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Staphylococcus aureus Nasal Colonization: An Update on Mechanisms, Epidemiology, Risk Factors, and Subsequent Infections

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Up to 30% of the human population are asymptomatically and permanently colonized with nasal *Staphylococcus aureus*. To successfully colonize human nares, *S. aureus* needs to establish solid interactions with human nasal epithelial cells and overcome host defense mechanisms. However, some factors like bacterial interactions in the human nose can influence *S. aureus* colonization and sometimes prevent colonization. On the other hand, certain host characteristics and environmental factors can predispose to colonization. Nasal colonization can cause opportunistic and sometimes life-threatening infections such as surgical site infections or other infections in non-surgical patients that increase morbidity, mortality as well as healthcare costs.

Keywords: *Staphylococcus aureus*, nasal colonization, epidemiology, surgical site infections (SSI), nasal microbiota, predisposing factors, nasal carriage

INTRODUCTION

Staphylococcus aureus is both a human skin and mucosae commensal but also a frequent cause of serious infections with high morbidity, mortality, and healthcare-associated costs (Schmidt et al., 2015). The most frequent carriage site is the *vestibulum nasi* (or anterior nares), which serves as reservoir for the spread of the pathogen (Williams, 1963; Sivaraman et al., 2009). This bacteria can establish solid interactions with nasal epithelial cells via various proteins and many cell surface components (Wertheim et al., 2005a; Mulcahy and McLoughlin, 2016), thus transforming into persistent carriage. *S. aureus* colonizes the anterior nares of 20% to 80% of the human population (Brown et al., 2014). Nasal carriage has been shown to play a key role in the pathogenesis of *S. aureus* infections (Kluytmans et al., 1997) in patients undergoing surgery (Perl et al., 2002; Bode et al., 2010), dialysis (Kluytmans et al., 1996; Nouwen et al., 2006), and in intensive care unit (ICU) patients (Garrouste-Orgeas et al., 2001), with higher infection risks in persistent carriers (Nouwen et al., 2006).

Previously published reviews on *S. aureus* carriage have usually focused independently on colonization or infections, or have issued a specific underlying condition or surgery.

Here, we will full review recent advances in nasal microbiota composition and interspecies interactions, epidemiology, and risk factors for *S. aureus* colonization as well as the link between nasal carriage and infections both in community and nosocomial context.

NASAL MICROBIOTA AND INTERACTIONS BETWEEN BACTERIA

The adult nasal microbiota differs between individuals, but species belonging to *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* genera are the most abundant bacteria (Frank et al., 2010; Human Microbiome Project Consortium, 2012; Yan et al., 2013; Kaspar et al., 2016). In a study conducted on the nasal microbiota of 178 adults, 88.2% were *Corynebacterium* carriers, 83.7% *Propionibacterium acnes* carriers, and 90.4% *Staphylococcus epidermidis* carriers. Proportional abundance varied considerably between individuals (Liu C.M. et al., 2015).

The health status may influence the nasal microbiota and vice versa. In a study involving healthy and hospitalized individuals, healthy adults harbored nares microbiota dominated by *Actinobacteria* (mainly *Propionibacterium* and *Corynebacterium* spp.) whereas patients microbiota were dominated by *S. aureus* and *S. epidermidis*. *S. aureus* colonization was negatively associated with the presence of other bacteria including *S. epidermidis* (Frank et al., 2010). Such counterweight effect between bacteria could be the result of interdependent activation-inhibition mechanisms as reviewed by Krismer et al. (2017). In fact, some bacterial species are capable of secreting anti-staphylococcal molecules modulating *S. aureus* abundance (**Figure 1**). For instance, *in vitro* production of H_2O_2 by *Streptococcus pneumoniae* can be bactericidal on *S. aureus* (Regev-Yochay et al., 2006; Selva et al., 2009). Recently, an *in vitro* and human study demonstrated that lugdunin, a non-ribosomal synthesized bioactive compound produced by *Staphylococcus lugdunensis*, can prevent *S. aureus* nasal colonization via a bactericidal effect (Zipperer et al., 2016).

In some cases, the bacteria-secreted molecules can modify *S. aureus* adhesion properties. Some types of *S. epidermidis* seem to be capable of synthetizing the serine protease Esp that eliminates nasal *S. aureus* in healthy humans (Iwase et al., 2010), probably by degrading staphylococcal surface proteins and human receptors critical for host–pathogen interaction (Sugimoto et al., 2013). As well, *Propionibacterium* species produce coproporphyrin III, a porphyrin metabolite that induces *S. aureus* aggregation which influences nasal colonization (Wollenberg et al., 2014).

Corynebacterium species are suggested to antagonize *S. aureus* by human cell binding competition mechanisms (Uehara et al., 2000; Lina et al., 2003). In 156 healthy volunteers, Uehara et al. (2000) observed a 71% total eradication rate of nasal *S. aureus* after performing up to 15 inoculations of a *Corynebacterium* sp. strain to the nares of *S. aureus* carriers.

Intra-species competition has also been described. In a cross-sectional clinical study, it was suggested that methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) compete for colonization, MSSA being protective with regard to MRSA carriage (Dall'Antonia et al., 2005). On the other hand, pre-existing nasal carriage with *S. aureus* could predispose adult patients to further staphylococcal colonization (Ghasemzadeh-Moghaddam et al., 2015).

SPREAD AND TRANSMISSION OF *S. aureus*

Staphylococcus aureus can be found in different body sites like the skin, rectum, vagina, gastrointestinal tract and axilla, the anterior nares appearing as the main reservoir. From a cutaneous commensal site, *S. aureus* can enter in contact with the nasal mucosa, then interact with epithelial cell ligands such as loricrin and cytokeratin 10 (K10) (**Table 1**). Once the host's defenses are overcome, *S. aureus* can propagate into the anterior nares so that the host becomes an *S. aureus* nasal carrier (Wertheim et al., 2005a). In human, nasal colonization may begin within the first days of life (Maayan-Metzger et al., 2017). This has been demonstrated in a cohort study evaluating nasal carriage of *S. aureus* in 100 pairs of infant–mother for a period of 6 months following delivery (Peacock et al., 2003). The carriage rate in the first 8 weeks of life was around 40–50%, thereafter it dropped to 21% at 6 months. In addition, this study found a nasal carriage concordance in 68% of infant–mother pairs attesting the role of environmental factors in *S. aureus* carriage (Peacock et al., 2003). Another study found identical strains in 80% of infant–mother pairs. In 90% of these newborns, the source of *S. aureus* was the maternal nasal strain (Leshem et al., 2012; **Figure 2**).

