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Coagulase-Negative Staphylococci

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ABSTRACT

Staphylococci are major pathogenic bacteria responsible for a range of diseases in humans. The most commonly isolated microbes in a hospital microbiology laboratory are staphylococci. The general classification of staphylococci divides them into two major groups;Coagulase-positive staphylococci (e.g, *Staphylococcus aureus)* and Coagulase-negative staphylococci (e.g, *Staphylococcus epidermidis*). Coagulase-negative staphylococci (CoNS) are common commensal colonisers of the human skin, several studies have been carried out in order to understand the pathogenicity mechanisms of CoNS. The well known determinants in the pathogenesis of CoNS infections are their ability to form biofilms and an exceptional resistance to several antibiotics. Additionally, it is now hypothesised that commensal bacteria might be a reservoir of pathogenic determinants .

This assignment will show the overview of CoNS ,pathogenicity,virulence factor,infections, risk factors,identification treatment and some discussion about the mechanism of antimicrobial resistance.

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General Overview Of CoNS

Staphylococcus genus consists of 47 species and 23 subspecies, of these, 38 described as coagulase-negative species. Coagulase-negative staphylococci (CoNS) are a type of staph bacteria that commonly live on a person's skin. Typically consider CoNS bacteria harmless when it remains outside the body. However, the bacteria can cause infections when present in large amounts, or when present in the bloodstream.

- Coagulase-negative staphylococci (CoNS)is characterised by a gram-positive, spherical cell of (0.5-1.5µm) in diameter, occurring as single cocci, in pairs,as a tetrad, short chains, or irregular cluster. Furthermore no-motile, no-spore forming,encapsulated, catalase positive, cytochrome negative in modified oxidase test, also susceptible to lysostaphin and resistance to bacitracin and they grown in presence of 10% NaCl between 18℃ and 40℃.
- These groups of bacteria are facultative anaerobes so they can grow in the presence of oxygen.
- Besides, they are reduced nitrate to nitrite, fermenting carbohydrate and producing pigments when growing on media that vary from white to deep yellow. Colonies appearance round, smooth, raised and glistening on solid media.
- Called coagulase-negative staphylococci because they lack coagulase is a surface protein, which can convert fibrinogen to fibrin and resulting in clot formation in plasma.
- The cell walls of CoNS contain important cell-adherence factor: peptidoglycan,teichoic acids,and protein.
- Their peptidoglycan chain cross-linked pentaglycine residue (affected by lysostaphin); micrococci do not have glycine-residue in their peptide bond (resistant to lysostaphin) and neither do they have teichoic acids.
- Recently CoNS got an important opportunistic pathogen associated with nosocomial infection and community-acquired infection.

- They can adhere to medicinal instruments and surfaces through a slime layer which has a mucopolysaccharide arrangement, therefore they can simply colonize and spread with-in the hospital environment. The slime feature also assists in pathogenicity by protecting them from phagocytosis, chemotaxis, and antimicrobial agents.
- CoNS are the most commonly isolated organism related with clinical infection and communal bacteria residents of the skin, and mucous membranes humans.
- They cause a variety of infections in immune-compromised individuals and people with implanted medical devices.
- The incidence of sepsis infections in neonates caused by CoNS is still very high and preventing and treating disease remains difficult in nosocomial patients and causes a significant number of deaths.
- CoNS isolated from hospital environments are sometimes resistant to various antimicrobial agents.
- About 80%-90% of CoNS isolates related with hospital infections are methicillin-resistant (MR_CoNS)

CoNS Species

CoNS include many species:-

- *S. epidermidis, S. caprae, S. saccharolyticus, S. capitis*
- *S. haemolyticus, S. devriesie, S.jeffensis*
- *S.petrasii(ssp.croceilyticus,ssp.petrasii) ,S. lugdunensis*
- *S. hominis (ssp.hominis, ssp.novobisepticus)*
- *S.warneri, S.pasteuri*
- *S. saprophyticus (ssp. Saprophyticus, ssp. Bovis)S.equorum (ssp. Equorum, ssp. linens), S.xylosus*
- *S. succinus (ssp. Succinus, ssp. Casei), S. gallinarum, S.pettenkoferi, S. massiliensis.*
- *S. conhii (ssp. conhii , ssp. urealyticus)*
- *S. nepalensis , S. klossi, S. arletta*
- *S. sciuri (ssp.sciuri, ssp.carnaticus, ssp.rodentium)*
- *S. fleurettii, S. lentus, S. stepanovicii, S. vitulinus, S .simulans, S. carnosus (ssp.utilis, ssp.carnosus)*
- *S. codimenti, S. piscifermentans, S. muscae, S. microti, S.rosteri*

In regard to other CoNS, the clinically defined "*S. epidermidis* group," comprising *S. epidermidis* and *S. haemolyticus* as the most prevalent species, along with other traditionally included species (e.g., *S. capitis, S. hominis, S. simulans,* and *S. warneri)*, can be distinguished from *S. saprophyticus* by the latter being a specific cause of acute urethritis. However, *S. saprophyticus* may also be found as a pathogen causing infections like those known for members of the *S. epidermidis* group. Some of the recently discovered CoNS species, such as *S. pettenkoferi* and *S. massiliensis*, might belong to this group as well. Notably, gradations in pathogenic capacity within this heterogeneous group occur not only at the species level but also at the strain level. Recently, *S. lugdunensis* has increasingly become known as a CoNS species in an "intermediate position" between *S. aureus* and the *S. epidermidis* group, displaying clinical features of both groups.

