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RESISTANT GRAM-POSITIVE BACTERIAL INFECTIONS

DİRENÇLİ GRAM POZİTİF BAKTERİ ENFEKSİYONLARI

Emine Kübra Dindar Demiray[1], Serpil Oğuz Mızrakçı[2]

[1] MD., Infectious Diseases and Clinical Microbiology, Bitlis State Hospital, Bitlis/TÜRKİYE,

ORCID ID: 0000-0001-6459-7182

[2] MD, Infectious Diseases and Clinical Microbiology, Lıv Hospital, Gaziantep/TÜRKİYE,

ORCID ID: 0000-0002-7331-5877

Corresponding Author:

MD, Emine Kübra Dindar Demiray,

Infectious Diseases and Clinical Microbiology, Bitlis State Hospital, Bitlis/ TÜRKİYE,

e-mail: *e.kubradindar@hotmail.com* , ***Phone:*** *+90 533474 3527*

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Abstract

With developing technology, the life expectancy of people such as immunosuppressed and elderly patients have increased, but the treatments and invasive procedures applied have increased with age. Thus, the emergence of healthcare-associated, hospital-acquired infections in these individuals has emerged as an inevitable result. In nosocomial infections and epidemics, the importance and contribution of the microbiology laboratory is great in terms of identifying the agent, determining the antibiotic resistance profile, determining the source, and taking the necessary precautions. Resistant gram-positive bacterial infections are common infections in these individuals and have led to increased antibiotic-resistant treatment failures and even deaths over the years. In this review, we planned to classify resistant gram-positive bacterial infections, review them in the light of the literature, and discuss what can be done to prevent them.

Keywords: *Resistant, Gram-Positive Bacteria, Infections.*

Özet

Gelişen teknoloji ile birlikte immünsüpresif ve yaşlı hastalar gibi kişilerin yaşam beklentisi uzamış ancak yaşla birlikte uygulanan tedaviler ve invaziv işlemler uzamıştır. Böylece bu bireylerde sağlık hizmeti ilişkili, hastane kaynaklı enfeksiyonların ortaya çıkması kaçınılmaz bir sonuç olarak ortaya çıkmıştır. Hastane enfeksiyonlarında ve salgınlarda etkenin belirlenmesi, antibiyotik direnç profilinin belirlenmesi, kaynağın belirlenmesi ve gerekli önlemlerin alınması açısından mikrobiyoloji laboratuvarının önemi ve katkısı büyüktür. Dirençli Gram-pozitif bakteriyel enfeksiyonlar, bu bireylerde sık görülen enfeksiyonlardır ve yıllar içinde antibiyotiğe dirençli tedavi başarısızlıklarının ve hatta ölümlerin artmasına neden olmuştur. Bu derlemede dirençli Gram pozitif bakteriyel enfeksiyonları sınıflandırmayı, literatür ışığında gözden geçirmeyi ve önlemek için neler yapılabileceğini tartışmayı planladık.

Anahtar Kelimeler: *Dirençli, Gram-Pozitif Bakteri, Enfeksiyonlar.*

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OVERVIEW / GENEL BAKIŞ

Introduction

Gram-positive bacteria infections are community-acquired infections or healthcare-associated infections whose clinical management is difficult despite advances in antibiotic therapy (1-6). While penicillin was accepted as the first choice for treatment, it was reported that Staphylococcus aureus strains produced penicillinase in 1941, and later on, the majority of Staphylococcus aureus strains were accepted as resistant to methicillin because they produced ß-lactamase (3). Methicillin-resistant S. aureus (MRSA) has been reported at approximately the same time as penicillin's clinical use. This has led to the elimination of all ß-lactam antibiotics in patients currently being treated for this infection. In addition, some of the MRSA strains have [Vancomycin-intermediate S. aureus (VISA)] strains with moderate susceptibility to vancomycin (MIC 4–8 µg/ml), which have been mentioned for about 25 years. Again, all strains of S. aureus [Vancomycin-resistant S. aureus (VRSA)] are completely resistant to vancomycin (MIC ≥16 µg/ml), which is rarely reported in the world, causing concern about the resistance problem we will experience in the future. In another case, it can be accepted that for the first time in Europe in 1988, vancomycin-resistant enterococci (VRE) were isolated, and then they were seen in the United States of America (USA) and became an important problem globally in the last three decades (1,4,8).