After birth, hands are the main vector for *S. aureus* transmission from surfaces to the nose (Wertheim et al., 2005a). The hypothesis of a link between hand and nose *S. aureus* carriage is supported by the double blind randomized placebo controlled trial from Reagan et al. (1991), who demonstrated that nasal decolonization with mupirocin applied to health-care workers resulted in a decrease of nose and hand carriage. In a cohort study including outpatients and healthy hospital employees, nasal carriage was evaluated by a single or several swabs. Participants completed a questionnaire about their nose picking behavior, a positive correlation between this habit and nasal carriage of *S. aureus* was found. However, it is unknown whether nose-picking patients were more frequently colonized at extra nasal sites (Wertheim et al., 2006).

Studies realized in individuals living in the same households have revealed that these people tend to carry genetically similar strains in their nares (Nouwen and Optima Grafische Communicatie, 2004; Muthukrishnan et al., 2013) suggesting horizontal transmission. Multisite MRSA carriage increases the risk for nasal MRSA colonization (Harbarth et al., 2000).

In spite infrequent, airborne transmission is another possible route of *S. aureus* dissemination (Wertheim et al., 2005a) and may play a role in hospital outbreaks (Sherertz et al., 1996).

During viral upper respiratory infections, the risk of disseminating endogenous *S. aureus* in the air increases and infection outbreaks may occur. In 1996, an MRSA outbreak involving 8 of 43 patients occurred in a surgical ICU of a

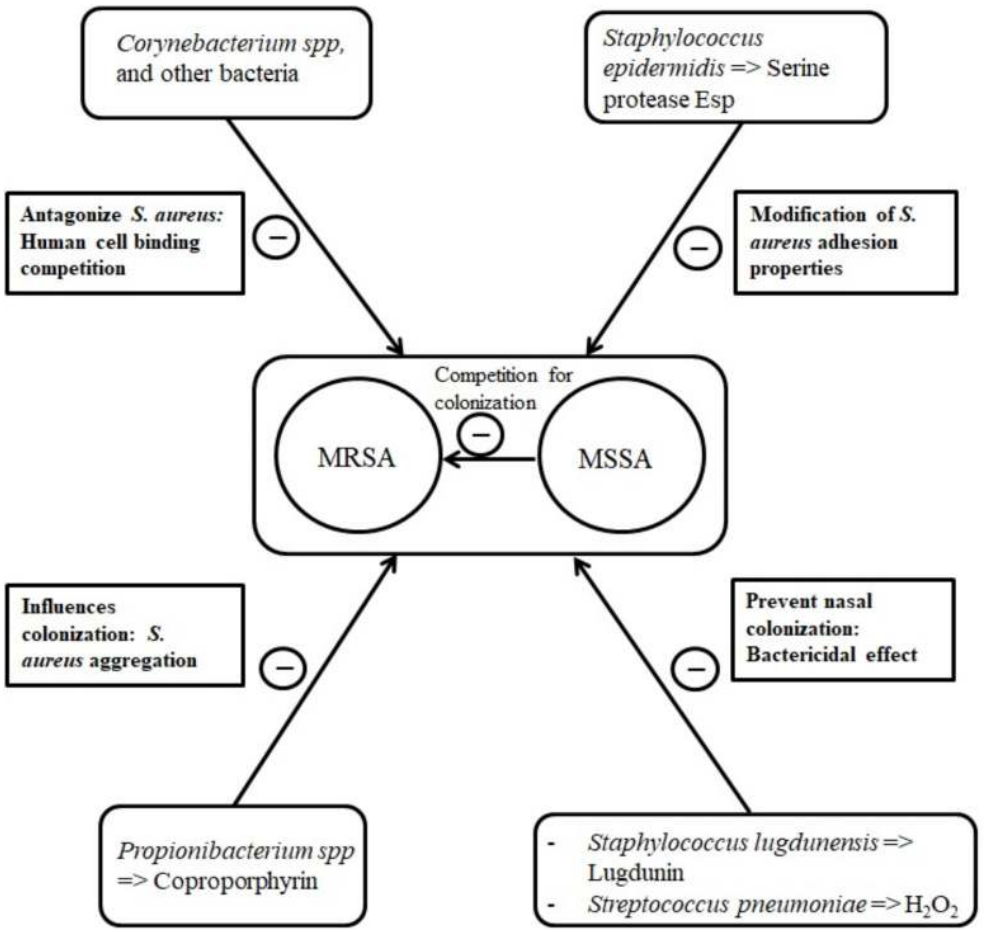

FIGURE 1 | Main bacterial interactions with nasal *S. aureus*.

university hospital in the United States. Investigations of the cause concluded that a single physician was the source of this outbreak; he was a nasal carrier of MRSA and suffered an upper respiratory infection. To assess airborne dispersal of *S. aureus*, the authors completed their findings by an experimental clinical test on this physician and showed that transmission of the bacterium increased by 40-fold when he was infected by a rhinovirus infection than when he was not. The use of a mask significantly reduced dispersal ($P = 0.015$) (Sherertz et al., 1996).

Healthcare workers who are asymptomatic nasal carriers can sometimes be the source of MRSA outbreaks (Wang et al., 2001; Vonberg et al., 2006; Haill et al., 2013; Lamanna et al., 2017). On the other hand, in nonoutbreak situations and in presence of control measures, healthcare workers are infrequently sources of transmission of *S. aureus* (Price et al., 2017).

