Impact of Staphylococcus aureus on Pathogenesis in Polymicrobial Infections

Nisha Nair,a Raja Biswas,a Friedrich Götz,b Lalitha Biswasa

Amrita Center for Nanosciences and Molecular Medicine, Amrita Institute of Medical Sciences, AIMS—Edapally, Cochin, Kerala, Indiaa; Microbial Genetics, Interfaculty Institute for Microbiology and Infection Medicine Tübingen (IMIT), University of Tübingen, Tübingen, Germanyb

Polymicrobial infections involving Staphylococcus aureus exhibit enhanced disease severity and morbidity. We reviewed the nature of polymicrobial interactions between S. aureus and other bacterial, fungal, and viral cocolonizers. Microbes that were frequently recovered from the infection site with S. aureus are Haemophilus influenzae, Enterococcus faecalis, Pseudomonas aeruginosa, Streptococcus pneumoniae, Corynebacterium sp., Lactobacillus sp., Candida albicans, and influenza virus. Detailed analyses of several in vitro and in vivo observations demonstrate that S. aureus exhibits cooperative relations with C. albicans, E. faecalis, H. influenzae, and influenza virus and competitive relations with P. aeruginosa, Streptococcus pneumoniae, Lactobacillus sp., and Corynebacterium sp. Interactions of both types influence changes in S. aureus that alter its characteristics in terms of colony formation, protein expression, pathogenicity, and antibiotic susceptibility.

Staphylococcus aureus is an opportunistic and resilient human pathogen that colonizes the mucosal surfaces. It is the causative agent of many serious acute and chronic infections. The anterior nares are the primary reservoirs of S. aureus. Asymptomatic colonization occurs in approximately 20% of the normal population, and 60% are transiently colonized, while 20% appear to be rarely or never colonized (1). Extranasal colonization of S. aureus also takes place in several locations, including the skin, rectum, axillae, vagina, pharynx, and gastrointestinal tract (2).

S. aureus causes numerous infections, including skin infections (boils, furuncles, styes, impetigo), surgical and trauma wounds, urinary tract infections, gastrointestinal tract infections, pneumonia, osteomyelitis, endocarditis, thrombophlebitis, mastitis, meningitis, infections on indwelling medical devices, toxic shock syndrome (TSS), and septicemia (3, 4). The factors contributing to the rise of this organism as a formidable pathogen involve multiple mechanisms of virulence. These include the evolution of strategies to resist antibiotics and evade host defenses, as well as the production of an arsenal of virulence factors such as capsule, coagulase, lipase, hyaluronidase, protein A, fibrinogen binding proteins, fibronectin binding proteins, and secreted toxins such as secreted enterotoxins (SEs), toxic shock syndrome toxin-1 (TSST-1), Panton-Valentine leucocidin (PVL), hemolysins, and phenol-soluble modulins (PSM) (5–9).

Several studies have confirmed S. aureus as one of the coinfecting microbes in many patients with polymicrobial infections (10). The interactions between S. aureus and the coexisting microbes are either cooperative, as with Candida albicans (11–14), Enterococcus faecalis (15, 16), Haemophilus influenzae (17–19), and influenza virus (20, 21), or competitive, as with Pseudomonas aeruginosa, Streptococcus pneumoniae (18, 19), Lactobacillus sp. (22–27), and Corynebacterium sp. (17, 28–30). Irrespective of whether the interactions are cooperative (Fig. 1) or competitive (Fig. 2), S. aureus within a community behaves differently with respect to its monomicrobial growth. This article focuses on reviewing the significance of interactions between S. aureus and other microorganisms and its effect on disease progression and outcome.

Interactions with Candida. Both Candida species and S. aureus usually exist as commensals and colonize human mucosal surfaces. Furthermore, they are opportunistic pathogens and cause a wide range of infections such as sepsis, pneumonia, detergent stomatitis, and neonatal sepsis. Despite causing a number of infections independently, C. albicans and S. aureus can also be coisolated from several diseases such as cystic fibrosis, superinfection of burn wounds, urinary tract infections, and diabetic foot wounds and from the surfaces of various biomaterials, including dentures, voice prostheses, implants, endotracheal tubes, feeding tubes, and catheters (31–34).