Resistant Gram-positive bacteria infections can cause complicated soft tissue and skin infections (burn wounds, infected ulcers, surgical site infections). There are many different clinical pictures, such as central nervous system infections, diabetic foot infections, blood and catheter circulation infections, urinary system infections, and respiratory tract infections (9-11). Infections with resistant Gram-positive bacteria [for example, Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE)] are also among the indications for hospitalization and cause labor loss as well as difficulties in treatment (4,11).

In this review study, it was aimed to review resistant Gram-positive bacterial infections.

a. Antibiotic resistance in Staphylococcus aureus strains

While methicillin-resistant Staphylococcus aureus strains were previously reported only for hospital-acquired/healthcare-associated infections, in the 1990s, there were reports of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) infections caused by new strains genetically

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different from traditional healthcare-associated MRSA. Various reports have emerged. CA-MRSA has been reported globally since then. It also has been seen in the United States in individuals who are unrelated to health care and do not have an underlying risk factor. Most importantly CA-MRSA; USA300 (12,13). Considering the risk factors for CA-MRSA infections, individuals living in crowded environments and low socioeconomic status; when occupational groups are examined, athletes, soldiers, residents of nursing homes, and prisoners are included in risk groups (14).

There are also cases reported in Turkey (15-17). Dundar et al. (17) defined 2 (1%) of 725 MRSA strains isolated from different regions of Turkey in 2013 as mec typing and epidemiologically as CA-MRSA. CA MRSA can be differentiated from hospital-acquired MRSA based on genotypic, epidemiological, and susceptibility factors (12). Methicillin resistance is encoded by the chromosomal mecA gene. Again, it is known that the mecA gene is found in S. aureus and all methicillin-resistant coagulase-negative staphylococci (MRCNS) strains. Isolates carrying this gene are resistant to all beta-lactam antibiotics due to the production of a new penicillin-binding protein (PBP). However, it should not be forgotten that methicillin resistance cannot always be detected by routine tests because it is affected by environmental conditions, so methicillin-resistant staphylococcus can sometimes be defined as methicillin-susceptible (18). In invasive infections in which MRSA is thought to be the causative agent, it has been reported that moderately susceptible (VISA), heterogeneous moderately susceptible (hVISA), and resistant (VRSA) S. aureus strains occur after frequent use of glycopeptide group antibiotics, especially vancomycin (19). Teicoplanin resistance develops more quickly than vancomycin. This resistance cannot sometimes be detected by the disk diffusion method, and it is necessary to determine the minimal inhibitory concentration (MIC) (20,21).

The new name “vancomycin-intermediate S. aureus (VISA, Mu50)” was introduced into the literature with the report of a moderately susceptible (MIC= 8 µg/ml) S. aureus strain (21,23). A different isolate called Mu3 with a vancomycin MIC value of 2 µg/ml was detected in one patient by the same investigators. In this isolate, the vancomycin MIC value was determined to be above the sensitive cutoff value to be seen in one cell per million (10-16). The pattern was named heterogeneous resistance and bacteria was named “heterogeneous VISA (hVISA)” (22,23).

The reason for the moderate resistance to vancomycin in staphylococci is the thickening and disorganization of the cell wall due to the change in peptidoglycan biosynthesis (24). In addition, it has been reported that excessive increase in penicillin-binding protein (PBP) 2 production and lack of PBP4 expression may also be effective in the resistance mechanism. It has been suggested that VISA isolates with different susceptibility patterns detected to date appear after long-term exposure to vancomycin (25).