Mobile phones of healthcare workers may be a reservoir of *S. aureus* (Chang et al., 2017). A recent study evaluated incidence of bacterial contamination of mobile phones belonging to medical staff working in the operating room. Seventy two healthcare professionals took bacterial cultures from their phones, anterior nares, and hands. The results revealed that 31 staff had *S. aureus* isolated from their nares, 8 from their mobile phones, and 4 from their hands. Genotyping confirmed that 7/8 of the mobile phones strains were identical to the ones isolated from the nares (Chang et al., 2017).

TABLE 1 | Major *S. aureus*-host ligands.

S. aureus ligand factor	Host ligand	Reference
ClfB	Loricrin, K10 (cytokeratin 10), K8 (cytokeratin 8), fibrinogen	Perkins et al., 2001; O'Brien et al., 2002; Schaffer et al., 2006; Wertheim et al., 2008; Haim et al., 2010; Mulcahy et al., 2012
IsdA	Fibrinogen, fibronectin	Clarke et al., 2004
SdrC	Unknown	Corrigan et al., 2009
SdrD	Desmoglein 1	Corrigan et al., 2009; Askarian et al., 2016
SasX	Unknown	Liu Q. et al., 2015
SasG	Unknown	Roche et al., 2003
WTA	Srec-1	Baur et al., 2014; Weidenmaier et al., 2004

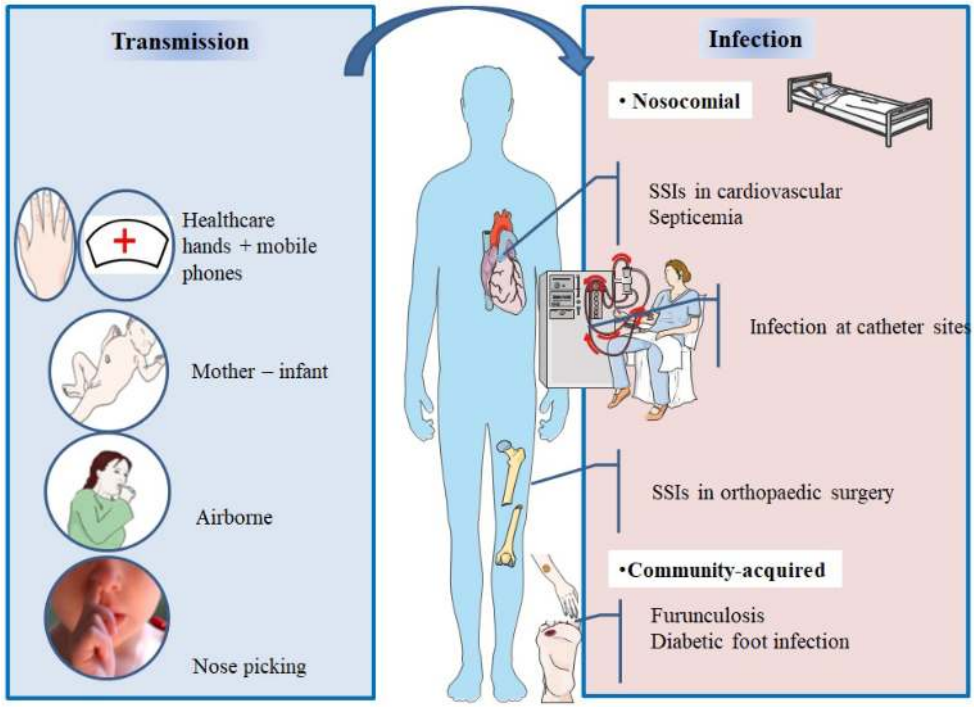

FIGURE 2 | Main spread and transmission mechanisms of *S. aureus* and impact of nasal carriage on subsequent infections.

MECHANISMS OF COLONIZATION

The *vestibulum nasi* or anterior part of the nares is lined by a stratified, keratinized nonciliated squamous epithelium, whereas the rest of the nasal cavity, that is, its inner part is lined with a ciliated columnar epithelium (Peacock et al., 2001; Weidenmaier et al., 2012).

Both epithelia have been described as habitats for *S. aureus* (Mulcahy et al., 2012; Baur et al., 2014) as it will be developed in this section. Intracellular localization in nasal tissue from healthy volunteers was also described (Hanssen et al., 2017). For a successful colonization, *S. aureus* expresses adhesive molecules (Burian et al., 2010), fundamental for the establishment of interactions with human cell surface components, as it was demonstrated *in vitro* and *in vivo* (Mulcahy et al., 2012; Baur et al., 2014; **Figure 3**). Major ligands interactions are listed in **Table 1**.

INTERACTION BETWEEN *S. aureus* AND THE SQUAMOUS EPITHELIUM OF THE ANTERIOR NARES

The *vestibulum nasi* is lined by skin (Cunningham, 1905; Vuyk and Watts, 2006). The uppermost layer of the epidermis is the *stratum corneum* or cornified layer (Candi et al., 2005; Eckhart et al., 2013). This layer contains keratinocytes that express proteins, such as loricrin, cytokeratin 10 (K10), involucrin, filaggrin, and other proteins (Eckhart et al., 2013).

Clumping factor B (ClfB) and iron-regulated surface determinant A (IsdA) are staphylococcal surface proteins that can adhere to cornified envelope proteins (Clarke et al., 2004, 2006; Schaffer et al., 2006; Wertheim et al., 2008; Mulcahy et al., 2012) and favor nasal colonization as it will be developed in this section.

Recently, Mulcahy et al. (2012) demonstrated that loricrin, the most abundant protein in the cornified envelope (Steinert and Marekov, 1995), was the major target ligand for ClfB during *S. aureus* nasal colonization. Nasal colonization by a ClfB$^+$ *S. aureus* strain was reduced by 80% in loricrin-deficient mice compared to wild-type mice. ClfB has also been shown to interact with cytokeratin 10 (O'Brien et al., 2002; Schaffer et al., 2006; Wertheim et al., 2008), cytokeratin 8 (Haim et al., 2010), and fibrinogen (Perkins et al., 2001; **Table 1**). The role of ClfB in the adherence of *S. aureus* to the nasal epithelium has been studied *in vitro* (O'Brien et al., 2002; Mulcahy et al., 2012), in animal models (Schaffer et al., 2006; Mulcahy et al., 2012), and in human studies (Wertheim et al., 2008).

