infection (e.g. third-generation cephalosporins), limiting vancomycin use, applying accurate microbiological identification methods, and maintaining hand-washing procedure (8-10).

Pneumococcal resistance

Treatment of pneumococcal infections is complicated by an increasing rate of resistance to antibiotics. *Streptococcus pneumoniae* is still a prime cause of otitis media in children and of pneumonia in all age groups, as well as a predominant cause of meningitis and bacteremia. In adults, bacteremia is still entailed with a mortality of over 25%. Although *S. pneumoniae* remained very sensitive to penicillin for many years, penicillin-resistance has emerged and increased dramatically over the last 15 years. During this period of time, the frequency of penicillin-resistant isolates has increased from < or = 1% to frequencies varying from 20 to 60% in geographic areas as diverse as South Africa, Spain, France, Hungary, Iceland, Alaska, and numerous regions of the United States and South America. The increase in penicillin-resistant pneumococci correlates with the intensive use of β-lactam antibiotics. (11). The mechanism of β-lactam resistance of *S. pneumoniae* involves genetic mutations which alter penicillin-binding protein structure, resulting in a decreased affinity for all β-lactam antibiotics (12). Antibiotics recommended against penicillin-resistant pneumococci include cefotaxime, ceftriaxone, imipenem and in some instances vancomycin. However, penicillin-resistant pneumococci tend to present cross-resistances to all the antibiotics of the β-lactam family and could even become resistant to the last resort drugs mentioned above (11).

Staphylococcal resistance

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare and community-associated infections worldwide. MRSA is a common bacterial pathogen, responsible for variety of infections. It may cause not only local infections, such as postoperative or injury wound infections and osteomyelitis, but also generalized infections. This pathogen is also responsible for infections related to prosthesis, catheters and others biomaterials. Some of them may be life-threatening, especially in the case of immunecompromised patients, causing bacteremia, endocarditis, sepsis or toxic-shock syndrome (8). Worldwide, 15-20% of the healthy population carry *S. aureus*, which has a natural

occurrence in the mucous membranes of the nose (2). Within the healthcare setting alone, MRSA infections are estimated to affect more than 150 000 patients annually in EU (13). The majority of HA-MRSA strains isolated in European countries have emerged from the introduction of the staphylococcal cassette chromosome mec (SCCmec) harbouring the methicillin-resistance gene mecA, into five *S. aureus* clonal complexes (CC), as defined by multi-locus sequence typing (MLST): CC5, CC8, CC22, CC30 and CC45 (14).

In 2008, the proportion of MRSA in *S. aureus* blood culture isolates was less than 5% in Denmark, Estonia, Finland, Iceland, the Netherlands, Norway and Sweden. In three countries (Austria, Luxembourg, Slovenia), a proportion of less than 10% was found, while in eight countries the proportion was between 10-24% (Belgium, Czech Republic, France, Germany, Hungary, Latvia, Poland, Switzerland) in total, 13 countries reported a proportion equal to or above 25% (Bulgaria, Croatia, Cyprus, Greece, Israel, Italy, Malta, Portugal, Republic of Ireland, Romania, Spain, Turkey, United Kingdom) indicating two countries (Malta, Portugal) with proportion above 50%. According to European Antimicrobial Resistance Surveillance System (EARSS) 2008 data, a significant declining trend of invasive MRSA infections has been observed in Austria, Poland, Latvia, Romania, Italy, France, Belgium and the United Kingdom over the last four years of surveillance (15).

Since MRSA is also resistant to many other antimicrobials, both β-lactams and non-β-lactams, vancomycin is generally relied on for the treatment of MRSA infections (16).

