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SUPERBUGS: CHALLENGE TO MEDICINAL CHEMISTRY

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ABSTRACT

Bacteria can cause serious and sometimes life threatening infections. However, bacteria “learn” to resist each new drug, making infections more difficult. Superbugs continue to be a challenge to physicians and health care workers. Studies of the genomes of strains of *Staphylococcus aureus* have provided evidence for the rapid evolution of drug resistance. Healthy adults are vulnerable to antibiotic-resistant infections, but children, seniors, the chronically ill often are particularly susceptible. At the same time, the pipeline of new antibiotics to treat these infections has slowed. The present review states different types of superbugs and preventive measures to it.

KEYWORDS: **Superbugs, *Staphylococcus aureus*, infections, antibiotic resistant.**

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INTRODUCTION

Bacteria can acquire the ability to survive in the presence of drugs that would normally kill them. Bacteria that are no longer susceptible to antibiotics and can survive in the presence of the drug are called antibiotic-resistant[1].Various strains of the same bacteria may be present in an infected person; treatment with an antibiotic kills susceptible but not resistant strains. This leads to the "selection" of resistant strains. In some instances, bacteria can be resistant to multiple drugs; these strains are considered multi-drug resistant (MDR) [2]. MDR bacteria are often referred to as "superbugs". Existing medicines may no longer be effective in treating these infections.

Gram-negative bacteria

Gram-negative bacteria are a source of both community and hospital-acquired infections. Overall, infections caused by Gram-negative bacteria now account for more than[3] percent of common hospital-acquired infections. In addition they are the leading causes of nosocomial pneumonia and UTI s. the structure of the Gram-negative cell wall provides a unique barrier to antibiotics, which are often not able to cross it[4]. The Gram-negative cell wall also contains proteins called efflux pumps, or pore proteins, that push medicines back out of the bacterium before they can have an effect. In addition, some Gram-negative species, such as *Pseudomonas*, are able to form a grouping of bacterial cells called a biofilm. The biofilm provides a further defense against antibiotics[5].

DRUG-RESISTANT GRAM-NEGATIVE INFECTIONS

Resistance is a growing problem with infections caused by gram-negative bacteria, particularly those found in hospital settings[6]. Treatment of these infections varies between species.

Table no.1
Common treatments and mechanisms of resistance

Treatment	Resistance seen	Mechanism of resistance
Beta lactams penicillins cephalosporins carbapenems	*P. aeruginosa* *Enterobacter* *Klebsiella* *Acinetobacter*	Cephalosporinases Extended spectrum-beta lactamases (eSbLs) Carbapenemases
Quinolone/ Fluoroquinolones	*P. aeruginosa* *Acinetobacter*	Mutations in target of antibiotic
Aminoglycosides	*P. aeruginosa* *Acinetobacter*	Modification of aminoglycoside by bacterial

STAPHYLOCOCCUS AUREUS

The *Staphylococcus aureus* is an important cause of sepsis in both community and hospital settings, a major risk factor for which is nasal carriage of the bacterium. Eradication of carriage by topical antibiotics reduces sepsis rates in high-risk individuals, an important strategy for the reduction of nosocomial infection in targeted patient populations. Understanding the mechanisms by which S. aureus adheres to nasal epithelial cells in vivo may lead to alternative methods of decolonization that do not rely on sustained antimicrobial susceptibility[7].

MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. It is also called oxacillin-resistant *Staphylococcus aureus* (ORSA). MRSA is any strain of *Staphylococcus aureus* that has developed, through the process of natural selection, resistance to beta-lactam antibiotics, which include the penicillins

(methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Strains unable to resist these antibiotics are classified as methicillin-sensitive *Staphylococcus aureus*, or MSSA. Healthy individuals have a small but finite risk of contracting an invasive infection caused by *S. aureus*, and this risk is increased among carriers. Hospital patients who are catheterized or who have been treated surgically have a significantly higher rate of infection. *S aureus*, including MRSA, will not normally cause infection unless it enters the body or bloodstream, for example via a cut or a catheter. People with weakened immune systems, the very old or young, and those who are ill are more susceptible to such infections. MRSA can cause a range of infections including of the skin, lungs and bloodstream (this latter is also known as bacteraemia). In a health care setting, MRSA can enter the body or bloodstream in a variety of ways, such as: during surgery via wounds or ulcers via intravenous lines, catheters or breathing tubes. In MRSA, the horizontally acquired *mecA* gene encodes a penicillin-binding protein, PBP2a, which is intrinsically insensitive to methicillin and all β-lactams that have been developed, including the isoxazoyl penicillins (e.g., oxacillin) that superceded methicillin, in addition to the broad spectrum β-lactams (third-generation cephalosporins, cefamycins, and carbapenems) that were introduced primarily to treat infections caused by Gram-negative bacteria[8] (Fig.1).

S. aureus acquires resistance to methicillin and its ability to express different virulence factors

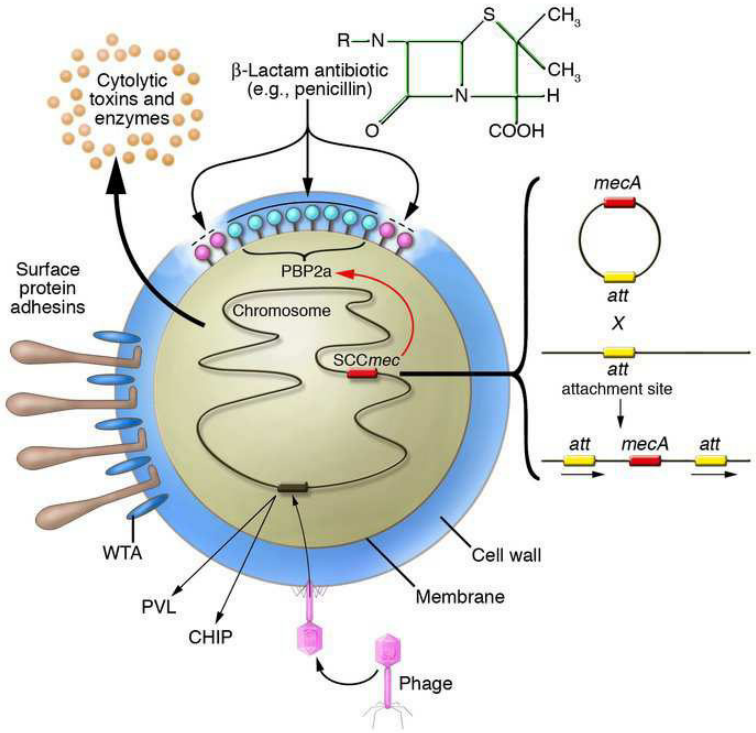

Figure 1: ***Schematic diagram illustrating how S. aureus acquires resistance to methicillin and its ability to express different virulence factors. The bacterium expresses surface protein adhesins and WTA and also secretes many toxins and enzymes by activation of chromosomal genes. Adhesins and WTA have been implicated in nasal and skin colonization. Resistance to methicillin is acquired by insertion of a horizontally transferred DNA element called SCCmec.***

CA-MRSA[9]

Community-acquired MRSA (CA-MRSA)strains are susceptible to drugs other than β-lactams. CA- MRSA symptoms are Most often causes skin and soft tissue infections: cellulitis, boils, or furuncles often in the thighs and buttocks. It

looks like a red, warm, painful boil May look like a "spider bite." Children may present with a severe pneumonia. More serious infections of the blood stream, joint, bone[10].