Schaffer et al. (2006) demonstrated that mutant strains of *S. aureus* deficient in ClfB resulted in a reduced nasal colonization in both mice and rats, as compared to the wild-type strain (ClfB$^+$). In human, the mutant strain ClfB$^-$ of *S. aureus* has been reported to be cleared faster than the wild-type strain (median 3 ± 1 vs. 7 ± 4 days, $p = 0.006$), whereas the wild-type strain persisted for 28 days after inoculation (Wertheim et al., 2008).

IsdA also plays a role in the adherence of *S. aureus* to nasal cells as demonstrated *in vitro* and *in vivo* (Clarke et al., 2004). Mutation in IsdA gene reduced the ability of the bacteria to bind

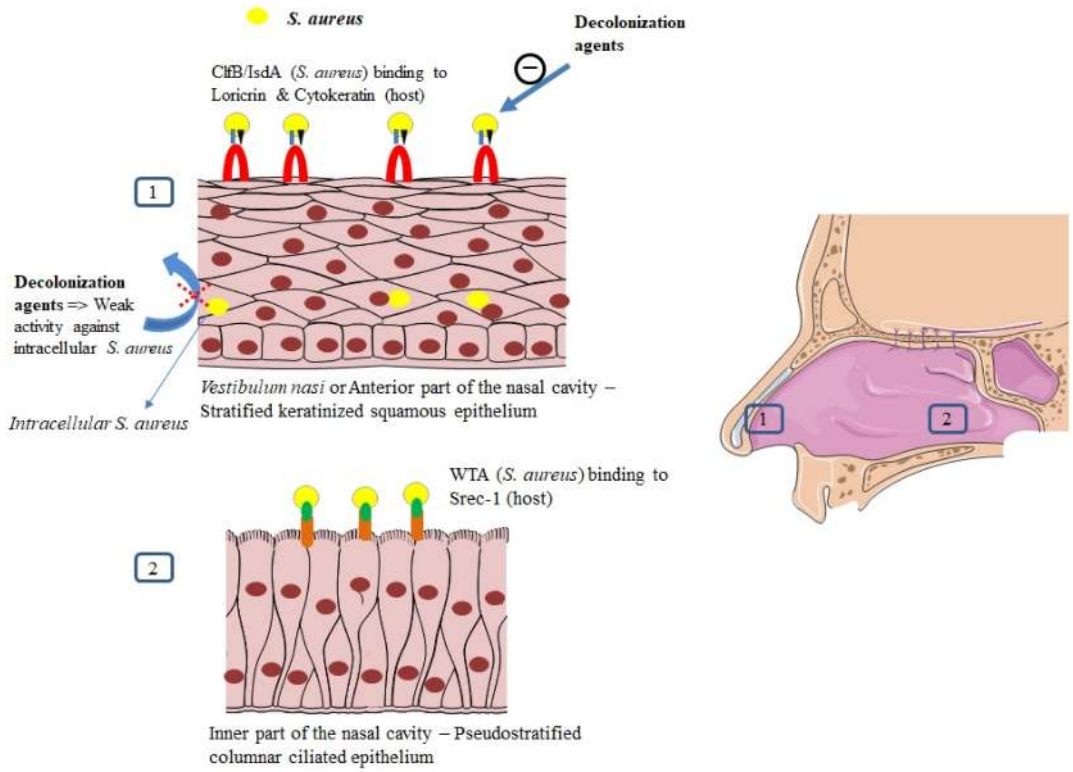

FIGURE 3 | Mechanisms of *S. aureus* nasal colonization.

human nasal cells *in vitro* and to colonize the anterior nares in cotton rats (Clarke et al., 2006). This surface protein has also been shown to bind to fibrinogen and fibronectin (Clarke et al., 2004). The role of IsdA in nasal colonization has not been clearly demonstrated in human studies yet.

Other *S. aureus* surface proteins, such as surface protein G (SasG), SasX, and the serine-aspartate repeat proteins SdrC and SdrD may also serve as ligands to the epithelial cells (Corrigan et al., 2009; Liu Q. et al., 2015). Desmoglein 1 was identified as a host ligand for SdrD (Askarian et al., 2016). Their roles in humans have not been tested yet (Mulcahy et al., 2012).

INTERACTION IN THE INNER NASAL CAVITY

Apart from the *vestibulum nasi*, the inner part of the nasal cavity constitutes another ecological niche for *S. aureus*. The staphylococcal nonprotein adhesin, named cell *wall teichoic acid* (WTA) is considered as an important factor for the colonization process (Weidenmaier et al., 2004). In an *in vivo* study, WTA-deficient *S. aureus* mutants could not adhere to nasal cells and were unable to colonize cotton rat nares compared to wild type control strains (Weidenmaier et al., 2004).

In a study combining *in vitro* and *in vivo* assessments, Baur et al. (2014) studied the molecular details of WTA adhesion to nasal cells. They first discovered that SREC-1 (a member of the F-type scavenger receptor) was expressed on epithelial cells in the inner nasal cavity of human and cotton rats. The authors further reported that SREC-1 interacted with WTA and confirmed these findings in infected cotton rats pretreated with antiSREC-1 antibody. A significant decrease in colonization was observed 8 h and 6 days after inoculation in the group receiving antiSREC-1 antibody, as compared to the controls (Baur et al., 2014). In agreement, Weidenmaier et al. (2008) previously demonstrated the role of WTA in the initial stages of *S. aureus* colonization.

INTRACELLULAR LOCALIZATION OF *S. aureus*

Intracellular localization of *S. aureus* in the nasal tissue has been described using techniques including immunohistochemical analysis, hematoxylin, and Eosin stains (Hayes et al., 2015; Ou et al., 2016, 2017). Epithelial cells, endothelial cells, and inflammatory cells, especially mast cells (Plouin-Gaudon et al., 2006; Tan et al., 2014; Hayes et al., 2015; Ou et al., 2016) have been described as habitats for intracellular *S. aureus* (ICSA). Using skin biopsies from the *vestibulum nasi* of randomly selected healthy participants, Hanssen et al. (2017) detected intracellular *S. aureus* in the *stratum spinosum*, one of the layers forming the epidermis. Intracellular localization of *S. aureus* has been reported both in patients with rhinosinusitis

(Clement et al., 2005; Plouin-Gaudon et al., 2006; Ou et al., 2016, 2017) and healthy volunteers (Hanssen et al., 2017). In the control population from the study of Ou et al. (2016), 38% had ICSA. However, in the absence of large scale population study, the true prevalence of ICSA in healthy individuals remains to determine.