Gram-negative resistance

Multidrug-resistant Gram-negative bacteria pose a serious and rapidly emerging threat to patients in healthcare settings, and are especially prevalent in intensive therapy units (ITUs). Infectious with Gram-negative bacteria also generate a serious therapeutic problem in ITU patients because of a high percentage of multi-resistant bacterial strains (13). The most important resistance problems that impact nosocomial infections are extended-spectrum β-lactamase (ESBL) in *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis*. High level third-generation cephalosporin (Amp C) β-lactamase resistance among *Enterobacter*, and multidrug resistance *Pseudomonas aeruginosa* and *Acinetobacter* is also concern (16). A particularly dangerous phenomenon is the emergence of pan-drug resistance in Gram-negative bacteria. Among most dangerous pathogens, called "alert-pathogens" with rapidly increasing antibiotic resistance four types of Gram-negative bacteria were listed: *Klebsiella*, *Enterobacter*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii* (17).

Klebsiella pneumoniae

Klebsiella spp. are among the most common pathogens isolated in intensive care units (ICUs), and

K. pneumoniae is the most frequently encountered carbapenemase-producing *Enterobacteriaceae*. Few antimicrobial therapy options exist for infections caused by carbapenem-resistant (CRKP) *Klebsiella pneumoniae*. *Klebsiella pneumoniae* carbapenemases (KPCs) hydrolyze all carbapenems and all the remaining β-lactam antibiotics. Strains of *Klebsiella pneumoniae* KPC+ are usually sensitive only to colistin, tigecycline, gentamycin, and sometimes to amikacin. The Centers for Disease Control and Prevention (CDC) reported that among HAIs, 8% of *Klebsiella* spp. isolates were carbapenem-resistant in 2007 compared with < 1% in 2000 (18). The widespread transmission of carbapenemase-producing *K. pneumoniae* has become the most common cause of carbapenem resistance among *Enterobacteriaceae* in the US. Data from Sanchez et al. study revealed that *K. pneumoniae* antimicrobial drug resistance increased for every antimicrobial class studied except tetracyclines (19).

Acinetobacter baumannii

The genus known as *Acinetobacter* has undergone significant taxonomic modification over the last 30 years. Its most important representative *Acinetobacter baumannii*, has emerged as one of the most troublesome pathogens for health care institution globally. Its clinical significance, especially over the last 15 years, has been propelled by its remarkable ability to up regulate or acquire resistance determinants, making it one of the organisms threatening the current antibiotic era. *A. baumannii* strains resistant to all known antibiotics have now been reported. The organism commonly targets the most vulnerable hospitalized patients, those who are critically ill with breaches in skin integrity and airway protection. The rapid global emergence of *A. baumannii* strains resistant to all β-lactams, including carbapenems, illustrates the potential of this organism to respond swiftly to changes in selective environmental pressure (20).

A. baumannii causes a wide range of serious infections and is a major cause of bacteremia, pneumonia (particularly ventilator-associated pneumonia), meningitis and urinary tract infections. Infections attributed to this organism have been reported around the world and are increasing in incidence (20).

The mechanisms of resistance generally fall into 3 categories: antimicrobial-inactivating enzymes, reduced access to bacterial targets, or mutations that change targets or cellular functions. *Acinetobacter* species can also acquire resistance genes from other organisms (21).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is an emerging opportunistic pathogen in healthcare settings and is amongst the leading causes of nosocomial pneumonia associated with high mortality rates (22).

According to surveillance data, *P. aeruginosa* was the third and fifth most common cause of hospital acquired urinary tract infections in the USA and in Europe (23).

Bacteraemia and septic shock caused by *P. aeruginosa* are mainly observed in immunocompromised parients (22).

Pseudomonas aeruginosa is intrinsically resistant to many antimicrobial agents. The AmpC chromosomal β-lactamase contributes to the intrinsic resistance to ampicillin, and to most cephem. The three-component MexA-MexB-OprM, MexC-MexD-OprJ, MexE-MexF-OprN and MexX-MexY-OprM systems provide an important defence against a wide variety of antimicrobial agents including quinolones, tetracycline, chloramphenicol, macrolides, sulphonamines, trimethoprim, aminoglycosides and most β-lactams (24).

Acquired resistance to any of the antipseudomonal agents has been described (22).

According to recent data from the largest multicentric surveillance study, amikacin, piperacillin--tazobactam and carbapenems remain the most active drugs against *P. aeruginosa* worldwide but isolates that exhibit resistance to virtually all available antipseudomonal agents are increasingly being reported (25).

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