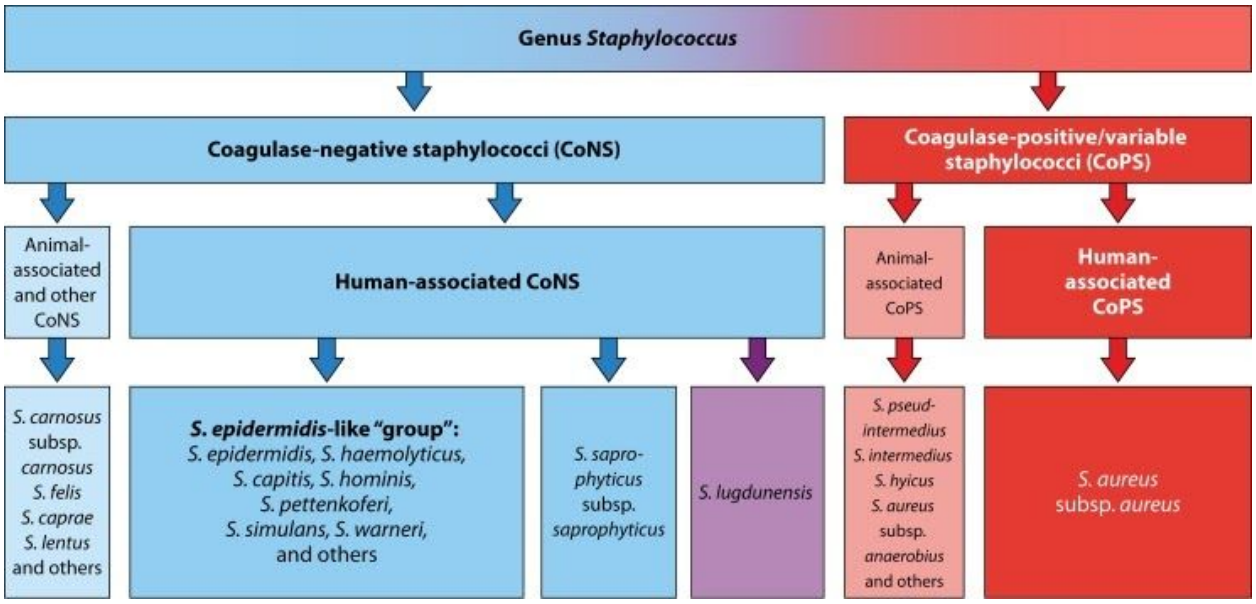


Table-1: Clinical and epidemiological schema of staphylococcal species, based on the categorization of coagulase as a major virulence factor and its resulting impact on human health .

Habitat

Many coagulase negative staphylococci are part of normal bacterial flora on human and animals. Along with diphtheroids, they form a large part of skin flora. The most common species is S. epidermidis, followed by S. hominis and S. hemolyticus. S. capitis colonizes the scalp, S. epidermidis is found on head and trunk while S. hominis is found on arms and legs. Whenever they were isolated from the clinical specimens, they were considered as contaminants from the skin or mucosal surfaces. Over the last two decades the roles of S. epidermidis and other coagulase-negative staphylococci have been recognized in causing nosocomial infections.

- ***S. epidermidis* group.**In humans, *S. epidermidis* is the most frequently recovered staphylococcal species . This bacterium colonizes the body surface, where it is particularly prevalent on moist areas, such as the axillae, inguinal and perineal areas, anterior nares, conjunctiva, and toe webs.

- ***S. lugdunensis*.** *S. lugdunensis* is an integral part of the normal skin flora. *S. lugdunensis* is found particularly in the pelvic and perineum regions, in the groin area, on the lower extremities, and in the axillae.

- ***S. saprophyticus* subsp. *saprophyticus*.** *S. saprophyticus* subsp. *saprophyticus* frequently colonizes the rectum and genitourinary tract, in an age- and season-dependent manner (preferentially in summer and fall)

- **Other CoNS.** *S. pasteuri* was found in a large percentage (65.7%) of drinking water samples from a distribution network responsible for supplying water to consumers . *S. carnosus*, *S. condimenti*, *S. equorum*, *S. piscifermentans*, *S. succinus*, and *S. xylosus* represent staphylococcal species that are typically associated with fermented foods and their starter cultures.

Pathogenicity

Staphylococci, with the capacity to colonize and infect human and animal hosts, own a species- and strain-specific arsenal of diverse strategies to enable adherence, aggression, invasion, persistence, and/or evasion of both innate and adaptive immunity. However, in comparison with *S. aureus*, clearly less is known about the virulence mechanisms in CoNS, except for aspects of biofilm formation by *S. epidermidis*. In general, CoNS isolates lack the virulence determinants responsible for aggression. Nevertheless, factors involved in colonization may successfully support the bacterium-host interaction, a phenomenon that may be based, at least partly, on the multifunctional character of various staphylococcal virulence factors known to exhibit redundant and overlapping functions.

1. Adherence to Surfaces and Phases of Biofilm Formation

The critical first event in establishing colonization and/or infection by staphylococci is adherence to host or—as a consequence of modern medicine—foreign body surfaces. The colonization of the polymer surface of a medical device by formation of a multilayered biofilm has been considered the critical factor in the pathogenesis of foreign body-associated infections caused by CoNS

Attachment to abiotic surfaces

The attachment of bacteria to various biomaterials is determined by the surface properties of the bacteria and the foreign bodies. It involves physicochemical forces, such as hydrophobic interactions, van der Waals forces, and charge. These interactions may be mediated by different surface components of CoNS, i.e., CWA proteins that are covalently linked to peptidoglycan; surface-associated proteins that are surface attached by different mechanisms, such as hydrophobic or ionic interactions; and non proteinaceous surface molecules, such as teichoic acids.