Intracellular localization of *S. aureus* seems to protect the bacteria from host defense mechanisms (Clement et al., 2005) and favor antimicrobial agents' failure, as it was demonstrated in a recent study evaluating systemic and topical antibiotics. Using a cell model of *S. aureus* nasal epithelium evasion, Rigaill et al. (2018) found that most of the decolonizing agents, including mupirocin, exhibited weak activity against ICSA. Elimination of ICSA was also studied in a mouse model using vancomycin. In this study, intracellular bacteria were able to establish infection even in the presence of this antibiotic (Lehar et al., 2015), whereas planktonic bacteria were eliminated by vancomycin and did not cause infection. The intracellular residency of *S. aureus* could explain re-colonization and failure in decolonization observed in some healthy carriers, and the recurrence of infections observed in patients with chronic rhinosinusitis (Clement et al., 2005; Ou et al., 2017; Rigaill et al., 2018).

IMMUNE SYSTEM AND *S. aureus* COLONIZATION

Our knowledge in terms of host response during *S. aureus* nasal colonization is still limited as compared to immune response in invasive *S. aureus* infection (Brown et al., 2014). The association between the host immune system and *S. aureus* nasal carriage has been recently reviewed by Mulcahy and McLoughlin (2016). The presence of *S. aureus* in the nares seems to induce both innate and adaptive immune system. *S. aureus* can otherwise overcome host defense mechanisms. The staphylococcal protein A (SpA) and the exoprotein staphylokinase could play a key role in the bacterial adaptation to the immune system and colonization process (Peschel and Sahl, 2006; Cole et al., 2016).

Innate Immune Response

Human nasal secretions have efficient natural antimicrobial activity (Cole et al., 1999). Indeed, they contain epithelial-cells secreted antimicrobial peptides (AMPs) contributing to the first line defense in the nose. Primary nasal epithelial cells yield AMPs such as hBD3 and RNase-7 after stimulation with cytokines (IFN-g, IL-1b, and TNF-a) (Burgey et al., 2016). Media containing *S. aureus* induce the expression of these AMPs less efficiently than inflammatory cytokines (Burgey et al., 2016). Differential expression profiles of AMPs could be primary determinants for different *S. aureus* carriage states (Burgey et al., 2016).

Anti-staphylococcal responses can be induced by the involvement of Toll-like receptors (TLR). Hence, the role of TLR2 has been documented in nasal *S. aureus* colonization (González-Zorn et al., 2005). Carrier strains of *S. aureus* have been shown to delay the host's immune response compared to non-carrier strains due to the delayed TLR2 expression they stimulate in nasal epithelial cells (Quinn and Cole, 2007). Different polymorphisms have been found in *S. aureus* nasal carriers and non-carriers; they target soluble or membrane-binding molecules such as genes encoding mannose-binding lectin, glucocorticoid receptor, C-reactive protein, beta-defensin 1, TLR-9, and interleukin-4 (van den Akker et al., 2006; Emonts et al., 2008; Ruimy et al., 2010; Mulcahy and McLoughlin, 2016; Nurjadi et al., 2018).

A study evaluating neutrophil depletion was performed in mice to determine the importance of neutrophil influx during carriage. Mice that received an antibody for neutrophil depletion had a significant increase in *S. aureus* colonization rate as compared to controls. This *in vivo* study highlights that neutrophil influx plays a role in clearance of *S. aureus* (Archer et al., 2013).

Adaptive Immune Response

As documented from serum analysis, *S. aureus* carriage induces an adaptive humoral immune response. Serum levels of immunoglobulin IgG and IgA specific to several staphylococcal proteins have been reported to be higher in persistent carriers than in non-carriers (van Belkum et al., 2009; Colque-Navarro et al., 2010). But evidence that these antibodies are protective against colonization are lacking.

In a murine model of nasal colonization, clearance of *S. aureus* was found to be B-cell independent but T-cell mediated. The Th17 cells, a functional T-cell lineage distinct from Th1 and Th2 are known to be involved in mucosal barriers and surface pathogen clearance. They typically produce IL-17 cytokine family. Archer et al. (2013, 2016) showed that IL-17A and IL-17F deficient mice failed to clear *S. aureus* experimentally inoculated through nasal route; IL-17A was required for AMP expression induced by nasal colonization. In a murine model, the IL-10 family cytokine IL-22 was secreted by Th17 cells and facilitated local expression of AMPs. IL-22 also reduced the expression of staphylococcal ligands loricrin and cytokeratin 10 and thus controlled nasal colonization (Mulcahy et al., 2016).

By contrast, in a human study evaluating nasal fluid inflammatory factors and nasal carriage with *S. aureus*, IL-17 was not detected (Cole et al., 2016). This was surprising and the authors suggested that IL-17 could be insoluble in nasal secretions (Cole et al., 2016). Low Th1 to Th17 cytokines ratio were found to be predictive of *S. aureus* carriage in volunteers after whole blood stimulation with *S. aureus* (Nurjadi et al., 2016). Future human studies should be conducted to better understand the role of Th17 cytokines in nasal carriage.

MICROBIOLOGY-BASED CLASSIFICATION OF NASAL CARRIERS

In order to confirm nasal carriage of *S. aureus*, samples are commonly collected using commercial dry or moistened sterile swabs, with no significant difference found between the two (Warnke et al., 2016). The protocol of sampling is not really standardized but generally consists of rubbing the swab in the anterior nares of each nostril for approximately four rotary movements (Wertheim et al., 2006; Bode et al., 2010). Swabs are then analyzed to check presence of *S. aureus*. The two

commonly used laboratory tests for the identification of *S. aureus* are the culture on chromogenic solid media – which is the less expensive test – and polymerase chain reaction, which is the gold standard and the most rapid technique for MRSA detection (Pournajaf et al., 2014). It is important to note that chronic carriage of *S. aureus* may not only result from nasal colonization. Sampling extra-nasal sites like oropharynx, rectum, wounds, axilla increases MRSA detection rate in patients at risk for *S. aureus* nosocomial infection (Miller et al., 2012; McKinnell et al., 2013).