Biofilm-embedded microbes are extremely resistant to both host clearance mechanisms and antimicrobial agents. S. aureus and C. albicans are often isolated concurrently from mixed bacterial-fungal biofilms on implanted medical devices (35). During biofilm-associated coinfections, C. albicans forms the base of the biofilm and facilitates the biofilm formation of S. aureus. C. albicans hyphal protein agglutinin-like sequence 3 (Als3p) mediates the binding of S. aureus with C. albicans hyphae (14, 36, 37). Within the polymicrobial biofilm, S. aureus exhibits enhanced resistance to vancomycin (13).

Independent studies demonstrated that the interactions between S. aureus and C. albicans enhance disease severity in several ways (33, 38). Candidal infections cause physical damage to organ walls, allowing S. aureus to penetrate the internal organs more easily. S. aureus, on the other hand, secretes different proteases that help C. albicans to enhance its adhesion to the mucosal layer (12). During systemic infections, each organism helps the other to evade phagocytic killing mediated by polymorphonuclear leukocytes (PMNs). C. albicans secretes a proteinase that degrades the Fc portion of immunoglobulin G (IgG) and greatly reduces the opsonizing activity of human PMNs against S. aureus (39). On the other hand, S. aureus secretes coagulase and extracellular
fibrinogen binding proteins (Efb) that protect Candida sp. from PMN-mediated phagocytosis. Coagulase activates prothrombin, which mediates the conversion of fibrinogen to fibrin. Formation of fibrin clots surrounding the candidal cells helps Candida spp. to evade phagocytic killing by granulocytes (40). Additionally, Efb binds to C3 complement and interferes with complement activation and C3-mediated opsonization (41). The cooperative infection of C. albicans and S. aureus represents a significant therapeutic challenge, and their coisolation from blood is an indication of a dire prognosis (42).

Competitive or antagonistic relationships between C. albicans and S. aureus have also been reported where the farnesol quorum-sensing molecule secreted by C. albicans inhibits the biofilm formation of S. aureus. Farnesol disrupts the S. aureus cell membrane integrity and thereby its viability. Additionally, in vitro results demonstrated that farnesol-treated S. aureus showed enhanced susceptibility to a variety of clinically important antibiotics (43). However, it is as yet unclear how much farnesol C. albicans secretes under in vivo conditions and whether the secreted concentrations are sufficient to inhibit the growth of S. aureus in vivo. Nevertheless, all available in vivo data suggest that S. aureus and C. albicans exist in synergy. Apart from Candida albicans, S. aureus was also isolated together with Candida tropicalis, Candida parapsilosis, and Trichosporon asahii (44, 45).

Interactions with influenza virus. The mechanisms of interaction of S. aureus with influenza virus are much more complex than the interactions between S. aureus and C. albicans. Superinfection of influenza virus and S. aureus is one of the major causes of severe influenza pneumonia, prolonged inflammation, and higher mortality rates. This represents the best-known model of bacterial-viral coinfection (20).

Influenza virus A infection promotes and enhances the nasopharyngeal adherence of S. aureus (46). On the other hand, S. aureus promotes the infectivity and spread of the influenza virus particles. Hemagglutinin (HA), a trimeric glycoprotein, present in multiple copies in the membrane envelope of influenza virus, is responsible for the attachment of the virus particle to sialic acid-containing receptors of the host ciliated columnar epithelial cells. Proteolytic cleavage of the hemagglutinin is an important prerequisite for the infectivity of the influenza virus and for the spread of the virus in the host organism and associated pathogenicity. Several strains of S. aureus have been found to secrete serine proteases that activate infectivity of influenza virus by proteolytic cleavage of the hemagglutinin (21).

Coinfections of S. aureus and influenza virus may lead to severe disease outcome, as influenza virus infection enhances the deleterious effects of staphylococcal enterotoxin B (SEB) and toxic shock syndrome toxin 1 (TSST-1) (47, 48). SEB and TSST-1 are superantigens that activate T cells in an uncontrolled manner and cause massive systemic release of cytokines. Concurrent S. aureus and influenza virus infection induces enterotoxin-mediated massive release of tumor necrosis factor alpha (TNF-α) and gamma interferon (IFN-γ). This results in fever, rash, hypotension, tissue injury, and shock. It has been hypothesized that the lethal synergism between concurrent influenza infection and S. aureus superantigen exposure may contribute to sudden and unexpected death from influenza virus infection (49).