(i) Noncovalently linked surface-associated proteins.
(ii) Covalently linked surface proteins
(iii) Teichoic acids

Attachment to biotic surfaces

Shortly after the insertion or implantation of a medical device, it becomes covered with ECM and plasma proteins, such as fibrinogen, fibronectin, thrombospondin, collagen, von Willebrand factor, and vitronectin, or with host cells, such as platelets. Some of these host factors may serve as receptors for specifically attaching staphylococci that express the respective adhesins on the cell surface . Thus, in the later steps of the adhesion process *in vivo*, adherence of CoNS to such host factors may be crucial. Moreover, in some instances, CoNS seem to be capable of attaching directly to the host tissue, i.e., to the endocardium in the pathogenesis of native infective endocarditis, which may be caused not only by *S. aureus* but also, occasionally, by *S. epidermidis.*

(i) Noncovalently linked surface-associated proteins
(ii) Covalently linked surface proteins
(iii) Teichoic acids

2. Biofilm accumulation and maturation

After succeeding in primary attachment to biotic or abiotic surfaces, bacteria multiply and accumulate in multilayered cell aggregates, in a process that necessitates intercellular adhesion. Intercellular adhesion may be mediated by different specific macromolecules, such as polysaccharide adhesins and certain proteins that induce cell aggregation. Moreover, due to its anionic character, eDNA generated by lysed cells and teichoic acids may interact with the positively charged polysaccharide adhesins, thereby increasing biofilm accumulation by additionally acting as a “glue.”

3. **Biofilm detachment**

Upon biofilm maturation, individual bacteria or clusters of bacteria may dissociate and disperse via the bloodstream. Following this step, further locations in the body may be colonized by circulating bacteria, leading to metastasis of infection. The disintegration of biofilms may be mediated by different mechanisms, such as a variety of extracellular enzymatic activities or the so-called phenol-soluble modulins (PSMs).