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For EUCAST, the clinical MIC breakpoint for vancomycin resistance in S. aureus is stated as > 2 mg/L. Today, the group defined as "intermediate" has been removed, and the limit values for vancomycin have been lowered. However, there are differences in resistance cascades according to VanA coding. High-level glycopeptide resistant S. aureus (GRSA) isolates are encoded by VanA, and low-level resistant isolates occur with non-VanA coding. Therefore, the terms glycopeptide "intermediate" S. aureus (GISA) and heteroresistant glycopeptide "intermediate" S. aureus (hGISA) continue to refer to low-level vancomycin-resistant isolates encoded non-VanA. It is important to determine the MIC value in order to use vancomycin for the treatment of S. aureus infection, especially for severe clinical courses. In some infections, hGISA should be investigated after treatment failure. Due to the difficulties in detecting hGISA, antimicrobial surveillance has generally focused on the detection of GISA and GRSA (21,23-26).

In summary, antibiotic resistance in S. aureus requires determination of clinical and/or epidemiologically important resistance features and mechanisms. According to EUCAST guideline V 1.0 (July 2013), antibiotic resistance in S. aureus strains is classified as follows:

*GRSA: S. aureus resistant to glycopeptides.

*S. aureus with high vancomycin (MIC > 8 mg/L) resistance,

*GISA: Glycopeptide "intermediate" S. aureus

*S. aureus with low level vancomycin (MIC 4-8 mg/L) resistance,

Heterogeneous glycopeptide "intermediate" S. aureus

S. aureus isolates (23-25) had vancomycin MICs of 2 mg/L, but population analysis revealed cells with vancomycin MICs greater than 2 mg/L in a very small population (1/106 cells).

According to data from single centers, the prevalence of hGISA among MRSA isolates in Europe is ≤ 2% and GISA is less than 0.1% (26). GRSA is rare all over the world and has not yet been reported in Europe (27). Depending on the spread of a particular clone, the prevalence of hGISA may be high with local values. Almost all isolates with high MIC (GISA) or resistant subpopulations (hGISA) are MRSA (28). The lack of well-evaluated prospective studies does not clearly demonstrate the clinical significance of hGISA. However, in severe infections, the hGISA phenotype is thought to cause worse clinical outcomes (27,28). Therefore, hGISA should be investigated in bloodstream infections that do not respond to treatment. Currently, there is evidence that strains with MICs close to the upper limit of susceptibility (MIC>1 mg/L) lead to higher mortality and worse outcomes (21,29,30). It may be more appropriate to say

that the mechanism of hGISA is complex and its detection is based on a population analysis method that requires special equipment, intensive labor and high technical expertise (31-34).

Sancak et al., in 2005, first conducted a study investigating the presence of hVISA in MRSA isolates in Turkey (35). In which 46 (18%) of 256 MRSA isolates were determined as hVISA by PAP-AUC method. Kuşçu et al. (25) investigated hVISA in 148 methicillin-resistant staphylococci strains and identified one (0.9%) hVISA isolate among 107 MRSA.

In the study of Mirza et al. (36), from the pediatric patient group for the first time, they studied population analysis profile-area under the curve (PAPAUC) in isolated MRSA isolates and found that 21.3% of them were hVISA (36). Korkut Tunç et al. (37) detected hVISA in nine (17.30%) of 52 MRSA strains according to the results of the population analysis profile. In Greece, Souli et al. (38) detected six (3.4%) hVISAs in 175 isolates. Khatib et al. (39) detected VISA in 1.6% (n=6) and hVISA in 8.1% (n=30) among 371 MRSA strains. In one study, the frequency of hVISA was found to be 1.2% (n=2) in 147 MRSA isolates (40). When the studies are evaluated, it is seen that the prevalence rates found are between 0.9% and 21.3% (21,37-40).

