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Mini Review

Staphylococcus aureus: A brief review

Microbiology

Staphylococcus aureus, also known as “golden staph”, is a gram-positive coccus belonging to the class Bacilli, order Bacillales, family *Staphylococcaceae* and genus *Staphylococcus* [1]. It is a facultative anaerobe often positive for catalase and nitrate reduction and is coagulase variable i.e. maybe coagulase positive or negative [2]. The bacterium is non-motile, non-spore forming and appearing as bunch of grapes, microscopically. On blood agar it shows large, round, golden-yellow colonies often with hemolysis.

Epizootiology and public health significance

Reservoir: *Staphylococcus* species are present worldwide. *S. aureus* is a ubiquitous organism colonizing the upper respiratory, gastrointestinal and urogenital tracts of about 20% to 30% humans, which act as long-term carriers [3]. Healthy food animals serve as reservoir [4]. *S. aureus* colonizes the skin of animals including the skin of teat and teat canal [5].

Modes of transmission and virulence factors

Due to its ability to colonize a wide range of species (all mammals including rodents and lagomorphs), *S. aureus* can readily be transmitted from one species to another; from humans to animals and reverse. Staphylococcal infections are zoonotic in nature. They can be transmitted from animals to humans through contamination of skin lesions while in contact with the animals having skin infections or the carrier animals, working with tissue or bones from infected animals and from bites and scratches [3]. From healthy food animals they may spread to a wide variety of food items and cause food poisoning [4].

The bacteria can spread from person to person by direct contact and also with the contaminated objects (such mobile

phones, telephones, door handles, tap faucets, computer keyboards and mouse, knife, currency, medical equipments, etc). There is even a possibility of transmission by inhalation of infected droplets which are dispersed at the time of sneezing or coughing [6].

Contaminated hands of milker and contaminated milking equipments are also responsible for transmission of the organism between animals [7]. Owing to its virulence factors like hyaluronidase, protease, lipase, nuclease which aids in bacterial penetration; coagulase which converts fibrinogen to fibrin; Clumping factors (Clf A); fibrinogen binding proteins (Fnbp A); Protein A which evades opsonization and phagocytosis; Pantone-Valentine leucocidin (PVL) responsible for tissue necrosis; Staphylococcal Enterotoxin (SE) A to SEE and SEG to SEU; Exfoliative toxin (A & B); Toxic shock syndrome toxin-1 (TSST-1); alpha and beta haemolysins *S. aureus* exhibits wide range of diseases [8-10]. It causes diseases ranging from minor skin infections to life threatening conditions such as bacteremia, endocarditis, necrotizing pneumonia, toxic shock syndrome, necrotizing fasciitis, necrotizing pneumonia, bone and joint infections accompanied by septic thromboembolic disease, purpura fulminans with or without Waterhouse-Friderichsen syndrome, orbital cellulitis and endophthalmitis, infections of the central nervous system owing to various virulent factors [11]. *Staphylococcus aureus* causes severe animal diseases; such as suppurative disease, mastitis, arthritis and urinary tract infections owing to the virulence factors, such as the production of extracellular toxins and enzymes [12].

In bovines, it can cause mastitis with moderate to serious local and systemic signs. It often causes subclinical mastitis, which remains persistent. Per acute and gangrenous forms are associated with severe systemic reactions. Alpha toxin produced by the bacterium is responsible for tissue necrosis by impeding the blood flow to the quarter and causing the release of lysosomal enzymes from leukocytes. Somatic cell count increases substantially in *Staphylococcal aureus* mastitis deteriorating the quality of milk [13].

Treatment and development of antibiotic resistance

β -lactam antibiotics are the first-line treatment for Staphylococcal infections. Alternative, drugs are available for treatment but with limitations such as less tissue penetration

and efficiency for vancomycin; cost for quinupristin - dalbopristin, tigecycline, daptomycin and linezolid and toxicity for rifampin [14].

Development of resistance to antibiotics has become a global issue and *S. aureus* owing to the selective pressure imposed by antimicrobials has the capability of developing resistance to drugs with more rapidity [15]. The resistance is chromosome or plasmid mediated and is attributed to transduction, transformation and conjugation [16].