Interactions with other bacteria. The majority of the interactions between S. aureus and other bacterial species are competitive in nature, and only a few interactions are cooperative. Cooperative interactions involving S. aureus exist with H. influenzae and E. faecalis. Competitive interactions are observed between S. aureus and other bacteria, viz., Pseudomonas aeruginosa, Streptococcus pneumoniae, lactic acid bacteria (LAB), Corynebacterium sp., or S. epidermidis. That the interactions are competitive does not mean that these organisms completely inhibit the colonization of S. aureus; rather, S. aureus employs numerous defense strategies for its
survival, counterattacking the competing bacteria and surviving in the same ecological niche. Cooperative or competitive interactions lead to the development of more-persistent S. aureus strains with altered colony morphology, antibiotic resistance, and increased virulence. The interactions of S. aureus with other bacterial species are listed below.

(i) Interactions with Haemophilus influenzae. S. aureus and H. influenzae both colonize the nasopharynx and, in some instances, the conjunctivae and genital tract. H. influenzae reaches higher colony densities when the resident colonizer is S. aureus. The higher H. influenzae colony densities have been attributed to the availability of nutrients that S. aureus provides to facilitate its growth (19). S. aureus produces three major hemolysins (α, β, and γ) which lyse erythrocytes by compromising their membrane integrity (50). The hemolysis of erythrocytes by S. aureus-secreted hemolysins releases nutrients such as hemin and NAD, which are vital for the growth of H. influenzae (51–53). Margolis et al. demonstrated synergistic interactions of S. aureus and H. influenzae in the rat nasopharynx (19). However, Pettigrew et al. and van den Bergh et al. studied the compositions of nasal microflora among children and have reported antagonism or negative association between S. aureus and H. influenzae (54, 55). Both of those studies were designed to determine the microflora composition among children in the age group between 6 and 36 months.

(ii) Interactions with Pseudomonas aeruginosa. The relation between S. aureus and P. aeruginosa is competitive in nature, although the two organisms are frequently found together in clinical settings. They have common niches within the host, for example, the lungs of cystic fibrosis (CF) patients, peritoneum of dialysis patients, catheters, diabetic foot wounds, and other type of wounds caused by skin injury or skin burn (44, 56). S. aureus is often reported as the primary pathogen infecting the lungs of the CF patients, followed by P. aeruginosa. Although coinfections of these pathogens are very common under in vivo conditions, several independent in vitro studies demonstrated that, when cocultured together, P. aeruginosa thrives better than S. aureus (57–59). The better survival of P. aeruginosa is attributed to its ability to produce respiratory toxins such as pyocyanin, hydrogen cyanide, and alkyl-hydroxyquinoline N-oxides that can block the electron transport pathway, thereby inhibiting the growth of S. aureus and other pathogenic staphylococci (57, 58).

Despite its sensitivity to respiratory inhibitors, S. aureus does not get completely cleared away by P. aeruginosa. To counter the effect of the respiratory toxins produced by P. aeruginosa, S. aureus forms electron transport-deficient small-colony variants (SCVs) that grow as tiny, nonpigmented colonies (57). Purified 4-hydroxy-2-heptylquinoline-N-oxide (HQNO) or pyocyanin produced by P. aeruginosa is sufficient to induce SCV selection in S. aureus (57, 59). These SCVs are auxotrophic to hemin or menadione and are resistant to antibiotics, especially aminoglycosides, trimethoprim-sulfamethoxazole (60), and the host antimicrobial peptide lactoferrin B (8). The resistance of SCVs is due in part to their severely decreased membrane potential as well as their reduced growth rate and metabolic processes. These SCVs also persist better than their normal counterparts.

P. aeruginosa also produces a 20-kDa endopeptidase, LasA, which selectively cleaves S. aureus peptidoglycan. LasA cleaves the glycol-glycine and glycl-alanine bonds of the pentaglycine interpeptide bridge in the S. aureus peptidoglycan and induces lysis (61, 62). Using the rat model of infection, Mashburn et al. showed that P. aeruginosa can lyse S. aureus cells and that the iron-containing proteins released from the lysed S. aureus cells serve as the source of iron, thereby increasing the pathogenic potential of P. aeruginosa (63, 64). However, this result is yet to be validated in clinical settings. P. aeruginosa exhibits a similar kind of antagonistic relationship with S. epidermidis, as well as with species representatives of S. haemolyticus, S. saprophyticus, S. hyicus, S. muscae, and S. lugdunensis (58).