Epidemiological studies over periods varying from 12 weeks to 3 years have described three nasal carriage patterns for *S. aureus* among healthy volunteers swabbed several times. Persistent carriers which rates ranged from 10% to 30% (Williams, 1963; Eriksen et al., 1995; VandenBergh et al., 1999; Nouwen et al., 2004; Muthukrishnan et al., 2013), non-carriers which rates ranged from 10% to 47%, and the rest who were considered intermittent carriers (Williams, 1963; Eriksen et al., 1995; VandenBergh et al., 1999; Nouwen et al., 2004). The definitions used for this classification varied from one study to another. In some studies, persistent carriers were the ones who had results of all of their swabs positive for *S. aureus* (Muthukrishnan et al., 2013). Other studies defined cut-off values for carrier–index (number of positive swabs/number of total swabs for each person) (Eriksen et al., 1995; VandenBergh et al., 1999). However, there is no clear definition on the number of swabs that should be taken and what fraction should be positive before determining carriage state.

Nouwen et al. (2004) proposed a culture rule based on the combination of qualitative and quantitative results of two consecutive nasal culture swabs taken approximately a week apart, to predict *S. aureus* nasal carrier state among healthy volunteers. When both cultures are positive over 10^3 colony forming units (cfu) a person is classified as persistent carrier. When only one of the cultures is positive, or when both cultures are positive with a low cfu, the person is considered as an intermittent carrier. van Belkum et al. (2009) performed a study in 51 volunteers with a known carriage state, who were artificially colonized with a mixture of *S. aureus* strains after a decolonization treatment and followed for 22 weeks. Median nasal bacterial survival was of 4 days in noncarriers, 14 days in intermittent carriers, and more than 154 days in persistent carriers ($P = 0.017$). The culture swabs of persistent carriers contained more bacterial loads compared to the other groups. Serum levels of anti-staphylococcal antibodies differed between persistent and nonpersistent carriers as previously stated. The authors concluded that intermittent and noncarriers share similar characteristics, and thus suggested a reclassification of *S. aureus* nasal carriers into persistent carriers and "other" carriers (van Belkum et al., 2009). Persistent carriers have been shown to have higher counts of *S. aureus* (Nouwen et al., 2004; van Belkum et al., 2009) and a higher risk of infection compared to other carriers (Wertheim et al., 2004; Nouwen et al., 2005). However, bacterial loads in persistent carriers are always variable and it is hard to determine a fixed threshold for diagnosis (Burian et al., 2010; Verhoeven et al., 2012; Nilsson et al., 2015). Persistent carriage is more common in children than in adults, but many people change their carrier state between 10 and 20 years old (Armstrong-Esther, 1976). Conclusions that persistent carriers harbor the same strain for many years, and intermittent carriers appear to have changing strains (Eriksen et al., 1995; VandenBergh et al., 1999) have been recently the subject of controversy (Muthukrishnan et al., 2013).

Cross-sectional studies yield a prevalence of approximately 20–30% of carriers in the general population which is a mix of persistent and intermittent carriers (Gorwitz et al., 2008; den Heijer et al., 2013; Saadatian-Elahi et al., 2013; Chen et al., 2017).

INDIVIDUAL RISK FACTORS FOR *S. aureus* NASAL COLONIZATION

Nasal colonization depends on host factors, such as the underlying condition or diseases (**Table 2**). Some studies have found that nasal carriage was more frequent in human immunodeficiency virus (HIV)-infected (Raviglione et al., 1990; Weinke et al., 1992; Kotpal et al., 2016) or obese patients (Olsen et al., 2013), compared to healthy individuals. This higher prevalence was also found among diabetic patients undergoing dialysis compared to non-diabetic patients in the same population (Luzar et al., 1990). Other diseases such as granulomatosiss with polyangiitis (formerly known as Wegener's granulomatosis), rheumatoid arthritis (Laudien et al., 2010), skin and soft tissue infections (Immergluck et al., 2017) atopic dermatitis (Breuer et al., 2002), and recurrent furunculosis (Demos et al., 2012) have been related with an increased carriage rate.

TABLE 2 | Predisposing factors for nasal carriage.

Predisposing factors for nasal carriage	Reference
HIV-infection	Raviglione et al., 1990; Weinke et al., 1992; Kotpal et al., 2016
Obesity	Olsen et al., 2013
Diabetic patients undergoing dialysis (compared to non-diabetic patients in the same population)	Luzar et al., 1990
Granulomatosis with polyangiitis	Laudien et al., 2010
Rheumatoid arthritis	Laudien et al., 2010
Skin and soft tissue infections	Immergluck et al., 2017
Recurrent furunculosis	Demos et al., 2012
Atopic dermatitis	Breuer et al., 2002
Hemoglobin in nasal secretions	Pynnonen et al., 2011
Histocompatibility antigen phenotype HLA-DR3	Kinsman et al., 1983
Polymorphisms in genes encoding for the glucocorticoid receptor, interleukin-4, C-reactive proteins, and complement inhibitor proteins	van den Akker et al., 2006; Emonts et al., 2008; Ruimy et al., 2010
Hormonal contraception use	Zanger et al., 2012
Active smokers: controversial	Olsen et al., 2012; Cole et al., 2018
Hospital workers: controversial	Elie-Turenne et al., 2010; Saadatian-Elahi et al., 2013; Chen et al., 2015; Price et al., 2017

In healthy subjects, Liu C.M. et al. (2015) found similar carriage rates in men and women, while men had higher bacterial density. Reports of a higher risk of nasal carriage of *S. aureus* among hospital workers than the rest of the population have not been confirmed (Elie-Turenne et al., 2010; Saadatian-Elahi et al., 2013; Chen et al., 2015; Price et al., 2017). The association between smoking and nasal carriage seems also controversial. In a study by Olsen et al. (2012), active smoking in healthy adults was found to be a protective factor for carriage of *S. aureus*, with a hypothesized bactericidal activity of cigarette smokes. Conversely, a recent study showed that smokers were more frequently colonized than non-smokers, and cessation from smoking improved clearance of nasal *S. aureus* in an experimental inoculation study (Cole et al., 2018). Many other host conditions have been punctually studied and reported as additional predisposing factor such as hormonal contraception (Zanger et al., 2012) and presence of hemoglobin in nasal secretions (Pynnonen et al., 2011).