HEALTHCARE-ASSOCIATED INFECTIONS

Healthcare-associated infections are infections that are acquired in a hospital or other health care setting, such as a hospice or care home, or as a result of a health care intervention or procedure. Healthcare MRSA First recognized in the 1970's causing outbreaks in healthcare settings. Generally it is resistant to most common antibiotics. The increased chances for HCA-MRSA are Long hospital stay Care in an intensive care unit, Long use of antibiotics, Surgical procedures[10]. There are many different types of healthcare-associated infections. These include infections caused by methicillin-resistant *Staphylococcus aureus* (*S aureus,* MRSA) and *Clostridium difficile* (*C difficile*), as well as other less well-known infective agents such as: glycopeptide-resistant enterococci, which can cause blood poisoning; norovirus, which causes a relatively mild, short-lived gastroenteritis but spreads easily in hospitals and other institutional environments sometimes leading to ward closures; the various *Pseudomonas* species, which can cause a range of illnesses in those who are already very ill, but are not as easily spread as MRSA or *C difficile*

CLOSTRIDIUM DIFFICILE

Clostridium difficile – C Diff for short – is fast emerging as a health threat rivaling and perhaps surpassing the severe staph infection, MRSA, in frequency and severity. First discovered in the 1970s as a cause of diarrhea in hospitalized patients requiring antibiotics. Many patients get C Diff infections as an unintended consequence of taking antibiotics for other illnesses. "Good" bacteria, normally found in a person's intestines, help keep C Diff under control, allowing the bug to live in the gut without causing illness. But when a person takes antibiotics, both good and bad bacteria are suppressed, allowing C Diff to grow out of control, since C Diff is resistant to most antibiotics that are used to treat common infections. Additionally, a new strain of C Diff has emerged, NAP/0127, which produces a more severe colon infection[11].

NDM-1

NDM-1 is a Metallo Beta-Lactamase essentially found in *Enterobacteriaceae* (principally *E. coli* and *K. pneumoniae*). NDM-1 stands for New Delhi Metallo-beta-lactamase-1, since it was first identified in a Swedish patient of Indian origin, who had been admitted to a hospital in New Delhi, India in 2008. The NDM-1 gene produces an enzyme which makes bacteria resistant to almost all ß-lactams, including carbapenems (imipenem, meropenem, ertapenem, doripenem). Carbapenems are powerful, broad-spectrum antibiotics, which are often considered to be the last line of defense against multi-resistant strains of bacteria, such as *E. coli* and *K. pneumonia.*The gene for NDM-1 is found on plasmids (DNA strands), which can easily spread from one strain of bacteria to another, particularly in patients receiving antibiotic treatment[12].

DIAGNOSIS[13]

Diagnostic microbiology laboratories and reference laboratories are key for identifying outbreaks of MRSA. New rapid techniques for the identification and characterization of MRSA have been developed. This notwithstanding, the bacterium generally must be cultured via blood, urine, sputum, or other body fluid cultures, and cultured in the lab in sufficient quantities to perform these confirmatory tests first. Consequently, there is no quick and easy method to diagnose a MRSA infection. Therefore, initial treatment is often based upon 'strong suspicion' by the treating physician, since any delay in treating this type of infection can have fatal consequences. These techniques include Real-time PCR and Quantitative PCR and are increasingly being employed in clinical laboratories for the rapid detection and identification of MRSA strains. Another common laboratory test is a rapid latex agglutination test that detects the PBP2a protein. PBP2a is a variant penicillin-binding protein that imparts the ability of S. aureus to be resistant to oxacillin.