(iii) Interactions with Streptococcus pneumoniae. The relation between S. pneumoniae and S. aureus is antagonistic. S. pneumoniae and S. aureus colonize the upper respiratory tract of children and compete with each other for the same niche (59, 65, 66). Various studies have shown that colonization of the upper airway by S. pneumoniae is negatively correlated with S. aureus colonization and that children who are vaccinated with pneumococcal conjugate vaccines are at major risk of S. aureus infections (18). This inverse relation suggests that one organism interferes with the colonization of the other. In vitro data demonstrate that hydrogen peroxide (H2O2), a byproduct of aerobic metabolism produced by S. pneumoniae, is responsible for the antagonistic relationship between these two pathogens (67). H2O2 production leads to the production of DNA-damaging hydroxides through the Fenton reaction that induces the SOS response. The SOS response induces the resident prophages, resulting in the lysis of lysogenic staphylococci. Because the vast majority of S. aureus strains are lysogenic, the production of H2O2 is a very effective antistaphylococcal strategy of S. pneumoniae. H2O2, at concentrations typically produced by pneumococci, kills lysogenic but not nonlysogenic staphylococci (68). Pneumococci, however, are not SOS induced upon exposure to H2O2, as they are resistant to the DNA-damaging effects of the Fenton reaction (69).

It is interesting that S. aureus, which produces so many antioxidants and free radical scavengers, including catalase, alkyl hydroperoxide reductase, superoxide dismutase (SodA and SodM), and staphyloxanthin (16, 70), is susceptible to H2O2 produced by S. pneumoniae. A possible explanation could be that the amounts of free radical scavengers that S. aureus produces are not sufficient to neutralize all the H2O2 produced by S. pneumoniae. Regev-Yochay et al. demonstrated that staphylococcal species that secrete higher concentrations of catalase are resistant to S. pneumoniae (67).

However, other studies have offered hypotheses suggesting that the production of hydrogen peroxide may not be the main reason for the antagonistic relationship between these pathogens in vivo (71). Although both pathogens colonize the upper respiratory tract, their microniches are different. Therefore, direct antagonism mediated by H2O2 is an unlikely reason for their antagonism. Rather, the antibody response generated during S. pneumoniae infection, although ineffective in restricting this pathogen itself, is effective in providing cross-protection against S. aureus (71, 72).

(iv) Interactions with LAB. The lactic acid bacteria (LAB) consist of a group of heterogeneous bacterial species comprising nonsporulating, Gram-positive cocci and bacilli that are able to ferment sugars predominantly into lactic acid. This leads to acidification of the environment down to a pH of 3.5. LAB colonize the gut and urogenital tract and contribute to defense against S. aureus-mediated food poisoning and genital infections. The antistaphylococcal activity of LAB strains is attributed to the production of H2O2, organic acids, antimicrobial proteins, biosurfactants, surface proteins, and quorum-sensing inhibitors. The most
commonly studied members of intestinal and vaginal LAB include *Lactobacillus acidophilus*, *L. casei*, *L. fermentum*, *L. salivarius*, *L. rhamnosus*, *L. gasseri* (25, 73–75). In similarity to the results seen with *S. pneumoniae*, LAB-produced hydrogen peroxide (*H₂O₂*) inhibits the growth of *S. aureus* (76, 77). Additionally, LAB secrete organic acids (lactic, acetic, formic, caproic, propionic, butyric, and valeric acids) that inhibit the growth of *S. aureus* (78). LAB-produced bacteriocins interfere with cell wall structure and biosynthesis and form pores in the *S. aureus* membrane (79). Among the bacteriocins produced by LAB, the most important are nisin, produced by *Lactococcus lactis*; pediocin, produced by *Pediococcus acidilactici*; and lacticin 3147, produced by *Lactococcus lactis* DPC 3147 (79, 80).

