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Methicillin Resistance to Staphylococcus Aureus: mechanism, virulence factors and treatment

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ABSTRACT

The invention of antibiotics is one of the most significant medical advancements in the treatment of infectious illnesses caused by pathogenic microorganisms. In 1928, Alexander Fleming made an unintentional discovery of penicillin.S. aureus, a gram-positive bacteriumbelonging to the family Microccaceae. This species give rise to a wide range of illnesses, including mastitis, pneumonia, skin infections, bacteraemia and osteomyelitis.MRSA is recognised as a historically potential zoonoticdisease (infection that are naturally spread between human and animals)which have involvement in both veterinary medicine and public health. Infected staphylococci express the PCIβ-lactamase enzyme can hydrolyseβ-lactamring. This reduces the activity of antibiotics.

Keywords: Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus, Pulse Field Gel Electrophoresis, Impetigo

I. INTRODUCTION

The invention of antibiotics major medical advancementfor the treatment of infectious illnesses caused by pathogenic microorganisms. Prior to the development of antibiotics, pathogenic microorganisms caused a considerable amount of death and morbidity. [4,6] In 1928, Alexander Fleming made a second unintentional discovery of penicillin.This rediscovery opens the door to further research into antibiotic classes, such as aminoglycosides, lipopeptides, sulphonamides, fluoroquinolones, and many more. [5,6]

1.1Staphylococcus Aureus

S.aureus is coccoid bacterium that is nonmotile, coagulase positive and gram positive belonging to family Micrococceae.

Its cells are usually found singly or, in the event that they divide, in pairs, tetrads, and unusual irregular forms that resemble grapes.S. aureus frequently colonises the outer skin surfaces of humans as well as the upper respiratory system, especially the nasal passages. [1,2]

20-40% of the general population carries human commensal bacteria in their nasal mucosa, including S. aureus. But bacteria is an opportunist pathogen which have the ability to produce more serious infection in the correct conditions. [3,4] S. aureus frequently invades burns and surgical site infections. When S. aureus produces toxins, it can cause toxic shock syndrome, which can result in fever, illness, and occasionally even death. S. aureus can cause a number of infections, including pneumonia (lung inflammation), mastitis (mammary gland infection), infections of the skin (including cellulitis, impetigo, and staphylococcal scalded skin syndrome), osteomyelitis (bone infection), endocarditis (heart and valve endothelial infection), and bacteremia (blood-borne bacteria).[1]. Due of the synthesis of enterotoxins, S. aureus can potentially result in food poisoning.[1]

1.2MRSA

Methicillin resistant Staphylococcus aureus (MRSA) is recognised as a historically potential zoonotic disease (infection that are spread between human and animal) which have involvement in both veterinary medicine and public health. MRSA is not only a nosocomial bacterium but also a major reason for community associated

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infections (CA- MRSA) and healthcareassociated infections (HA- MRSA).

II. MECHANISM OF MRSA

Beta-lactam antibiotics continue to be productive against S. aureus bacteria. Intrinsic penicillin binding protein 2a enzymecan bind to beta-lactam antibiotics.[7,8,9]. Staphylococci that are infected with MRSA show PCIbeta lactamase enzyme can hydrolyse the beta lactam ring. This can reduce the activity of antibiotics and it bring about the encrypting the gene modified penicillin binding protein, which is called PBP2a.[7,10]Because PBP2a detritus neutralises PBP enzymes, this enables beta lactam antibiotics to help in cell wall synthesis.

This helps explain how β-lactam antibiotics proliferate. (fig. 1) [7]