Detection of glycopeptide group antibiotics as pseudo-susceptible may lead to failure in the treatment of infections caused by strains with reduced susceptibility to glycopeptides. The possibility of VISA and h-VISA should be considered, especially in patients in whom vancomycin therapy has not worked or who initially show improvement and suddenly worsen while treatment is continued (41). S. aureus isolates found resistant to glycopeptide or linezolid by automated systems must be confirmed with a reference method. Along with necessary infection control measures, hospital resistance profiles should be followed regularly, treatment options should be updated, and hospitals' limited antibiotic use policies should be implemented more strictly (42).

b. Antibiotic resistance in enterococci

Enterococcus spp. are found in human intestinal, as normal bacterial flora in the mouth, urethra, vagina, and biliary tract. Although they have low virulence, they can cause serious infections (43). They can cause various infections such as pelvic infections or intra-abdominal, skin, and soft tissue infections, meningitis, bacteremia, and neonatal sepsis, especially due to the endogenous flora of individuals with weakened immune systems (44). First identified in the 1980s, in Turkey, the origin of vancomycin-resistant enterococci (VRE) was first reported in 1996 in Antalya. Later, VRE infections were seen in various centers such as Ankara, Istanbul, and Bursa (45).

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Enterococcus faecium and Enterococcus faecalis species cause most of these infections, and nosocomial urinary tract (16%) and wound infections (12%), nosocomial bacteremia (9%), and endocarditis are the causative agents (46). Especially VRE strains can easily multiply and spread in the hospital environment and cause serious morbidity and mortality in hospitalized patients. Glycopeptide resistance is mostly in E. faecium and less in E. faecalis. In Turkey, VRE tends to be a cause of colonization and sometimes infection in the gastrointestinal system (GIS) of patients hospitalized in critical areas such as intensive care units (ICUs) where antibiotics are widely used in hospitals, as well as in pediatrics, nephrology, oncology, and hematology clinics (47). Because antıbiotics used in infections are very lımıted and the microorganism can spread rapidly between units, early detection of VRE colonization in hospitalized patients and determination of risk factors. Enterococci are in fourth place among the nosocomial bloodstream infections in the USA, and in fifth place according to European data. In Turkey, Enterococci are isolated in an average of 13-15%.

In addition, it is the second most frequently isolated pathogen in hospital-acquired urinary system and surgical site infections, and the third most common pathogen in bloodstream infections E. faecium and E. faecalis are the most common. Widespread use of third generation cephalosporins, which they are structurally resistant to, increase in invasive procedures, long-term hospitalization, and increase in immunosuppressed patients (21,43-52).

Especially E. faecium, are resistant to most of the antimicrobial agents generally in use. Therefore, VRE infections treatment is difficult and there are few treatment options. VRE spreads easily, remains in the hospital setting for a long time, and can colonize large numbers of individuals. Isolates carrying the VanB gene are phenotypically susceptible to teicoplanin. There are two case reports showing teicoplanin resistance during the treatment of VanB carrying enterococci (21,52,53).

Clinically significant resistance is most mediated by the plasmid-encoded VanA and VanB ligases that replace terminal D-Ala with D-Lac in the peptidoglycan chain. This displacement reduces the binding of glycopeptides to the target. While VanA strains are resistant to both vancomycin and teicoplanin, VanB strains generally retain their teicoplanin susceptibility because the resistance operon is not induced. Other Van enzymes with lower prevalence are VanD, VanE, VanG, VanL, VanM and VanN (21,54-58). Other enterococci species (e.g. E. raffinosus, E. gallinarum and E. casseliflavus) may contain vanA, vanB or other van genes encoding the enzymes listed above, but these strains are less frequent. Chromosomally encoded VanC enzymes are found in all E. gallinarum and E. casseliflavus isolates. VanC causes low-level vancomycin resistance (MIC 4-16 mg/L) but is generally not considered important for infection control (21,59).