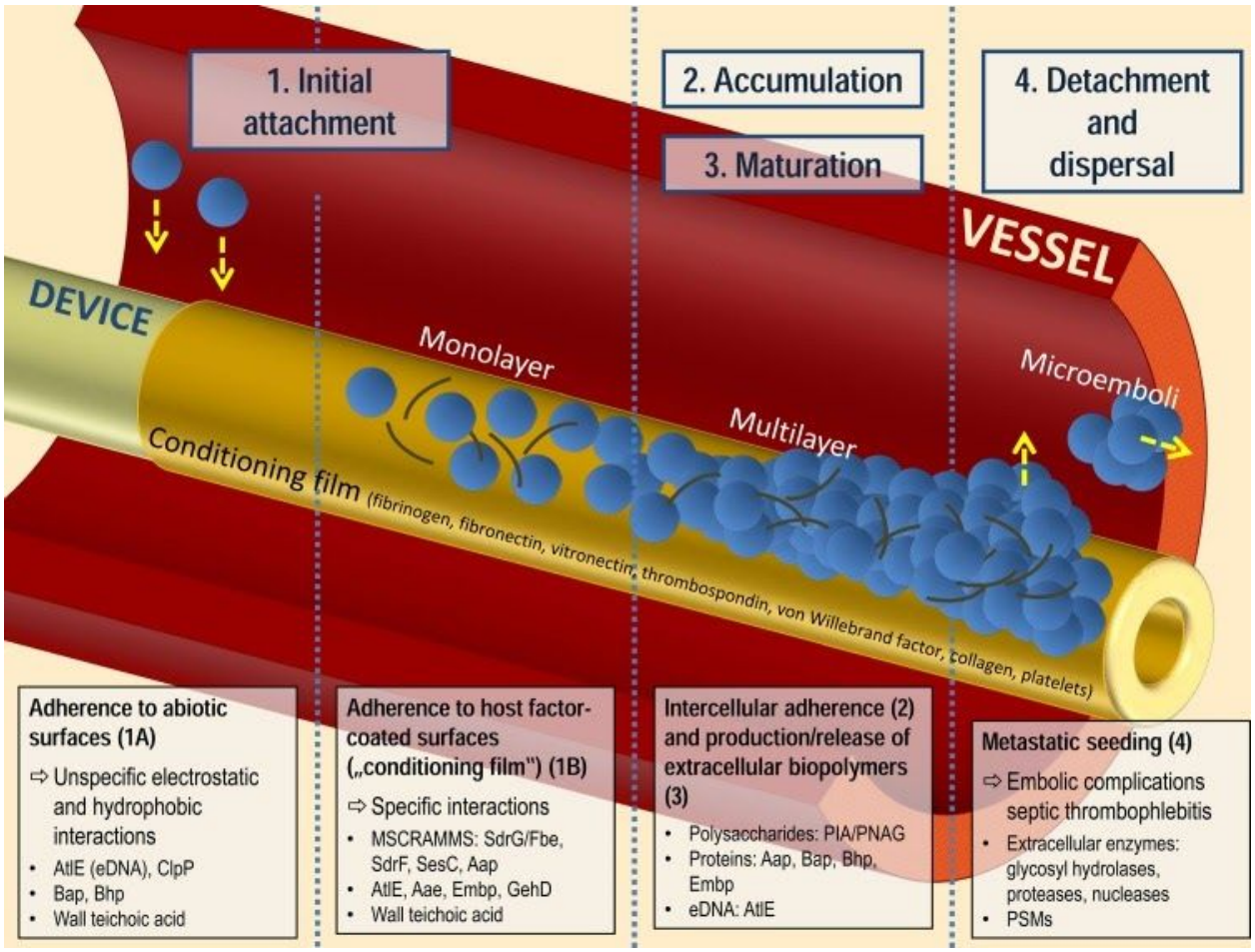


Fig 1: Pathogenesis of catheter-related infections and factors influencing biofilm genesis. The image shows the three-step process of biofilm formation on the surface of an intravascular catheter, with rapid initial adhesion and attachment of CoNS microorganisms to the polymer foreign body surface resulting in a monolayer (1), followed by a prolonged accumulation phase which involves cell proliferation, intercellular adhesion processes, and maturation (2 and 3). (4) Finally, microorganisms may disaggregate from the macrocolony and drift into the bloodstream, resulting in metastatic and embolic complications.

Virulence Factors

Virulence factors in CoNS are not very clearly established and documented but many such factors are already known for S. aureus. Compared to S. aureus, no major virulence factors or toxins have been found in CoNS and it is clear that development and persistence of CoNS infections must be due to alternative mechanisms (Huebner and Goldmann,1999). The following are some of the proposed structural components involved in CoNS virulence.

Plasmids and Transposons

Plasmids are involved in the spread of antibiotic resistance determinants among staphylococci including CoNS (Forbes and Schaberg, 1983; Malachowa and Deleo,2010). For example, Mobile Genetic Elements (MGEs) which encode methicillin resistance are frequently transferred from S.epidermidis to S. aureus (Hanssen et al., 2004)

Surface Proteins

Certain structural components are thought to be involved in the adherence process. Veenstra et al. (1996) reported that a fimbria-like protein is responsible for this attachment. Other investigators have suggested that a 140-kD extracellular protein is an important adherence tool of S.epidermidis (Hussain et al,1997). According to Rupp and Archer (1992) an uncharacterized heam-agglutinin is also involved in adherence to polymer surfaces. Rohde et al. (2006) described Autolysin (AtlE) in attachment to various surfaces.

Capsular polysaccharides

Capsular polysaccharides have a major role as virulence factors but little is known about their chemical nature and specific roles. Bayston and Penny (1972) was the first to propose the role of polysaccharides in the pathogenesis of S. epidermidis infecting Central Nervous System (CNS) shunts when they observed a substance they named as “ slime “ which could not be stained by dye specific for polysaccharides. Tojo wt al. (1998) characterized a specific polysaccharides which was named Capsular polysaccharides. Polysaccharide adhesion (PSA) due to its involvement in adhesion.The exact role of the different structural components ofCoNS virulence factors is still poorly understood .It is essential to determining the structural components of CoNS is still poorly understood.

Infection Types

Several different types of CoNS bacteria fall within this category. Often, each bacteria type may cause a different infection. Examples of these types include the following:

S. epidermidis

This CoNS bacteria commonly live on the skin and don't usually cause infections. A person who has a condition that compromises the immune system, such as lupus, is more likely to experience this infection type. Higher risk is also seen in people who have a foreign body implant, such as:

- indwelling urinary catheters
- central intravenous (IV) lines
- prosthetic joints

This bacterium causes skin infections and fever. The skin may be red, swollen, and inflamed. Sometimes the skin may leak pus.

S. saprophyticus

This CoNS bacteria type can collect in the urinary tract and cause urinary tract infections (UTIs). Symptoms associated with UTIs include:

- pain when urinating
- fever
- flank pain, or pain in the lower back that radiates to the stomach
- blood-tinged urine

S. lugdunensis

This bacteria species can cause infectious endocarditis. This is a serious infection on the heart valves, which can affect heart function and vessels away from the heart. The infection itself closely resembles endocarditis caused by S. aureus.
Symptoms of endocarditis may include:

- fever
- chills
- aching joints
- shortness of breath
- chest pain when breathing
- a new-onset heart murmur

These aren't the only CoNS bacteria types. Others include:

- *S. simulans*
- *S. hominis*
- *S. haemolyticus*
- *S. warnerii*

The CoNS bacteria tend to thrive in warm, moist environments. These include the:

- armpits
- feet
- groin
- behind the knees
- in the crook of the elbow
- in the folds of the stomach