Apart from inhibiting the growth of *S. aureus* by the use of *H₂O₂*, organic acids, and bacteriocins, LAB compete with *S. aureus* for the host cell adhesion sites. Biosurfactants and surface proteins of LAB strains are involved in this competitive exclusion process. *L. fermentum*, *L. acidophilus*, *L. crispatus* CRL 1266, *L. paracasei* subsp. *paracasei* CRL 1289, *L. salivarius* CRL 1328, *L. rhamnosus* GG, *Lactococcus lactis* subsp. *lactis*, and *Propionibacterium freudenreichii* subsp. *shermanii* were shown to disrupt the adherence of *S. aureus* to the intestinal and urogenital tract by competing for the same adhesion sites. Some LAB strains were also shown to displace previously adhered *S. aureus* from the vaginal epithelial cells (27). In a recent study, it was also shown that the small signaling molecule cyclic dipeptides cyclo(1-Tyr-1-Pro) and cyclo(1-Phe-1-Pro), produced by the human vaginal isolate *L. reuteri* RC-14, are able to interfere with the staphylococcal quorum-sensing system *agr*, a key regulator of virulence genes, and repress the expression of staphylococcal exotoxin TSST-1 (81).

To counter the detrimental effects of LAB species, *S. aureus* produces bacteriocins that have antibacterial activity against LAB. For example, *S. aureus* secretes bacteriocins such as staphylococcin Au-26, Bac1829, BacR1, aureocin A70, and aureocin A53 that inhibit the growth of lactobacilli (80).

(v) **Interactions with Corynebacterium sp.** *S. aureus* and *Corynebacterium* sp. are two of the most important species infecting the skin and nasopharynx. Both organisms are associated with catheter-related infections. A lower incidence of *S. aureus* colonization has been observed in individuals heavily colonized by *Corynebacterium* sp. (C. acocens, *C. pseudodiptheriticum*, and *C. tuberculosisaricarum*). *Corynebacterium* spp. utilize competitive exclusion strategies similar to those of LAB in competing with *S. aureus* for the same adhesion site with host mucosal epithelial cells (30). No bacteriocin-like activity of *Corynebacterium* sp. against *S. aureus* has been reported. However, a number of bacteriocins secreted by *S. aureus* are active against *Corynebacterium* sp. These bacteriocins include BacB729 (17), aureocin A70 (29), aureocin A53 (82) and staphylococcin 188 (28).

(vi) **Interactions with *S. epidermidis***. Besides these interactions, *S. aureus* is also known to interact with members of the same genus. Several reports indicate antagonistic relationships between *S. aureus* and *S. epidermidis*. Both *S. aureus* and *S. epidermidis* are opportunistic and nosocomial pathogens. Unlike *S. aureus*, which causes severe acute infections, *S. epidermidis* frequently causes chronic infections and has an exceptional capacity to attach to the indwelling medical devices during surgery and form biofilms. The presence of *S. epidermidis* in the nasal cavities has been reported to correlate with the absence of *S. aureus* (83). Similar to *S. pneu-
tant *S. aureus* (VRSA) strains showed that transposon Tn\textsubscript{1546} harboring the vanA gene either jumped into a staphylococcal plasmid or integrated into the *S. aureus* chromosome \( (16, 91, 95) \). The acquisition of vanA by *S. aureus* resulted in incorporation of D-alanyl-D-lactate (D-Ala-D-Lac) precursors into the peptidoglycan instead of D-alanine-D-alanine (D-Ala-D-Ala). The *E. faecalis* and *S. aureus* cell wall harboring the D-Ala-D-Lac precursors has 1,000-fold less affinity for vancomycin, a drug that is considered the last-resort antibiotic to treat methicillin-resistant *S. aureus* (MRSA) infections \( (96) \). Interactions between these two bacteria have led to an increase in the numbers of multidrug-resistant staphylococci.

