Staphylococcal Carriage Status: Implications, Mechanisms and Practical Guidelines

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Introduction

Staphylococcus aureus is a commensal and a constituent of the cutaneous microbiome, which has been implicated in a number of conditions like recurrent furunculosis, abscesses, and Staphylococcal scalded skin syndrome. It remains dormant in a large number of populations viz hospital workers, sanitation workers, and asymptomatic carriers.

Factors allowing S. aureus to adapt to the skin microbiota

By adapting to the local skin milieu, *S. aureus* has become a successful member of the cutaneous microbiota. However, for any bacterium (note: The singular of bacteria is bacterium) to successfully adapt to host conditions, the following conditions, must be fulfilled:

A. Downregulation of virulence factors: *S. aureus* possesses a multitude of virulence factors e.g. ET A, B, and many more that allows it to quickly lyze the cell and cause havoc to the immune system. However, if such virulence was allowed to continue, *S. aureus* would have been quickly detected by the host immune response and destroyed. To avoid detection, *S. aureus* tightly downregulates its virulence during its stay as commensal. This is achieved by a complex genomic pathway that involves three factors – agr quorum sensor system, the sarA protein family, and alternative sigma factors. It has been shown that compared to *Staphylococcus* isolated from hospital-acquired pneumonia patients, the *Staphylococci* that colonize an individual possess higher levels of alternative sigma factors – namely sigB and sigH, both of which work in tandem as negative repressors of the genes for virulence. In addition, *Staphylococcus* isolated from colonization sites possess higher levels of regulatory factors - such as SarA, Rot, and MgrA, which down-regulate the gene expressions of virulence factors. This is believed to offer an evolutionary advantage by allowing the bacteria to escape detection by the host immune system.[1-4]
B. Adhesion mechanism: There is evidence that adhesion to cell membranes is tighter in *S. aureus* colonizing the skin than in pathogenic virulent ones. The tighter adherence ensures it is not rubbed off the skin regularly during washing/itching.
C. Genes that enhance colonization such as defense against Reactive Oxygen Species (Remember nose is exposed to a lot of Oxygen), and evasion of the immune response are upregulated.

Colonization risk factors

There are many risk factors postulated for Staphylococcal carriage status and these include:

1. Living in a hot and humid environment
2. Healthcare occupation
3. Having anemia or other hematological deficiencies
4. Diabetes, gout, metabolic diseases
5. Blood dyscrasias

Colonization sites[5,6]

Various sites have been reported to have been colonized by *S. aureus* and they include[5-7]

1. The squamous epithelium on the nasal septum adjacent to the nasal ostium
2. Axillae (8%)
3. Chest and abdomen (15%)
4. The perineum (22%)
5. The intestines (17-33%)

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6. Vagina (5%)
7. The pharyngeal wall (4-64%)
8. The umbilicus (30-53%)
9. Fingertips (5-30%)

Types of carriage[6,7]

Based on the methods of sampling, three types of carriage have been detected:

- Persistent: Defined as two or more cultures performed 1 week apart and both are positive
- Intermittent: Defined as only one out of two cultures performed 1 week apart is positive
- Non-carriage: Both cultures are negative.

It is well known that persistent carriers have a higher bacterial load than non-persistent carriers.

Duration of carriage[8]

The duration of carriage is 4 – 14 days post inoculation for intermittent and non-carriers while it is on average 154 days for persistent carriers.

Determinants of bacterial carriage

There are many factors both from the host side and from the bacteria side which determine whether successful bacterial colonization will occur or not. They are:

Bacterial determinants

Expression of adhesion molecules sdr C, sdr D, sdr E: In general, the skin is exposed to a lot of rubbing and scrubbing which in a normal setting usually dislodges the bacteria. These adhesion molecules ensure tight adhesion to the cell membranes, particularly of the skin.

Clumping proteins clf A, clf B, fnb A, fnb B: They help in clumping of RBCs around them to protect them from further attacks of leukocytes. Clf (A and B) represent clumping factors present in the staphylococcal cell wall. They help in clumping of RBCs and thereby form a protective layer of fibrin and RBC meshwork around them. Fnb A and B represent fibronectin-binding proteins which also work in the same way.