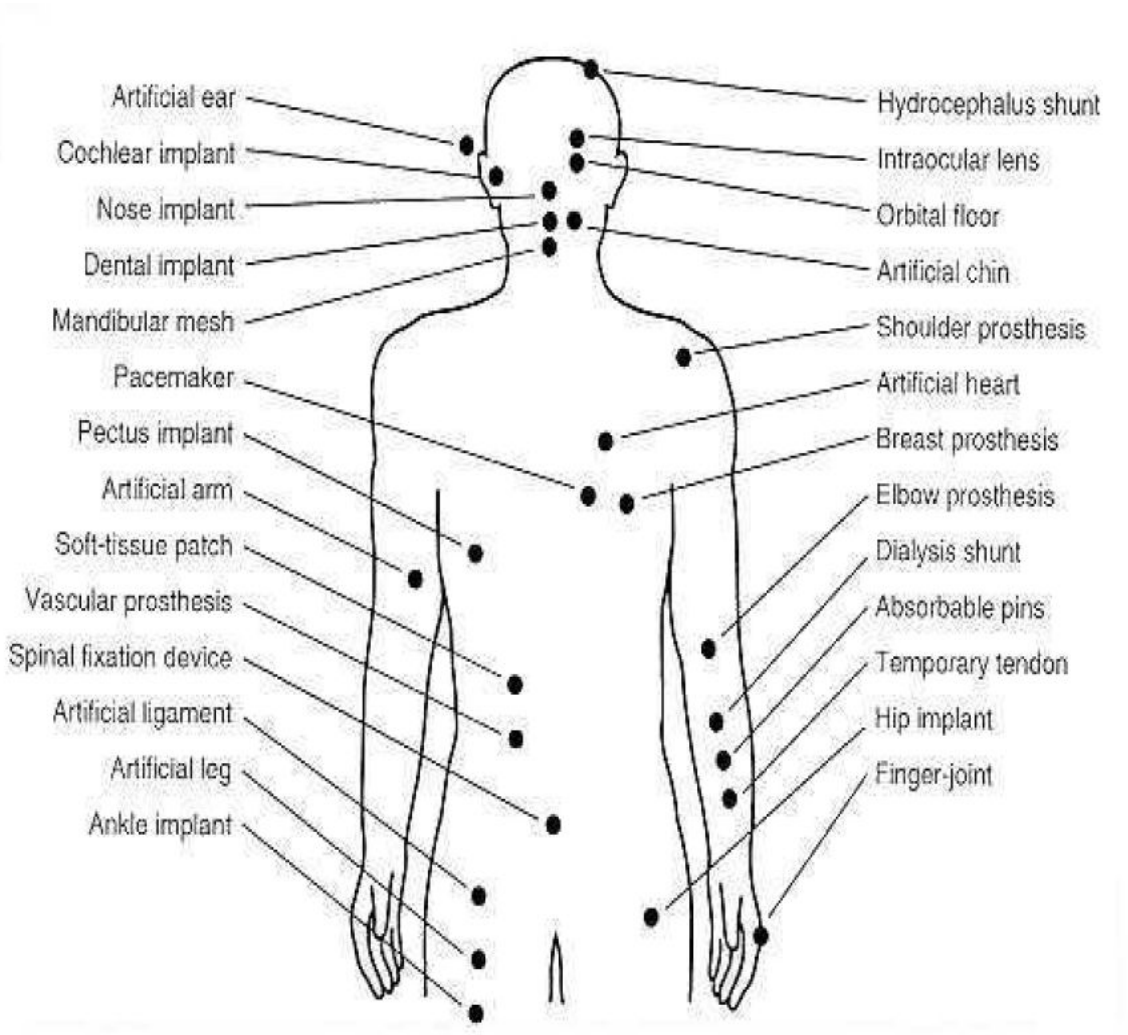


Fig 2 : Infections associated with indwelling devices (Adapted from Foster,2009)