TREATMENT

Both CA-MRSA and HA-MRSA are resistant to traditional anti-staphylococcal beta-lactam antibiotics, such as cephalexin. CA-MRSA has a greater spectrum of antimicrobial susceptibility, including to sulfa drugs (like co-trimoxazole/trimethoprim-sulfamethoxazole), tetracyclines (like doxycycline and minocycline) and clindamycin, but the drug of choice for treating CA-MRSA is now believed to be vancomycin, according to a Henry Ford Hospital Study. HA-MRSA is resistant even to these antibiotics and often is susceptible only to vancomycin. Newer drugs, such as linezolid (belonging to the newer oxazolidinones class) and daptomycin, are effective against both CA-MRSA and HA-MRSA. Linezolid is now felt to be the best drug for treating patients with MRSA pneumonia. Ceftaroline and ceftabiparole, new fifth generation cephalosporins, are the first beta-lactam antibiotics approved in the US to treat MRSA infections (skin and soft tissue only).[13] Vancomycin and teicoplanin are glycopeptide antibiotics used to treat MRSA infections[14].Teicoplanin is a structural congener of vancomycin that has a similar activity spectrum but a longer half-life. Because the oral absorption of vancomycin and teicoplanin is very low, these agents must be administered intravenously to control systemic infections[15].Treatment of MRSA infection with vancomycin can be complicated, due to its inconvenient route of administration. Moreover, many clinicians believe that the efficacy of vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against methicillin-susceptible *Staphylococcus aureus* (MSSA).[16] Several newly discovered strains of MRSA show antibiotic resistance even to vancomycin and teicoplanin. These new evolutions of the MRSA bacterium have been dubbed Vancomycin intermediate-resistant *Staphylococcus aureus* (VISA)[17]. Linezolid, quinupristin/dalfopristin, daptomycin, ceftaroline, and tigecycline are used to treat more severe infections that do not respond to glycopeptides such as vancomycin[13]. The psychedelic mushroom *Psilocybe semilanceata* has been shown to strongly inhibit the growth of *Staphylococcus aureus*[18].

INFECTION PREVENTION

Although infection prevention can be surprisingly simple, it must be done without fail precisely because the stakes are high and the problems are complex. According to Peter Pronovost, M.D., a “ruthlessly simple” five-step checklist developed by his Johns Hopkins University team includes: washing hands with soap, wearing sterile gowns and gloves, cleaning the patient with an antiseptic, using sterile drapes, applying sterile dressings. Special attention to cleaning the environmental surfaces and equipment should also be part of infection prevention strategies. Private rooms are also suggested for infected patients. If a private room is not available, cohorting patients with similar infections and cohorting their care givers is suggested. Infection Control Precautions fall into different categories depending on the identified infection. However, protecting the patient by preventing spread of any potential bug, known or unknown, is the goal. Infection Prevention Specialists can assign a particular precaution when warranted as a notice to health care workers, family and visitors. Personal protective equipment should be provided as needed. Standard Precautions are used for all patient care contact, and includes thorough hand hygiene (washing your hands with soap and water or using alcohol hand rubs) and the use of gloves to control infection. Gowns, masks and eye protection are also recommended when a splash of body secretions is possible. Hand hygiene and personal protective equipment changes are recommended for care givers whenever they move between patients, and even when they perform procedures on the same patient to different areas of the body. Contact Precautions are intended to prevent transmission of particular infectious agents, including Multi-Drug Resistant Organisms (MDROs) that are transmitted by direct or indirect contact with the patient or the patient’s environment. In addition to Standard Precautions, wearing a gown and gloves upon entering the room and removal of the items before leaving the room is recommended. Using private rooms, avoiding sharing of equipment and having the patient stay in the room, are all strategies used with Contact

Precautions. Masks and eye protection may also be required for splash potential. Droplet and Respiratory Precautions are also implemented for airborne infections when warranted. The majority of health-care associated infections can be prevented by utilizing appropriate hand hygiene. Health care consumers are encouraged to insist that their health care providers wash their hands and use gloves[19]. In most patients, MRSA can be detected by swabbing the nostrils and isolating the bacteria found inside. Combined with extra sanitary measures for those in contact with infected patients, screening patients admitted to hospitals has been found to be effective in minimizing the spread of MRSA in hospitals in the United States, Denmark, Finland, and the Netherlands[20].The problems caused by the development of antibiotic-resistant *S. aureus*, vaccination may well have a significant role to play in controlling this organism in the future. A number of companies are developing products intended for active or passive immunization against *S. aureus* infections, including a capsular polysaccharide vaccine that has been subjected to a clinical trial[8].

CONCLUSION

As resistance in several Gram-negative species, such as *P. aeruginosa*, becomes more prevalent, doctors are turning to older treatments since few other options exist. The new and safer agents are needed to treat these infections, but novel agents that work in different ways than existing medicines are necessary to prevent cross-resistance to drugs in the same class. It is necessary to take into account the problems related to Superbugs and the increasing importance of cleaning and infection control work.

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