Biofilm formation by binding of clf B to CK 8 and 10 on keratinocytes: A biofilm is a collection of bacterial slime, bacteria, and host keratinocyte slough which results in a tough membrane, restricting the access to antibiotics and host immune cells. Biofilm formation is now implicated in many cases of emerging bacterial resistance.

Other bacterial flora: Corynebacteria on the nose significantly reduces staphylococcal carriage. *Corynebacterium accolens* releases various factors, including triacylglycerol lipase named LipS1 which breaks down the triacyl glycerol in the niche sites into free fatty acids e.g., myristic and palmitic acid which is detrimental to the growth of *Staphylococcus aureus*; auxotrophic competition is also responsible.[9]

Quorum sensing: *Staphylococcus* can self-regulate their number on many occasions – if the cell number is too great, the cells signal to other cells to stop multiplying and in this way, the population is kept in check. This mechanism might explain why *Staphylococcus* has been so successful in the colonization of our skin since any excess bacteria would be detected by the immune cells and rapidly killed.

Host determinants[8]

Toll-like receptor polymorphisms: These are a part of the innate immune system. Their signaling is mediated through protein receptors on the surface that look like lamp posts, hence the name Toll. They detect molecular patterns that are common to all pathogens and thereby mount an immune system in a non-specific manner. There are around 20 types of TLR discovered so far and each has specific functions; polymorphism can enhance susceptibility to staphylococcal carriage.

Defensin, and cathelicidin polymorphisms: They are natural antipathogenic molecules, which are reduced in some conditions like atopic dermatitis. Their deficiency can account for increased staphylococcal carriage in these conditions as well as host carriage.

Mutations in glucocorticoid receptor genes: A 80% reduced carriage is seen in those with a particular mutation in GCR, which results in a hyperactive immune system.[9]

Reduced Vit D levels: It has been postulated that reduced vitamin D levels correlate with altered immunological functions which may allow *Staphylococcus* to proliferate.[9]

Chronic Inflammation – viz atopic eczema: It has been shown that atopic eczema is associated with increased colonization by *Staphylococcus aureus*. It has been postulated that impaired barrier function, the predominance of Th2 phenotype, and reduced expression of antimicrobial peptides allow *Staphylococcus* to successfully colonize the skin.

Host occupational status: This is especially an important and widely accepted cause of colonization. Working in hospitals or being associated with the health care settings has been proven to be an important risk factor in colonization. It is also believed that such carriage in hospital workers is responsible for the transfer of bacteria from colonized to non-colonized hosts.

1. The risks of staphylococcal carriage status[10]
   The carriage has been identified as an important risk factor for serious infections in these patients:
   Those undergoing surgery, or hemodialysis
   Those with HIV infection and AIDS,
   Those with intravascular devices and those colonized with MRSA.
   Primary and secondary immunodeficiencies (including people living with HIV and AIDS) and Type 2 diabetes mellitus
   Those on systemic immunosuppressants

Elimination of carriage appears to be an attractive preventive strategy in patients at risk.

2. Staphylococcal Niche sites: These are the sites where *staphylococcus* is most often found and have been included in Table 1:[9,10]

Table 1: Various niche sites for staphylococcal colonization

Nose: At anterior nares, at the junction where bony nasal septum meets mucosae
Axillae
Chest and abdomen: Periumbilical
Perineum
Posterior pharyngeal mucosae
The umbilicus
Fingers, especially in hand eczema patients

3. How to eliminate staphylococcal carriage:[10-13] The regimens commonly used have been summarized in Table 2.

Guidelines for staphylococcal elimination carriage

Indications of staphylococcal carriage elimination

Recurrent SSTI around mouth and nose: These most often take the form of recurrent furunculosis and abscesses. Perianal abscesses are also seen. The benefits of weekly pulses of mupirocin are well established - in a recent study, the relative incidence before and after mupirocin prophylaxis was 0.84 vs 0.03, which was statistically significant.[11-13]

Before undertaking surgery on the skin and soft tissues: This is associated with a reduced rate of post-operative