**CONCLUSION**

Most infections are polymicrobial in nature and can be seen in almost every niche in the human body, particularly in mucosal surfaces, where different species of microorganisms such as bacteria, fungi, and viruses coexist as communities. *S. aureus* is one of the most common pathogens found in polymicrobial infections. In polymicrobial infections, *S. aureus* differentially modulates host immune responses and disease severity and acquires altered growth and antibiotic susceptibility patterns. The altered immune response during polymicrobial infections could be beneficial or detrimental for *S. aureus*. For example, influenza virus infection inhibits Th\textsubscript{17}-mediated adaptive immune responses \( (97) \). Activated Th\textsubscript{17} cells are necessary for protection against *S. aureus* infection, because this subset of T cells enhances neutrophil recruitment to sites of infection and kills *S. aureus* \( (98, 99) \). Therefore, Th\textsubscript{17} cell-mediated immune activation is necessary to limit *S. aureus* infections. By inhibiting the Th\textsubscript{17} cell-mediated immune response and subsequent neutrophil infiltration, influenza virus helps *S. aureus* to colonize and to cause severe secondary bacterial pneumonia \( (97, 100) \). In contrast to the immune suppression mediated by influenza virus that aids *S. aureus*, *S. pneumoniae*-mediated immune activation is detrimental to *S. aureus*. The antibody response generated during *S. pneumoniae* infection against its glyceraldehyde-3-phosphate dehydrogenase, although ineffective in inducing osonophagocytic killing of *S. pneumoniae*, can cross-react with staphylococcal protein 1-pyrroline-5-carboxylate dehydrase and induce osonophagocytic killing of *S. aureus* \( (71, 72) \). *S. pneumoniae* itself is protected from osonophagocytic killing due to its antiopsonic polysaccharide capsule.

Additionally, *S. aureus* in polymicrobial infections displays enhanced persistence and antibiotic tolerance. *S. aureus* acquired vancomycin resistance genes from *E. faecalis* and became resistant to vancomycin \( (16, 91, 95) \). *S. aureus*, during coinfection with *C. albicans*, showed increased vancomycin resistance \( (13, 101) \). This bacterium forms electron transport-deficient small-colony variants during coinfection with *P. aeruginosa* \( (57, 58) \). These SCVs persist better than their normal counterparts and are resistant to aminoglycosides and trimethoprim-sulfamethoxazoloids \( (102) \).

A 23-valent polysaccharide vaccine against *S. pneumoniae* which was recently introduced into the market indeed prevented *S. pneumoniae* nasopharyngeal colonization, but the vaccinated individuals were subject to an increased risk of *S. aureus* nasal colonization \( (72) \). Therefore, prevention of one pathogenic infection provides opportunities to the competing pathogens to cause disease. These findings highlight the potential complications that could arise from conventional treatment and disease prevention strategies that target a single organism, thereby necessitating the need to introduce modified therapeutic approaches that take into account the coinfeting organisms. Several strategies could be used to address the difficulties in treatment of polymicrobial infections of *S. aureus*. One could be the use of combined vaccines against two or more coinfeting microbes; however, such vaccines are still in the experimental stages. The next approach could be the judicious use of antimicrobial drugs. A coinfection of *S. aureus* and influenza virus should be treated with antiviral and appropriate antibacterial drugs. A third approach is the use of LAB strains to prevent not all but some of the *S. aureus* infections. Probiotic LAB can prevent intestinal and urogenital tract coinfections. Studies have shown that regular intake of probiotic LAB and fermented milk can even reduce *S. aureus* colonization in the upper respiratory tract. Similarly, probiotic LAB species also confer protection against influenza virus by modulating innate immunity. Thus, probiotic bacteria can be used to prevent coinfections of *S. aureus* and influenza virus.

In summary, *S. aureus* in polymicrobial infections represents a clinical challenge greater than that of *S. aureus* in monomicrobial infections. The coexisting microbes significantly influence the outcome of the infection by altering invasion ability, growth, gene expression, and drug sensitivity patterns. Further investigations are required to design appropriate treatment strategies to tackle polymicrobial infections mediated by *S. aureus*.

**ACKNOWLEDGMENTS**

N.N. is supported by a doctoral fellowship from Indian Council of Medical Research (ICMR; 45/16/2011/IMM-BMS), and R.B. is supported by a Ramalingaswami fellowship, Department of Biotechnology (DBT), Government of India. This study was supported by a DBT grant (BT/PR13125/GBD/27/193/2009) to R.B. and an ICMR grant (AMR/14/2011-EC11) to L.B.

We thank Shantikumar V. Nair for valuable comments and for critically reviewing the manuscript.

We declare that we have no conflicts of interest.

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