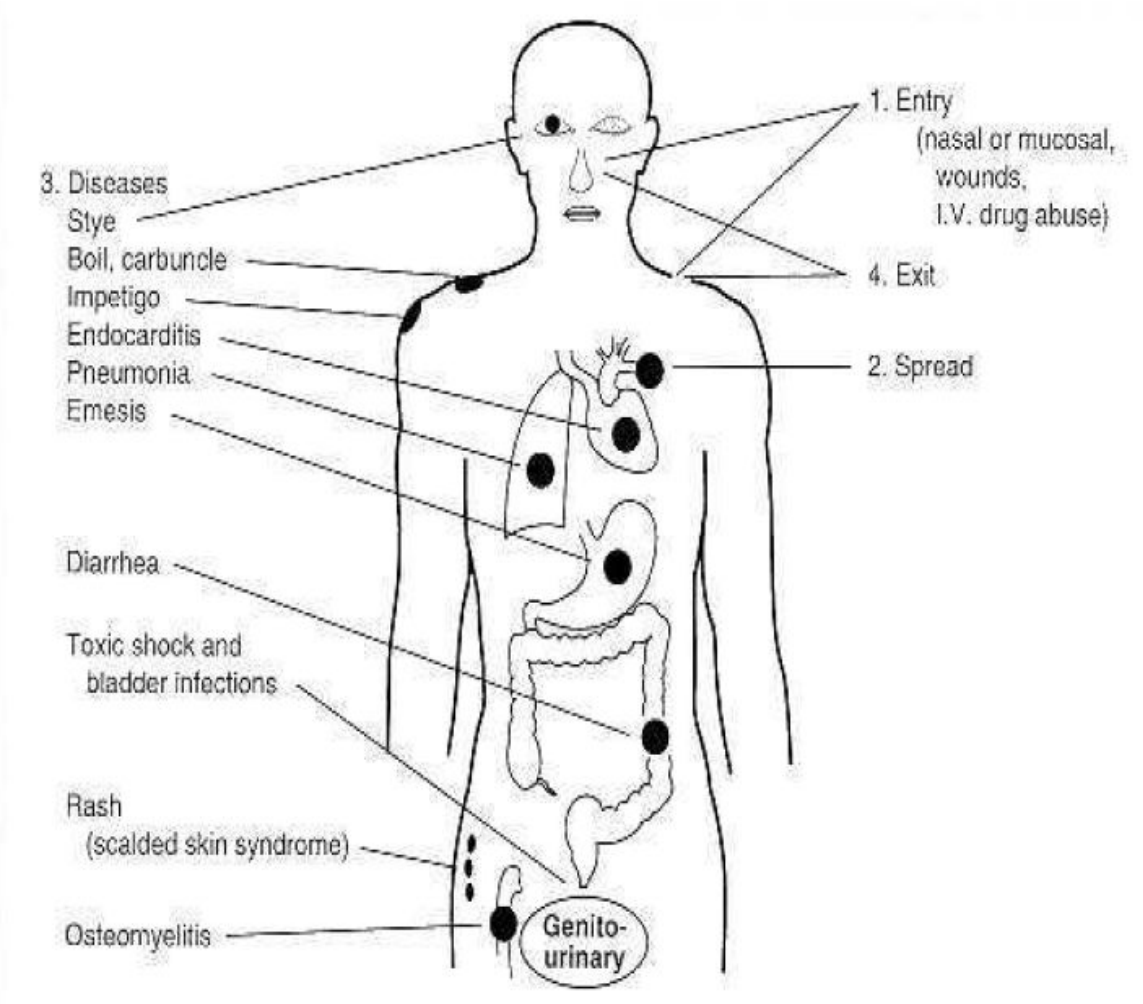


Fig 3 : Pathogenesis of staphylococcal infections (Adapted from Foster,2009)

Causes And Risk Factors

According to a 2007 review, most CoNS infections are nosocomial. This means a person is exposed to the bacteria in a hospital. A person may have had surgery or an illness that required a stay in the hospital where CoNS bacteria outside the body got into the body.

For this reason, it's important that healthcare providers practice excellent hand hygiene. It's also vital they practice sterile techniques when inserting catheters, starting IVs, and performing surgery.

Those who are at greatest risk for CoNS infections include:

- People with a compromised immune system. This includes people with cancer, older adults, the very young, or those who have an autoimmune disorder.
- People with an indwelling urinary catheter.
- People with a central IV line. An example is a peripherally inserted central catheter (PICC) line.
- People who've undergone certain procedures. This includes people who've had joint replacement surgery, a cerebrospinal fluid shunt, or a pacemaker, ocular, or cosmetic implant.

The presence of these risk factors is why many orthopedic surgeons won't perform a joint replacement surgery on someone who has a skin infection. They will wait until the infection has healed.

Treatment

Treating CoNS infections are traditionally difficult because many bacterial strains have become resistant to antibiotics. The medications doctors normally prescribe to kill the bacteria aren't effective.

- Vancomycin is generally the cornerstone for treatment of infections due to S. epidermidis and other CoNS, because 80-90% of strains responsible for nosocomial infections are resistant to semi-synthetic, penicillinase-stable penicillins, such as oxacillin and nafcillin. Dosing of vancomycin is based on actual weight and renal function. The benefit of higher-dose vancomycin (trough levels of 15-20 ug/mL) is not well-defined for CoNS infections and may lead to increased risk of nephrotoxicity. Many clinicians add rifampin (600 mg/day) to regimens containing vancomycin when treating a biomaterial-based infection (prosthetic joint infection, prosthetic valve endocarditis, etc.).
- A characteristic of CoNS infections involving medical devices (intravascular catheters, vascular grafts, prosthetic joints, CSF shunts, etc.) is the presence of biofilm and "persister" cells. Biofilm-associated CoNS are generally much less susceptible to antibiotics than planktonic cells, and, oftentimes, effective therapy of biomaterial-based infections requires removal of the device.
- CoNS responsible for nosocomial infections are almost always resistant to multiple classes of antimicrobial agents.

  Approximately 95% of strains of S. epidermidis isolated from well-defined healthcare-associated infections are resistant to penicillins due to production of beta-lactamase. Most strains are also resistant to methicillin due to mecA-mediated production of PBP2A. Further complicating the picture is the fact that phenotypic expression of methicillin resistance is much more heterotypic than observed in S. aureus. In addition, resistance to other classes of antibiotics is common, including resistance to fluoroquinolones, macrolides, lincosamides, and trimethoprim-sulfamethoxazole.
  To detect heterotypic oxacillin-resistance in CoNS, the MIC breakpoint is

lower for CoNS (except S. lugdunensis) than S. aureus (0.5 ug/mL versus 4 ug/mL, respectively). Commercial assays are available for detection of mecA or PBP2A. The commercially available automated identification and susceptibility testing systems (e.g., MicroScan, Vitek, etc.) perform adequately in defining susceptibility to other classes of antibiotics.

Fortunately, several newer antibiotics have been introduced that have activity against multiple-resistant CoNS. These newer antibiotics include linezolid, daptomycin, tigecycline quinupristin-dalfopristin, telavancin, and ceftaroline.