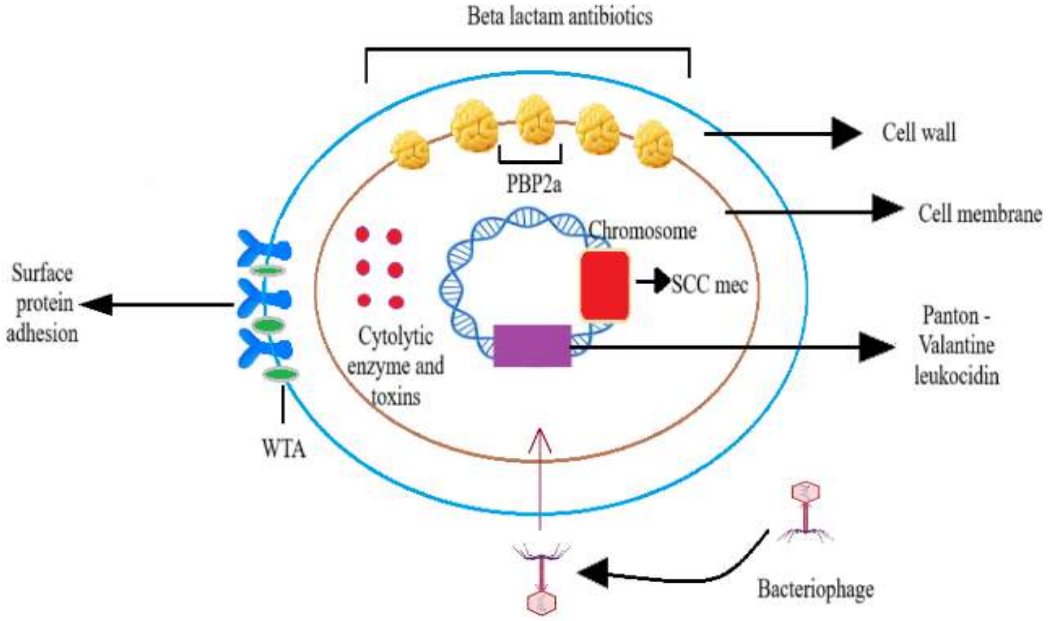

fig. 1: The process by which methicillin resistance in S. aureus evolves.[7]

III. VIRULENCEFACTORS

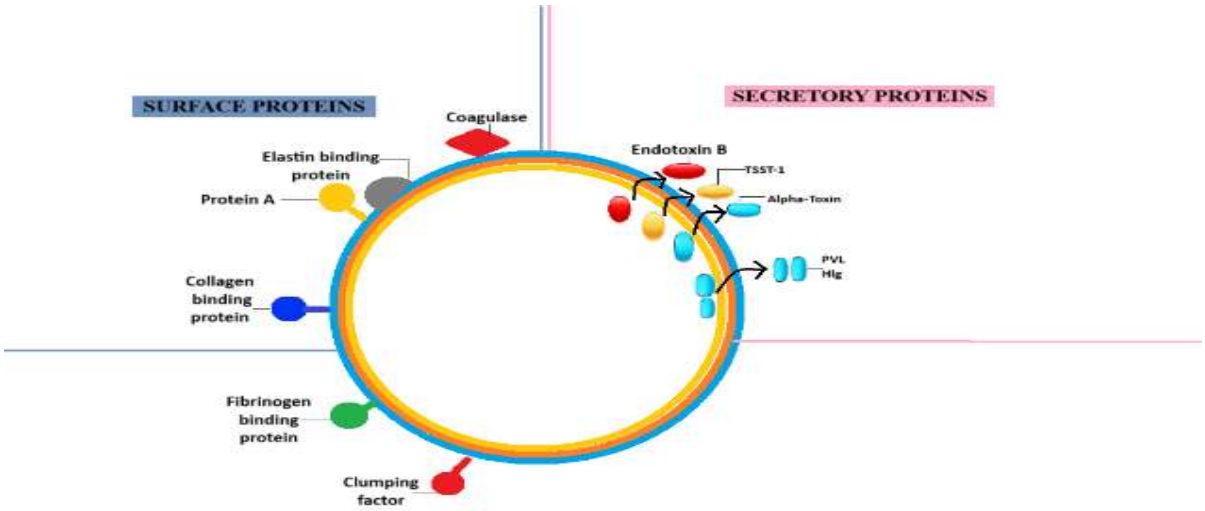

Fig 2: Virulence factors

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3.1 Capsular Polysaccharides

Capsular polysaccharides, found in MRSA, envelope its cell wall. About 76-90% of MRSA strains produce these, with 11 different types known (CP 1-CP11). They boost S. aureus virulence by blocking complement and antibody opsonization, as well as inhibiting phagocytosis.[11-14]

