Review Article

Coagulase Negative Staphylococci (CONS): A review

Abstract:

Coagulase-negative staphylococci (CoNS) has gain more importance as pathogenic organism in recent years as causative organism for infections in both human and animals. CONS are specially prevalent in immunocompromised patients ,critically ill patients, patients having invasive medical devices .

The incidence of CoNS varied across different geographic locations in humans and animals. Also, there is varying antibiotic resistance patterns observed in CoNS species, with high methicillin resistance and cross resistance against many antibiotics. Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus xylosus are most commonly reported species in various studies. Various virulence factors in CONS are responsible for enhanced pathogenicity. Because of advancement in diagnostic techniques understanding of molecular mechanisms of CONS pathogenicity is possible. Recent advances in identification and typing methods, virulence screening methods will help to assess true pathogenic potential of CoNS species.

Keywords: CONS, speciation, Infection

Comment [YV1]: Check writing, there are plenty of spaces

Comment [YV2]: Change letter to italic

Comment [YV3]: 1.It is necessary to mention from the ABSTRACT what is the importance of the article.

Comment [YV4]: 2.The keywords speciation, Infection are irrelevant since when adding any of these in a search engine the result does not speak specifically about cons, it is recommended to change it.
For example: biofilm, staphylococcus, etc.

Introduction

Coagulase-negative Staphylococci (CONS) classified as mere contaminants, are becoming relevant clinically because of widespread antibiotic resistance, biofilm formation and increased use of medical devices. As there is marked species diversity in CONS, there is need for increased laboratory capacity for effective speciation .

Coagulase-negative Staphylococci (CONS) are normal flora of human skin and mucous membranes, they have previously been considered nonpathogenic or contaminant having little clinical significance. [1].But now they have been considered as significant potential pathogen responsible for hospital acquired infection because of widespread antibiotic resistance and increasing use of medical devices and occurs specially in immunocompromised patients and patients having indwelling devices.[1]

Because of bioflim formation on medical devices, maximum of hospital acquired infections are caused by CONS. Biofilm formation also increases the resistance to antimicrobial agents and host defense mechanisms and because of that, it is very difficult to eradicate biofilm associated infections by conventional antibiotic treatment [1,2].

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Milestones in CONS:

Table1. Milestones in CONS.

Year	Scientists	Milestones
1884	Rosenbach	First described CONS as Staphylococcus albus, an avirulent Staphylococcus [3].
1958	Smith and coworkers	First reported pathogenicity of CONS in patients with septicemia[3].
1965	Wilson and Stuart	Identified CONS in pure culture form [4].
1962	Pereira	UTIs were caused by certain group of CONS which is now known as S. saprophyticus [5].
1971	Pulverer and Pillich(Cologne, Germany)	Investigated pyogenic infections in Cologne, Germany and reported 10% infections were due to CONS and CONS were found in pure culture[6].
1971	Holt	Reported that CONS were responsible for colonization of ventriculoatrial shunts followed by septicemia[7].

Development in classification of Staphylococci have made clinicians more aware of various CONS species present in clinical specimens and as etiological agents. [8].

Table 2 shows various Staphylococcal species and subspecies.

Table2. staphylococcal species and subspecies (Lamers et al).[9]

Oxidase	**Negative**							
Novobiocin	**Susceptible**							
Coagulase	**Negative**		**Positive –variable-negative**				**Negative**	
Species group	**Hyicus-Intermedius**			**Epidermidis-Aureus**				
Cluster group	Muscae	Hyicus	Intermedius	Aureus	Epidermidis	Warneri	Haemolyticus	Lugdunensis
Species	S.muscae S.microti	S.hyicus S.agnetis	S.intermedius	S.aureus	S. epidermi	S.warneri	S.haemolyticus	S.lugdunensis

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	S.rostri	S.chromogenes S.felis	S. delphini S.lutrae S.pseudintermedius S.schleiferi sp. Schleiferi sp. coagulans	ssp. Aureus ssp. Anaerobius S.simiae	dis S. capitis Sp. Capitis Sp. Urealyticus S.caprae S. saccharolyticus	S.pasteuri	S.devriesei S.jettensis S.hominis Sp.hominis Sp.novobiosepticus S.petrasii Sp.croceilyticus Sp.petrasii	

Oxidase	**Negative**						**Positive**
Novobiocin	**Susceptible**		**Resistant**				
Coagulase	**Negative**						
Species group	**Auricularis**	**Simulans**	**Saprophyticus**				**Sciuri**
Cluster group	Auricularis	Simulans-Carnosus	Pettenkoferi-Massiliensis	Saprophyticus	Cohnii-Nepalensis	Arlettae-Kloosii	Sciuri
Species	S.auricularis	S.simulans S.carnosus sp. Carnosus sp utilis S.condimenti S.piscifermentans	S.pettenkoferi S.massiliensis	S.saprophyticus sp.saprophyticus sp. Bovis S.equorum sp.eqorum sp.linens S.gallinarum S.succinus sp. Succinus sp. Casei S.xylosus	S.cohnii sp.cohnii sp.urealyticus S.nepalensis	S.arlettae S.kloosii	S. Sciuri sp. Sciuri sp.carnaticus sp.rodentium S.fleurettii S.lentus S.stepanovicii S.vitulinus

Habitat:

CONS is a normal flora of skin and mucous membranes of humans and animals. [10,11].