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The presence of enterococci in the gastrointestinal flora of healthy people suggests that most of the infections caused by these agents originate from the patient's own flora. However, patient-to-patient transfer of all enterococci, including VRE, also occurs directly or indirectly through medical devices, contaminated hands or surfaces. Both VanA and VanB-type resistant VRE strains have been isolated in colonization or infection seen in hospital epidemics (60). Widespread and inappropriate antibiotics uses in the hospital is an important risk factor for resistant microorganisms' infections. Also, cephalosporins pose a risk of VRE colonization by suppressing enteric aerobic and metronidazole by suppressing anaerobic flora (61). In a case-control study it was reported that the use of intravenous third generation cephalosporins, metronidazole and fluoroquinolones was associated with VRE positivity in a total of 880 cases, 223 of which were positive for VRE (62). In another study conducted in Brazil (63), it was reported that the use of carbapenems was significant in terms of VRE risk. Many studies among them show that the use of vancomycin, third generation cephalosporin, and metronidazole, as well as the presence of GI bleeding and the use of antacids, increase the risk of VRE (52-57).

In a study conducted in Hong Kong, the use of beta-lactam/beta-lactamase inhibitor group antibiotics, carbapenem and fluoroquinolone group antibiotics, and vancomycin were found to be independent risk factors for GIS VRE colonization (64). The transfer of colonized patients between different units of hospitals or between hospitals leads to the spread of VREs. While VRE colonization rarely results in infection in immune-compromised individuals, the probability of developing infection after colonization is increased in people with hematological disease, organ transplant recipients, and severe disease (65). VRE colonization can continue for weeks, sometimes months. In one study, spontaneous VRE decolonization occurred in only 18 (34%) of 53 patients at the end of three weeks in liver and kidney transplant recipient samples taken at one-week intervals (66). It was reported that (17.9%) developed VRE bacteremia (67). Kamboj et al. (68) found VRE colonization in 27.5% of the patients in their study, including 247 patients who had hematopoietic stem cell transplantation. The same investigators reported that 23 (53.5%) of 43 patients with VRE growth in their blood cultures developed VRE bacteremia in the first 30 days following the transplant, and the mortality that developed in 9% of patients with VRE bacteremia in the first 30 days was directly related to VRE infection. In addition, in this study, age, primary disease, low T cells in the blood, and GIS VRE colonization were found to be directly related to VRE bacteremia (68).

In nosocomial infections and epidemics, the importance and contribution of the microbiology laboratory is great in terms of identifying the agent, determining the antibiotic resistance profile, determining the source and taking the necessary precautions. Especially in recent years, molecular methods,

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which are widely used in rapid diagnosis, contribute to the treatment of patients in a short time (69). Various studies have been conducted comparing classical methods with molecular methods for the detection of VRE. In the study of Marner et al. (70), it was reported that the examination of perianal swab samples with the GeneXpert vanA/vanB PCR method is a fast and reliable method (70). In another study by Jayaratne et al. (71), PCR and conventional culture method for rapid identification of VRE genotype in nosocomial surveillance samples were compared; The specificity, sensitivity, positive and negative predictive value of the PCR method were found to be 99.8%, 95.4%, 98.8% and 99.3%, respectively. In this study, the average cost was calculated as $8.26 for PCR and $9.45 for the phenotypic method; The time required to detect VRE was determined as 48 hours by PCR and 96 hours by conventional method (71). Researchers have stated that PCR can be an alternative to culture for VRE surveillance in laboratories with a heavy routine workload, and they emphasized that it is cost-effective, especially in hospitals where the prevalence of VRE is low (21,72).

SUMMARY / SONUÇ

As a result, knowing the risk factors for the colonization of resistant gram-positive bacteria in hospitals, rational antibiotic practices, taking appropriate contact isolation precautions, applying appropriate disinfection methods, and training health personnel will decrease the infection rates, and both morbidity and mortality due to infections with resistant bacteria and treatment costs will decrease.

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