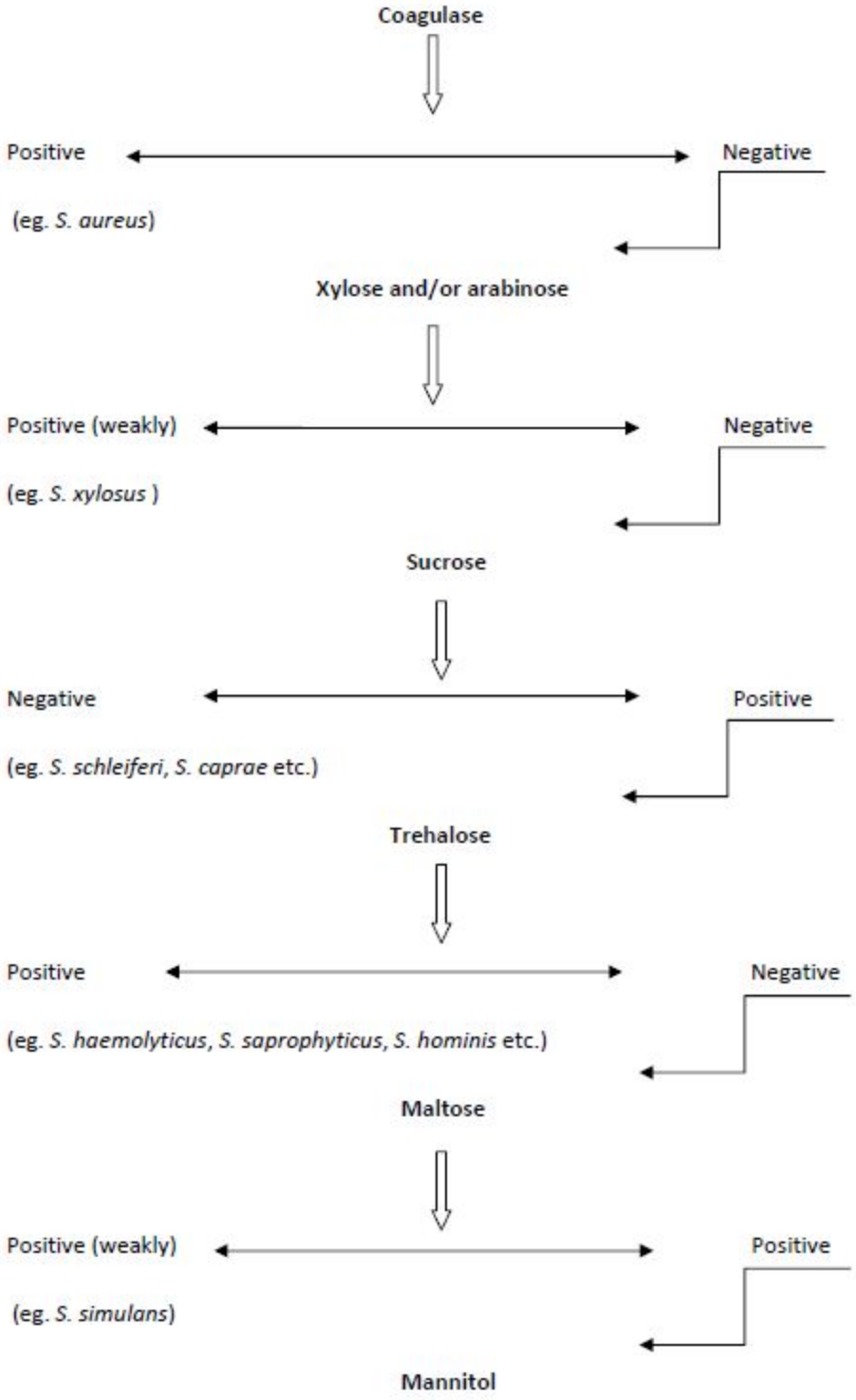
Host Factors

- The key immune system factor that protects against invasion by CoNS is intact skin and mucosal barriers and functional neutrophils.
- Patients at higher risk of infection because of CoNS are those with intravascular catheters and prosthetic medical devices. In addition, neonates and neutropenic patients are at higher risk of infection. *S. saprophyticus* causes urinary tract infection in premenopausal, sexually active women. *S. lugdunensis* behaves more similarly to S. aureus than other CoNS and can cause invasive infection in normal hosts.
- Histopathology of CoNS biomaterial-associated infections often reveals evidence of acute and chronic inflammation, as well as foreign body reaction (multinucleated giant cells). In animal models of antibiotic treated CoNS biomaterial-associated infection, organisms are often cleared from the immediate interface between the device and tissue but persist in the peri-implant tissues. In addition, viable organisms are often recovered from the biofilm that is a hallmark of CoNS biomaterial-based infections.

Identification

Traditional methods such as biotyping, antibiotic resistance profiling and plasmid analysis have limited discrimination and reproducibility. A number of tests such as biochemical tests, chromatography, genotyping, ribotyping etc. are used to classify new species and strains. Increasing the number of tests used to analyze *S. epidermidis* is beneficial as it would result in further differentiation and identification of various strains and species (Becker et al., 2004; Carretto et al., 2005). Molecular techniques such as PCR combined with phenotyping is more informative compared to conventional phenotypic tests alone (O'Gara and Humphreys, 2001). Pakla-Santini et al. (2007) found that biochemical, immunological and enzymatic methods, such as the coagulase test, are not very accurate as various strains have varying biochemical and immunologic characteristics. They used a PCR-based assay which proved much better than routine testing because it not only reduced the time to get results but also was able to detect other properties such as virulence components and antibiotic-resistance encoding genetic elements simultaneously.
This technique was able to not only differentiate *S. aureus* from Gram-negative bacteria but also successfully separated them from CoNS.