At the genetic level, no correlation was found between genetic factors and *S. aureus* carriage. No significant heritability for *S. aureus* nasal colonization was detected in twins and family studies (Roghmann et al., 2011; Andersen et al., 2012). Interestingly, some polymorphisms in host inflammatory response genes have been associated with *S. aureus* nasal carriage. The presence of the histocompatibility antigen phenotype HLA-DR3 could be a predisposition (Kinsman et al., 1983).

As previously said, at the immune system level, polymorphisms in genes encoding some proteins and differential expression profiles of AMPs could be the determinants of the various carriage states.

In a study involving 93 type 1 diabetes patients, vitamin D receptor polymorphisms were determined in Deoxyribonucleic acid (DNA) extracted from peripheral blood leukocytes. Analysis showed that presence of specific alleles coding for vitamin D receptors were associated with an increased rate of *S. aureus* colonization (Panierakis et al., 2009).

NASAL CARRIAGE OF *S. aureus* AS A RISK FACTOR FOR INFECTIONS

Staphylococcus aureus nasal colonization has been identified as a major risk factor for the development of patent staphylococcal infections, weather community acquired, or nosocomial (Von Eiff et al., 2001; Wertheim et al., 2004, 2005b) which increases the risk by 2 to 10 times (Perl and Golub, 1998). The risk of infection in nasal carriers has been mainly studied in surgical patients (general, orthopedic, cardiac, and neurosurgeries) (Perl et al., 2002; Bode et al., 2010; Walsh et al., 2017), patients on hemodialysis (Kluytmans et al., 1996; Katneni and Hedayati, 2007), patients on chronic ambulatory peritoneal dialysis (CAPD) (Luzar et al., 1990), HIV-infected patients (Nguyen et al., 1999; Sissolak et al., 2002), and intensive care unit patients (Nardi et al., 2001). It has also been shown to be the primary risk factor for recurrent furunculosis, nasal colonization being present in almost 60% of individuals with furuncles and impetigo (Durupt et al., 2007) (**Figure 2** and **Table 3**).

SURGICAL SITE INFECTIONS

Developing a post-operative infection is a multifactorial process usually combining preoperative, intraoperative, and post-operative factors (Savage and Anderson, 2013). Nasal colonization can actually be considered as a preoperative risk factor for MRSA and MSSA infections. *S. aureus* can spread from the anterior nares to other areas on the skin surface and thus contaminate the surgical wound during the operative procedure (NICE Clinical Guidelines, 2008; Savage and Anderson, 2013). It has been shown that around 80% of strains causing a staphylococcal infection at the site of surgery have molecular identity with *S. aureus* isolates in the nares of concerned patients (Perl et al., 2002).

Surgical site infections (SSI) are one of the most common post-operative complications and represent 20 to 30% of healthcare associated infections (HCAI) (Klevens et al., 2007; Magill et al., 2012; Savage and Anderson, 2013). While enterobacteria and other uro-digestive bacteria are dominant in infections after gastrointestinal, urological and gynecological surgeries (Trautman et al., 2007), *S. aureus* predominates in orthopedic and cardiac surgery settings (Lepelletier et al., 2005; Trautman et al., 2007; Muñoz et al., 2008). In orthopedic patients, biofilms can form on the implants leading to therapeutic challenges (Chen et al., 2013). According to the French Institute for Public Health Surveillance in 2014, *S. aureus* composed 19.4% of isolated germs in SSIs after coronary surgeries, 51.9% of organisms causing SSIs in orthopedic surgeries, and 29.3% of organisms causing infections in gynecologic obstetric surgery in 2014 (Le Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales (Raisin), 2015). Similar implications have been also found in other countries (Saadatian-Elahi et al., 2008; Negi et al., 2015).

Several studies including case–control and multivariate analysis have identified nasal carriage of *S. aureus* an independent risk factor for SSIs (Kluytmans et al., 1995; Kalmeijer et al., 2000; Muñoz et al., 2008). In the case–control study from Kluytmans et al. (1995), cardiac surgery patients were screened for their

TABLE 3 | *S. aureus* nasal colonization, a risk factor for infections.

***S. aureus* nasal colonization, a risk factor for**	**Reference**
Surgical site infections after orthopedic surgeries	Kalmeijer et al., 2000; Yano et al., 2000; Weiser and Moucha, 2015
Surgical site infections after cardiac surgeries	Kluytmans et al., 1995; Muñoz et al., 2008
Bacteremia in nonsurgical patients	Wertheim et al., 2004
Catheter-related infections in dialysis patients	Luzar et al., 1990; Katneni and Hedayati, 2007
S. aureus infections in HIV-infected patients	Nguyen et al., 1999; Sissolak et al., 2002
ICU-associated *S. aureus* infections	Honda et al., 2010
Recurrent furunculosis and impetigo	Durupt et al., 2007; Demos et al., 2012
Diabetic foot ulcer infections	Dunyach-Remy et al., 2017

nasal carriage status the day before surgery and followed for the development of an SSI. *S. aureus* wound infections occurred in 40 patients as opposed to 120 controls who did not develop infection. Nasal carriage, identified in 52% of cases as compared to 12% of controls, was found to be a significant risk factor for the development of these post-operative infections with an OR = 9.6, 95% CI (3.9–23.7). In a study involving 357 patients undergoing major heart surgery, nasal carriers had a higher incidence of SSI than non-carriers (12.5% vs. 5%, $P = 0.01$) (Muñoz et al., 2008). Similar conclusions were obtained for orthopedic patients with an incidence increasing from 3- to 11-fold (Kalmeijer et al., 2000; Yano et al., 2000; Weiser and Moucha, 2015).

