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Review Article

Methicillin-resistant *Staphylococcus aureus*: An update on the epidemiology, treatment options and infection control

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen in hospitals and the community. In the past, most of the infections caused by MRSA were confined to elderly patients in healthcare facilities and they were described as healthcare-associated MRSA (HA-MRSA). However, the epidemiology of MRSA changed overtime with the emergence of strains in patients with no previous history of hospitalization which were known as community-associated MRSA (CA-MRSA). CA-MRSA strains are more genetically diverse and belong to different clones than HA-MRSA. Some clonal complexes are epidemic and are spread internationally while others are restricted to certain regions. The spread of epidemic MRSA clones globally is of concern since it limits antibiotic options for treating MRSA infections. Vancomycin has remained the drug of choice for the treatment of MRSA infections. However, in recent years the emergence of vancomycin-resistant *S. aureus* (VRSA) has posed additional limits to treat infections caused by MRSA. Consequently, new antibiotics have been developed and licensed for the treatment of MRSA infections. Despite the development of new antibiotics, the battle against resistance continues as long as antibiotics are misused. This requires strict implementation of antibiotic stewardship programs which provide tools and guidelines to help clinicians choose the right antibiotics at the right time for the right duration and that to control antimicrobial resistance.

Contents

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1. Introduction

*Staphylococcus aureus*is a common human opportunistic pathogen which causes a wide range of infections affecting the superficial skin and soft tissue[1,2] as well invasive infections including pneumonia, bloodstream infections, bone and joint infections.[2]

S. aureus also causes toxin-mediated diseases when *S. aureus* toxins are introduced into the bloodstream or ingested through contaminated food. *S. aureus* toxin-mediated diseases include toxic-shock syndrome (TSS), scalded-skin syndrome (SSS) and food poisoning. Toxic-shock syndrome was first recognized in 1978, initially among healthy menstruating women causing it to be referred to as Staphylococcal menstrual TSS,[2,3] and later among non-menstrual related Staphylococcal TSS cases associated with invasive infections such as pneumonia and infective endocarditis.[3] The syndrome is characterized by flu-like symptoms, rash, fever, hypotension, muscle pain, vomiting, diarrhea, confusion, abdominal pain and eventually multiple organ failure.[2] Staphylococcal Scalded-Skin (SSS) syndrome also known as Ritter von Ritterschein disease in newborns is a common infection in children but rare in adults.[4] The syndrome is caused by exfoliative toxin (ET) secreted by *S. aureus*.[4] It is characterized by rash all over the body and peeling off of the skin which resolves within 10 days of treatment.[2] Staphylococcal food poisoning occurs when food contaminated with one or more heat-stable Staphylococcal enterotoxins (SEs) is consumed.[5] SEs reported to cause food poisoning include SEA to SEE, SEG to SEI, SER to SET with SEA and SEB responsible for most cases.[5] Since *S. aureus* is a normal skin flora, contamination of food is usually through direct contact of colonized food handlers with enterotoxin-producing *S. aureus*.[5] Some coagulase-negative Staphylococci also produce SEs and may also be implicated in cases of staphylococcal food poisoning.[6]

1.1. Emergence of methicillin-resistant S. aureus (MRSA)

Penicillin was the first beta-lactam antibiotic developed for the treatment of *S. aureus* infections. Prior to the introduction of penicillin, infections caused by *S. aureus* were usually fatal.[1] However, the introduction of penicillin to treat infections caused by *S. aureus* greatly improved the prognosis of patients with severe staphylococcal infections.[7] However, *S. aureus* strains resistant to penicillin soon appeared following its clinical use.[7]

Penicillin resistance is due to the production, by the bacteria, of penicillinase, which inactivates the antibiotic. Penicillinase hydrolyzes the beta-lactam ring that is central to the antimicrobial activity of these drugs. The emergence of penicillin resistance in *S. aureus* stimulated the development of new antibiotics such as streptomycin, tetracycline, erythromycin, and chloramphenicol in the 1950s.[7] However, as these new antibiotics were developed and put into clinical use, resistance to them also appeared.[7,8] The continuous search for antibiotics active against penicillin-resistant *S. aureus* led to the development of methicillin also known as meticillin or Staphcillin.[9]

Methicillin is a semisynthetic derivative of penicillin developed, in the late 1950s, by a modification of the penicillin structure which conferred resistance to penicillinase.[9] Methicillin kills bacteria by inhibiting bacterial cell-wall synthesis, a mechanism of action similar to that of other penicillins.

The emergence of methicillin-resistant strains of *S. aureus* (MRSA) in the 1960s in the UK rendered the drug clinically ineffective.[10] Methicillin resistance occurs due to the acquisition of *mec*A or *mec*Cgene by previously susceptible strains.[11] The *mec*A gene codes for an altered penicillin-binding protein called penicillin-binding protein-2a (PBP2a) with reduced affinity to the entire beta-lactam class of antibiotics including penicillin, cephalosporin and carbapenems[11] except the recently approved beta-lactams, ceftaroline and ceftobiprole.[12]

MecC gene is a homolog of *mec*A. It was initially designated $mecA_{LGA251}$. It shares 69% nucleotide homology with *mec*A.[11] MRSA isolates carrying *mec*Chave been isolated from human as well as animal hosts.[13] The detection of *mec*C in the diagnostic laboratory can be problematic because although the disk diffusion method using cefoxitin will correctly identify the isolate as MRSA, the *mec*A PCR or PBP2a latex agglutination test fails to detect *mecC*. In sensitivity testing, using bothcefoxitin and oxacillin, *mecA*-MRSA show resistance to both antibiotics whereas the majority of *mec*C-MRSA will express resistance only to cefoxitin.[13] This discrepancy is explained by the observation that PBP2a produced by *mecC* strains have higher affinity to oxacillin than cefoxitin.[13] Although *mecC* carrying MRSA was identified in 2007, a retrospective search of archived collections found *mecC* in isolates collected as early as 1975 indicating that these strains have been around for a long time possibly as long as the *mecA*-MRSA strains.[11] Similar to *mecA*-MRSA, *mecC*-MRSA have a broad host range causing infections in a wide range of animals and humans. In humans, they have been associated with skin and soft tissue infections, severe bone infections, nosocomial pneumonia and fatal bacteremia.[13]

1.2. Types of MRSA

When MRSA strains first occurred, they were usually confined to elderly patients admitted to healthcare facilities especially those with previous antibiotic use. However, over time MRSA strains were also isolated from apparently healthy individuals in the communities with no previous contact with healthcare facilities. These new MRSA strains were designated community- associated MRSA or community- originated MRSA (CA-MRSA).[14] Further studies revealed that CA-MRSA strains could be distinguished from the other MRSA types on the basis of their microbiological, genotypic and epidemiological characteristics. Subsequently, MRSA strains circulating in the healthcare settings and the community were classified as either nosocomial or healthcare-associated MRSA (HA-MRSA) and community- associated MRSA (CA-MRSA).[15] This was followed by a new type of MRSA that arose from animals, designated Livestock-associated MRSA (LA-MRSA) has recently been described.[15]

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