3.2 Surface Associated Proteins

3.2.1 S. Protein-A

S. protein A, mainly help in cell wall formation in Staphylococcus that's mainly used to circulate IgG, and helps the microbes from cell eating.[11,15,16]

3.2.2 Clumping Factors

Fibrinogen is the main part on the host. S. aureus will bind to this fibrinogen by the help of clumping factors that are mainly seen on MRSA cells. The different clumping factor protiens are, clumping factor A and B.[11,17-20]

3.3 Extracellular Toxins

3.3.1 Staphylococcal Hemolysins

A major virulence factor is alpha toxin that is in connection with cell death of mammary gland and high death rate in animals which are infected. Methicillin resistant Staphylococcus aureus strains also include beta, gamma, and delta toxins. The main cause of food poisoning in people and animals is enterotoxins generated by MRSA. [11,21-26]

3.3.2 S. aureus Enterotoxins

S. aureus endotoxins are categorised as type A, type B, type C, type D & type E. S. aureus superantigens that are mainly linked to human food poisoning, most notable SEA. [11,27,28]As superantigens, these toxins can increase the gene expression of Interleukin 4 & Interleukin 10, which in turn activates TH2 cells and inhibits the removal of pathogens. The blood-brain barrier can be broken down by MRSA's panton-valentine leukocidin, which can seriously harm human polymorphonuclear cell membranes.[11,29-31]

3.3.3 Panton-Valentine Leukocidin

The powerful staphylococcal exotoxin panton-valentine leukocidin (PVL) is made possible by the F and S classes of secretory proteins. In humans, PVL causes harm to polymorphonuclear cells' plasma membrane and causes basophils to emit histamine, interleukin 8, oxygen metabolites, and lysozymes. When PVL is injected into rabbits, it causes necrotic lesions, leukocytic infiltration, basophil degranulation, and complicated inflammatory reactions. There are two components of panton valentine leucocidin- S & F.Toxin release occurs when these genes are transferred to PVL-negative strains by bacteriophages, like fSLT.[11,32]

3.4 Extracellular Enzymes

3.4.1 Staphylococcal Coagulase

Staphylococcal coagulase, initially discovered in 1903, causes human plasma to coagulate by releasing the Coa enzyme. This chromosomally encoded enzyme is capable of coagulating plasma of humans and rabbits.[11,21,22]

3.4.2 Staphylokinase

It is a protein produced by S. aureus. Which can increase the activity of plasminogen, resulting in fibrin clot breakup and bacterial growth. Lysogenic MRSA strains and certain prophages, such as serotypes B and F phages, release it. Staphylokinase is predominantly species-specific, active in goat (Capra aegagnushircus), sheep (Ovis aries), and plasma of human and it is inactive in buffalo (Bubalina) and plasma of mouse(Mus musculus) . One advantage is that it reduces biofilm formation, therefore MRSA strains that produce staphylokinase build less biofilms invitro or during non-invasive human infections. [11,22,34,35]

3.4.3 Staphylococcal hyaluronidase

Staphylococcal hyaluronidase, also known as "spreading factor," degrades hyaluronicacid, a polysaccharide that is essential for the integrity of mammalian cells and tissues as well as host immunological control. Hyaluronidase converts hyaluronic acid into disaccharides, which aids bacterial spread in both extracellular matrix and biofilms.[11,22-29]

IV. TREATMENT OF MRSA

4.1 Impetigo

To avoid antimicrobial resistance, consider using hydrogen peroxide 1% cream instead of fusidic acid or mupirocin to treat MRSA impetigo while patient is therapeutically alright. For secondary treatment, fusidic acid or mupirocin can be considered. Based on the results of susceptibility testing, treat complex impetigo with systemic antibiotic therapy.[36]

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4.2Abscesses

Use incision and drainage as the primary treatment (strong suggestion). Avoid routine antibiotic usage for drained MRSA abscesses with a diameter of less than 5 cm and no systemic symptoms or immunosuppression (strong recommendation). Antibiotics should be administered with a cut or withdrawal of fluids for abcessesdue to strain USA300 of MRSA PFGE (pulse field gel electrophoresis)which is highly suggested. Clindamycin or Cotrimoxzole can be used in case of oral treatment.[36]

4.3 Skin Infections

4.3.1 Cellulitis:

- Vancomycin i.v as the primary treatment.
- Daptomycin i.v, linezolid oral or i.v used as alternatives.