Table 2: Various regimens used for eradication of staphylococcal carriage status

Intervention	Regimen	Success rate	Comments (if any)
Mupirocin	Application twice daily×5 days every month for 3 months over niche sites (mentioned above).	94% after 1 week from nose	Efficacy rate equal for MSSA and MRSA Efficacy rate is higher for regimens that also include other body sites viz axilla than only nose Resistance rate of only 1%
Bacitracin nasal oint	Apply twice daily×7 days as above	29%	Effective only in 29%. Efficacy same for MRSA and MSSA
Tea Tree oil	Apply once to twice daily×7-14 days	44% at 2 weeks from nose	Compared to Mupirocin, Odds ratio of treatment failure is 1.88
Povidone iodine 10%	Single application if planned for surgery (unrelated)	Very potent 1-6 hours post application	Not for daily prophylaxis
Chlorhexidine washings	Nasal and oral washings. Chlorhexidine nasal spray, gel	Not yet determined; used chiefly in combination with other agents	Also reduces covid 19 load by log 3-4 times
Neomycin ointment	Twice daily for 2 weeks	No longer recommended since resistance	No longer used
Cotrimoxazole DS tablets (800/160 mg)	1 tablet orally×7-14 days Often combined with Tab Rifampicin 600 mg Once daily or Nasal fusidic acid	64%	Usually used in combination
Tab Clarithromycin 500 mg	1 tablet orally per day for 7-14 days	88%	Rapid development of macrolide resistance among other bacteria
Tab Ciprofloxacin 500 mg	1 tablet orally for 2 weeks	Not known, since trial was terminated prematurely following widespread emergence of MRSA in an unrelated incident	?
Cap Doxycycline 100 mg	1 cap once daily×2 weeks	Combined efficacy 74%	Often in combination with ointment mupirocin
Tab Rifampicin	1 tab once daily×2 weeks	62% at two weeks	Often in combination with topical agents
Tab Vancomycin oral 40 mg/kg	Orally daily	Very potent at clearing gastrointestinal carriage	Before major surgery etc
Bleach Baths	Half cup of household bleach is added to a bath tub of 40 gallons of water. Bathing time is 10 minutes. The skin is again cleaned with warm water after bath	Considered very potent	Considered effective especially in atopic eczema, where it reduces exacerbations of atopic eczema by reducing bacterial colonization
Fusidic acid	Locally twice daily in niche sites	Not known, but considered very potent	Important especially in mupirocin resistant cases

infections. This has also been validated in major surgeries involving infected sites.[13,14]

Community-acquired pneumonia and bacteremia prevention in the elderly and other immunocompromised: The incidences of pneumonia and other fatal infections are reduced. Yearly or twice-yearly prophylaxis is probably enough to reduce carriage status; however formal studies are needed.[15]

Predictor of pneumonia in post-burn patients: Staphylococcal carriage status is one of the best predictors of pneumonia and bacteremia in post-burn patients. Elimination of carriage status might help in improving the survival among these patients.[16-18]

Severe recalcitrant hand eczema: The evidence that in non-infected hand eczema, elimination of staphylococcal carriage results in improvement is at best equivocal. It is mostly derived from the coincidental elimination of hand *staphylococcal aureus* when mupirocin is also applied in the nasal nares. In many cases, improvement is also seen, coincident with such elimination.[19--22]

Atopic dermatitis and psoriasis: Current guidelines do not recommend routine decolonization in either condition. However numerous studies have revealed worsening episodes of atopic eczema with colonization by *staphylococcus* and improvement on decolonization.[23] It may be prudent to attempt decolonization in particularly recalcitrant atopic eczema where other indicators of staphylococcal colonization (such as recurrent folliculitis around the nose, and mouth) are present. In chronic plaque psoriasis, due to barrier defect, in spite of high levels of cathelicidins, human beta-defensin 2, and other antimicrobial peptides, staphylococcal colonization occurs. It has been noted that psoriatic lesions tend to worsen in both thickness and area with increased colonization. Hence decolonization can be attempted in such cases.[24]

Conclusion

The dermatologists should familiarize themselves with the various modalities available to eradicate *staphylococcus* from the skin, which often translates to a reduction in systemic, skin and soft tissue infections. Being simple, cost-effective, and of a relatively shorter duration, such prophylaxis should be given wherever indicated.

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Conflicts of interest

There are no conflicts of interest.

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