blaZ gene in the organism mediates the resistance to β -lactam antibiotics *i.e.* penicillin and its derivatives (Oslen *et al* 2006). *mecA* gene which encodes the Phosphate binding protein which may have an altered binding capacity or new PBP (PBP2') may be responsible for resistance to methicillin and other β -lactam antibiotics. There are some strains which are named as Boderline Oxacillin resistant *S. aureus* (BORSA). These strains are β -lactamase hyperproducers and show resistance to Oxacillin in absence of *mecA* or *mecC* [16]. Aminoglycosidal resistance may arise because of the mutations in the genes regulating the ribosome leading to the structural changes in the ribosomal proteins which may hinder the binding capacity of the antibiotic and further its action. Diminished uptake of the antibiotic or modification of antibiotic due to the cellular enzymes such as aminoglycoside acetyltransferases (AAC) or aminoglycoside phosphotransferases (APH) catalyzed by a bifunctional protein encoded by *aacA-aphD* gene may also be responsible for the aminoglycoside resistance [17,18]. Tetracycline resistance is due to *tetK* and *tetL* genes that are located on the plasmid. These genes control the active efflux. The ribosomal protection is mediated by *tetO* or *tetM* genes present on transposon or chromosome [19]. Vancomycin intermediate resistance is due to *vraSR* operon [20] and *graS* gene [21]. Acquisition of *Enterococci vanA* gene may lead to development of VRSA (Vancomycin resistant *S. aureus*). Altered peptidoglycan synthesis on exposure to Vancomycin may lead to an increase in the thickness of cell wall thus impairing the diffusion of drug into the bacterial cell [22]. Inducible resistance to macrolide antibiotic is commonly due to *ermC* gene present on the plasmid [23]. Resistance mediated by *ermA* gene can be due to chromosomal mutations [24]. Constitutive resistance is mediated by *ermB* gene on plasmid. Less commonly *msrA*, *msrB*, *mphC*, *lnuA* genes are associated with resistance to this antibiotic

S. aureus can be categorized as Methicillin susceptible *S. aureus* (MSSA) or Methicillin resistant *S. aureus* (MRSA). As per Clinical and Laboratory Standards Institute (CLSI), MRSA are those isolates which have minimum inhibitory concentration (MIC) ≥ 4 $\mu\text{g/mL}$ for methicillin.

Global scenario: molecular epidemiology of MRSA isolates with special Reference to India

The global prevalence of MRSA in human infections is quite high. It has been reported as 40% in southern Europe and less than 1% in northern Europe. In Asian countries the prevalence rates in hospitals has been found as 41% in India, 42% in Pakistan, 18% in Philippines, 38% in Malaysia, 50% to 70% in Korea, 53% to 83% in Taiwan and 70% in Hong Kong

and Japan. According to a report from Australian Group of Antimicrobial Resistance, the prevalence of MRSA in Australia was 31 per cent [25].

Chatterjee *et al.* [26], showed in his study that 3.89% of children of an Indian community setting were MRSA carriers. In Delhi, 18.1% of healthy parents attending a well-baby clinic were shown to be MRSA carriers [27]. According to a survey conducted in the hospitals in India by INSAR (Indian Network for surveillance) in 2008–2009, the overall prevalence of MRSA in India was 41%. Incidence reported from hospitals from western parts of India was 25% whereas from south India it was fifty percent [28]. In a study on clinical specimens (pus, urine, blood etc.) in Amritsar (north India) in 2008–2009, the prevalence of MRSA was reported as 46% [28]. In another study carried out in the neonatal intensive care unit in Amritsar, the rate of MRSA in blood cultures was 57.3% [29].

According to CDC [30], in Odisha, eastern India; out of the 47 nosocomial isolates of *S. aureus*, 28 (60%) were resistant to oxacillin and cefoxitin. Two MRSA isolates were highly resistant to vancomycin and linezolid. PCR amplification of both isolates indicated presence of all 3 genetic determinants: *mecA* (methicillin resistance), *cfr* (linezolid resistance), and *vanA* (vancomycin resistance).

In a hospital located in eastern Uttar Pradesh, 54.8% of the *S. aureus* isolates were reported as MRSA. These isolates were also resistant to multiple antibiotics: over 80% were resistant to penicillin, cotrimoxazole, ciprofloxacin, gentamicin, erythromycin and tetracycline [31].

The issue of antibiotic resistance is increasing and taking its toll [32]. Emergence of antibiotic resistance can be attributed to its sub therapeutic usage for growth promotion and disease prevention leading to the evolution of resistant microorganisms. MRSA associated infections are reported worldwide. Mixing of the population due to international travel or contact with infected person/food/fomites facilitate transmission of resistant strains to susceptible population [33]. So it is important to track transmission of these antibiotic resistant isolates for formulating mitigation strategies [34].

Researchers around the world are involved in tracking the presence and transfer of isolates in different regions using various techniques some examples being Pulse Field Gel Electrophoresis (PFGE), Polymerase Chain Reaction (PCR), Multilocus Sequence Typing (MLST), Multilocus variable number tandem repeat analysis (MLVA), bacteriophage typing, Staphylococcal Protein A (*spa*) locus typing and Staphylococcal Clonal Complex *mec* (SCC*mec*) typing.

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