Species were identified based on morphological, physiological and biochemical characteristics, antibiotic susceptibility patterns, and cell wall composition but this method was not very specific as it was designed to identify all known CoNS(i.e. Clinical, veterinary, and alimentary isolates) and was too time-consuming to be used in routine diagnostic laboratories. De Paulis et al. (2003) developed a scheme to identify CoNS species or species groups 9i.e. A group approach) that can be used by most clinical laboratories. This five-test simple scheme of identification concentrates on the species or species groups as follows :


Coagulase
Positive
Negative
(eg. S. aureus)
Xylose and/or arabinose
Positive (weakly)
Negative
(eg. S. xylosus)
Sucrose
Negative
Positive
(eg. S. schleiferi, S. caprae etc.)
Trehalose
Positive
Negative
(eg. S. haemolyticus, S. saprophyticus, S. hominis etc.)
Maltose
Positive (weakly)
Positive
(eg. S. simulans)
Mannitol

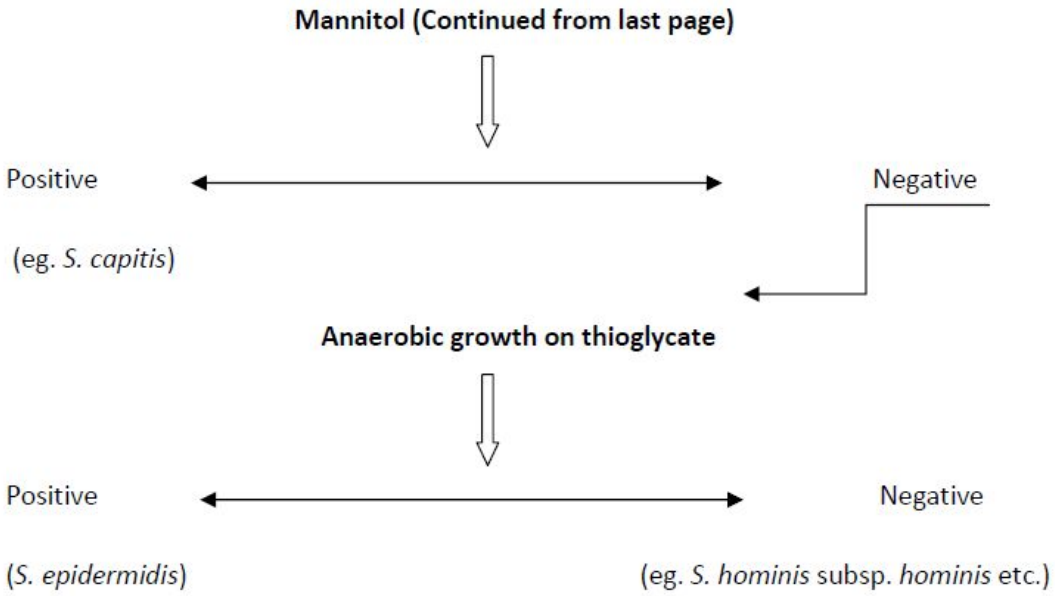


Fig 4 : Identification scheme for CoNS(Simplified from Cunha et al.,2004).

Species of coagulase negative Staphylococci are identified primarily on basis of negative coagulase test. Further identification to the species level is usually not required, but may be performed on the basis of growth characteristics, sugar fermentation, novobiocin resistance and detection of enzyme activity. S. saprophyticus is novobiocin resistant while S. epidermidis is sensitive.

Mechanism of Antimicrobial Resistance

1. Antimicrobial resistance may be acquired through mutation and selection of resistant bacteria strains or horizontal transfer of resistance genes from other bacteria of the same or different species.
2. The common famous resistance mechanisms in CoNS are the production of enzymes that inactivate or destroy the antibiotics (e.g., stated by the genes ermA, ermB, ermC,Blaz, and aac-apD), active deletion of antibiotics from the cell (e.g., efflux-mechanisms pumps),and decrease of the antibiotic binding affinity to the drug.
3. A large and theatrical increase in the number of resistant strains has detected, in particular to penicillin,oxacillin, methicillin, clindamycin, erythromycin, ciprofloxacin, and gentamicin.
4. Resistance to β-lactamase, that is, MR-CoNS (methicillin-resistant CoNS) is determined by the presence of mecA gene, which encodes other penicillin binding protein(PBP-2a) and is inserted into a mobile-gene element(MGE),called the staphylococcal cassette chromosomal mec(SCCmec).
5. The mecA gene, which encodes a PBP-2a, with reduced affinity for methicillin compared with the attractions of other PBP. In addition to methicillin resistance, CoNS strains have acquired resistance to several other antibiotics, including rapamycin,fluoroquinolones,gentamicin, tetracycline, erythromycin, chloramphenicol, clindamycin and sulphonamides .

Conclusion

CoNS resemble very heterogeneous and versatile Gram-positive bacteria. Their main ecological niches are skin and mucous membranes of humans and animals, and they are therefore always in a very close, and mainly symbiotic, relationship with their natural hosts. This also holds for the CoNS species preferentially found in humans. Except for *S. saprophyticus* and *S. lugdunensis*, CoNS rarely attack a healthy host, because of a lack of aggressive virulence properties. However, groups of especially susceptible patients are increasing, either due to still undeveloped or impaired host response functions or due to inserted or implanted foreign bodies. Consequently, CoNS have become a major nosocomial pathogen. Despite the normally subacute and low inflammatory course of these infections, they present a substantial clinical burden because of broad and severe treatment difficulties. In the case of foreign body infections, the removal of the infected device is most often ultimately required.

Many questions regarding the phylogeny, ecology, and pathogenesis of CoNS are still not answered. Just recently available new methodological tools will enable further research approaches. This may lead to new measures for effective therapy and for the prevention of CoNS infections.

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