4.3.2 mild skin infection:

- Clindamycin, cotrimoxazole, doxycycline as oral treatment.
- Ceftaroline, delafloxacin, oritavancin and telvancin as substitute.[36]

4.4 Urinary Tract Infection

4.4.1 Before treatment:

Before starting treatment for MRSA isolated from urine, ensure there is no MRSA bacteremia (weak recommendation).

4.4.2 Lower UTI:

Lower UTI due to MRSA can be treated with doxycycline, ciprofloxacin or cotrimoxazole orally.

4.4.3 Complicated UTI:

- In case of complicated UTI vancomycin i.v can be suggested.
- Daptomycin can be considered as an alternative if glycopeptides are contraindicated.
- Linezolid isn't recommendation due to poor kidney excretion.

4.4.4 Catheter-associated UTI:

The possible option is to replace the catheter.[36]

4.5 Joints and Bone Infection

- Surgery can be done if necessary.
- For MRSA infections, the primary treatment is intravenous glycopeptides (vancomycin or teicoplanin).
- Consider a treatment plan consisting of 2 weeks of intravenous glycopeptides then orally or i.v antibiotics can be used for around 4 weeks in case of septic arthritis and around 6 weeks in case of osteomyelitis.[36]

4.6 Bacteraemia

- Intravenous vancomycin is suggested for simple MRSA bacteraemia.
- If vancomycin is ineffective, linezolid is recommended as an alternate first-line therapy.
- If first-line treatments are not effective, daptomycin or teicoplanin can be considered.
- Co-trimoxazole should not be considered for treatment.
- 14 days of continuous antibiotic required for uncomplicated bacteraemia but in complicated stage, 28 days of treatment is required.[36]

4.7 Necrotizing Pneumonia

- For MRSA-related illnesses, intravenous vancomycin or linezolid is strongly recommended.
- If the MRSA isolate is sensitive, consider adding clindamycin or rifampicin, albeit this advice is regarded weak.[36]

4.8 ENT and upper respiratory tract infection

- In extreme cases, vancomycin in i.v form or linezolid can be reccomended
- Co-trimoxazole or doxycycline can be used orally for small or less severe infections.[36]

4.9 Spinal Infection

- Antibiotics alone may be taken into consideration for treating minor epidural abscesses in situations without neurological impairments, albeit this advice is not strong.
- Although this advice is also regarded as poor, take into consideration intravenous vancomycin or linezolid as the main therapeutic options for MRSA-caused intracranial and spinal infections.
- It is highly advised to use intravenous vancomycin for meningitis caused by MRSA. Based on susceptibility, rifampicin may be taken into consideration for severe infections; nevertheless, this suggestion is not strong.
- To guarantee that serum concentrations of vancomycin (15–20 mg/L) are acceptable, therapeutic drug monitoring is highly advised.[36]

4.10Meningitis

It is highly advised to transfer the patient to a neurosurgical centre for direct ventricular instillation of vancomycin in severe cases or if the patient does not react to intravenous vancomycin. It is strongly advised against treating MRSA

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meningitis using clindamycin, chloramphenicol, or linezolid due to their lack of bactericidal activity.
At this time, there is no advice for the use of teicoplanin in this particular clinical situation.[36]

4.11Eye Infection

- In sensitive cases, gentamycin or chloramphenicol eye drops are highly suggested.
- When diagnosing MRSA-induced endophthalmitis, consider bacteraemia-related dissemination.
- For deep-seated eye infections, based on the sensitivity drugs can be selected like intravitreal vancomycin and systemic quinolones.[36]

V. CONCLUSION

MRSA is not just a nosocomial bacterium,also it is major reason for community-acquired infections and hospital – acquired infections. Many virulence factors have been identified which include capsular polysaccharides, surface associated proteins, extracellular toxins, extracellular enzymes. Many treatment options also identified which include Hydrogen Peroxide 1% cream for impetigo by cut or withdrawal of fluids are considered as the major treatment for abscesses, Use intravenous glycopeptides for skin infections. Consider using gentamicin or chloramphenicol eye drops for eye infection.

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