Surgical site infections have an important impact on the patient and the healthcare system. These infections increase hospital stay (Leaper et al., 2004), mortality and healthcare costs and decrease health-related quality of life (Anderson et al., 2009; Lamarsalle et al., 2013; Savage and Anderson, 2013). A retrospective database analysis in France concluded that staphylococcal infections led to approximately 1.0 and 1.4 additional hospitalizations per patient, 22.1 and 22.4 additional hospital days, and an excess cost of €15,475 and €13,389 after cardiothoracic and orthopedic surgeries respectively (Schmidt et al., 2015). The rate of in-hospital mortality was 2.6 times and six times higher among infected patients than non-infected patients in cardiothoracic and orthopedic procedures (Schmidt et al., 2015).

Methicillin-resistant *S. aureus* carriage could increase the risk for the development of SSIs. In a systematic review, patients colonized with MRSA were four times more likely to develop invasive infection than patients colonized with MSSA (Safdar and Bradley, 2008). MRSA infections are reported to cause up to 40% of HCAI worldwide with particularly high incidence in the United States and many European countries (McKinnell et al., 2013) and have been shown to have increased morbi-mortality as compared to MSSA (Anderson et al., 2009). In a study carried out by Anderson et al. (2009), patients with SSI due to MRSA had a 2.6 higher risk of dying within 3 months, the duration of hospital stay was 6 days longer, and the related cost was increased of $23,000 compared to patients with SSI due to MSSA. On the other hand, a meta-analysis of 31 cohort studies on *S. aureus* bacteremia, showed significantly higher mortality with MRSA than with MSSA (Cosgrove et al., 2003). However, the reasons for increased fatality rate with MRSA infections are unclear. Some authors suggest that MRSA and MSSA bacteria are equally virulent but MRSA infections usually develop in patients previously treated with antibiotics. Thus, as previously suggested, the differences in patients' fatality rate may rather reflect the severity of underlying conditions than a higher bacteria-related increased virulence (Humphreys, 2012; Hraiech et al., 2013).

INFECTIONS IN NONSURGICAL PATIENTS

Nasal carriage of *S. aureus* has also been found to be a risk factor for subsequent infections in nonsurgical patients. Wertheim et al. (2004) screened 14,008 adults who had nasal swab on admission in a nonsurgical department, 3420 (24%) were positive for *S. aureus*. The follow-up identified 81 patients who developed *S. aureus* bacteremia between 2 and 120 days after swabbing, which was three times more frequent in carriers than in non-carriers. Interestingly, the death rate from *S. aureus* bacteremia was higher in non-carriers than carriers. This could be due to the protective immunity of anti-staphylococcal antibodies (Wertheim et al., 2004; Holtfreter et al., 2006). Approximately, 80% of *S. aureus* blood isolates causing bacteremia were of endogenous origins and identical to those isolated from the anterior nares of corresponding patients, thus confirming previous report (Von Eiff et al., 2001).

A prospective cohort study evaluated the occurrence of *S. aureus* infections in 5161 patients who were screened for nasal carriage when admitted to the ICU. ICU-associated *S. aureus* infections were defined by the development of infection >48 h after their admission to the unit. These infections occurred in 113 patients and nasal colonization was associated with a 2.5 to 4.7-fold increased risk (Honda et al., 2010).

In HIV-positive patients, a prospective cohort study evaluating 231 subjects every 3 months for a minimum of two years, has reported a 6% incidence of *S. aureus* infections, nasal carriers being more at risk [$p = 0.04$, OR = 3.6 (0.9–15.4)] (Nguyen et al., 1999).

In hemodialysis and chronic peritoneal dialysis patients, most of infectious complications come from endogenous origin (Luzar et al., 1990; Ena et al., 1994). *S. aureus* is the most common isolated agent from central venous catheter-related bacteremia (Katneni and Hedayati, 2007), or exit-site infections of peritoneal dialysis catheters (Luzar et al., 1990). Nasal carriers are at increased risk of contracting these infections (Nouwen et al., 2005; Ong et al., 2017).

Staphylococcus aureus is the most frequently isolated pathogen from diabetic foot infections. A study compared the genotypic profiles of *S. aureus* strains isolated from the nares and diabetic foot ulcer infections of 276 patients. The bacterium was isolated from both sites in 36% of the population, and identical strains were found in 65% of cases. Further investigations should be performed in order to confirm the benefit of screening and treating nasal carriers in this population (Dunyach-Remy et al., 2017).

Nasal carriage of *S. aureus* constitutes a risk factor for the development of skin and soft tissue infections caused by this germ in non-hospitalized and non-diseased subjects (Chou et al., 2015). It has been shown to be the primary risk factor for recurrent furunculosis (Demos et al., 2012). Nasal carriage is also a risk factor for secondary bacterial pneumonia in patients having influenza A virus infection. The viral infection causes host physiologic changes that generates the dissemination of *S. aureus* from nasal tissue to the lungs as demonstrated in a mouse model (Reddinger et al., 2016).

PERSPECTIVES

Nasal carriage of *S. aureus* is multifactorial and can predispose carriers to subsequent infections. Nasal decolonization of carriers is therefore recommended in patients undergoing cardiothoracic and orthopedic surgeries (De Jonge et al., 2016).

A full understanding of host-pathogen interactions can help find new decolonization strategies. New fields on colonization mechanisms should be investigated. For example, the role of mycobiota starts to be described in the pathophysiology of chronic respiratory diseases (Brégeon and Rolain, 2015). Interaction of nasal *S. aureus* with the nasal fungal communities would be an interesting perspective to develop. On the other hand, some reports suggest that *S. aureus* can regulate host inflammatory gene expression (Modak et al., 2014). Epigenetics mechanisms could be interesting to investigate in order to better understand tolerance mechanisms in *S. aureus* colonization processes.

AUTHOR CONTRIBUTIONS

AS wrote the review paper. FB, J-LM, OB, and J-MR corrected the manuscript. All authors approved and revised the final version of the manuscript.

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