Table 3 shows colonizing areas of different CONS species.

Table 3. Colonizing areas of different CONS species.

CONS species	Colonizing areas
S.epidermidis	axillae, inguinal and perineal areas, anterior nares, conjunctiva, and toe webs[12]
S.hominis S.haemolyticus	axillae and pubic region[12].

S. capitis	forehead and scalp following puberty [13].
S. lugdunensis	Pelvic and perineum regions, lower extremities, axillae [14].
S. saprophyticus subsp. saprophyticus	Rectum and genitourinary tract [12].
S. auricularis	Human external ear[15].

Transmission:

Maximum CONS infections are hospital-acquired or health-care related infections as they have the ability to survive in ICU , on medical devices and medical equipments for months [16,17,18]. Some clones are probably endemic in the hospital environment. [18 19]The mecA gene carriage in these clusters is usually very high, which suggests that antibiotic resistance is one of the major selective forces [20-23]

Comment [YV7]: Specify the acronym in the text

Emergence and spread of CONS in hospitals is dependent on following factors:

- Duration of hospital stay (especially ICU stay),
- Antibiotic treatment period
- antibiotic pressure in the environment
- hygiene standards[16].

Hand hygiene precautions is extremely important for preventing nosocomial colonization and infections.

Risk factors for CONS infections:

Risk factors for CONS infections includes medical conditions such as [24]

- immune suppression
- premature birth
- neutropenia
- dependence of renal dialysis
- malignancy
- cardiothoracic surgery
- long term hospitalization

Microbiological Profile of CONS:

Morphology:

CONS are gram-positive, nonmotile, non-spore-forming cocci. They are usually arranged in irregular (grape-like) clusters or singly, in short chains (three or four cells), in pairs or tetrads.

Classical approach for separation of CONS from coagulase positive Staphylococci:

Coagulase can contribute to pathogenicity by inhibiting the bactericidal activity of normal serum and by inhibiting phagocytosis through deposition of fibrin on the bacterial cell walls. In the laboratory, two types of coagulase tests are used such as slide test and tube test. Table 2 shows all the coagulase positive and coagulase negative Staphylococci species.

Grouping of CONS by novobiocin testing:

For CONS isolates which have been recovered from urinary tract specimens, novobiocin resistance is used to distinguish the intrinsically resistant S. saprophyticus subsp. saprophyticus from other clinically important CONS, using a 5 ug novobiocin disc on Mueller-Hinton agar[25].

Novobiocin resistant species are S. saprophyticus subsp. Saprophyticus ,S. vitulinu S. xylosus

S. hominis subsp. Novobiosepticus,S. sciuri subsp. Sciuri,S. cohinii,S. cohinii subsp urealyticus.

CONS species and subspecies:

Currently at present, there are 32 recognized species and eight subspecies present in the genus Staphylococcus **(Table 2)** and about one-half of these are indigenous to humans.

EX. S. epidermidis S. capitis S. saccharolyticus S. warneri S. hominis S. lugdunensis S. auricularis S. cohnii S. saprophyticus S. xylosus S. caprae S. haemolyticus

Table 4 shows various CONS species causing human infections.

Table 6.CONS species causing human infections [25].

CONS species or subspecies	Site or source of infection (humans)	Clinical association on frequency	
		Device associated infections	Other infections
S.epidermidis	Skin (axillae, head, arms, legs) and mucous membranes of the nasopharynx	++++	Blood stream infections in neonates (++++)
S.auricularis	External auditory canal	-	Blood stream infections in preterm infant
S.capitis subspecies capitis	mainly scalp, arms,	+	Blood stream infections in neonates (+)
S. capitis subsp. urealyticus	skin of (heads,ears and foreheads)	+	Blood stream infections in neonates (++)
S. caprae	Skin, anterior nares	+	Urinary tract infection(+)
S. cohnii subsp. cohnii	Skin	++	Blood stream infections in burn patient(+)

S. cohnii subsp. urealyticus	Skin		Blood stream infections (+)
S.haemolyticus	Skin ,(legs and arms)	+++	Blood stream infections neonates(+++)
S. hominis subsp. hominis	Skin of axillae, arms, legs, pubic, inguinal regions)	++	Blood stream infections(+)
S.lugdunensis	Skin of lower abdomen and extremities)	++	wound infection (++)Native valve infectious endocarditis,(++)SSI (++)
S. saprophyticus subsp.saprophyticus	Skin	+	Urinary tract infections(++++) Blood stream infections (+) , Native valve infectious endocarditis(+)
S. schleiferi subsp.schleiferi	Skin (preaxillary)	+	Blood stream infections(+) ,wound Infection(+)
S. sciuri subsp. carnaticus	Skin	-	Blood stream infections (?)
S. sciuri subsp. rodentium	Skin	-	Blood stream infections (?)
S. sciuri subsp. sciuri	Skin	+	wound infection (?) Blood stream infections (?)
S. simulans	Skin (legs, arms, and heads of children)	+	-
S.warneri	Skin (mainly nares, head, legs, and arms)	++	Septic arthritis(+)
S. xylosus	Skin (rare)	+	-

Abbreviations:; **?**, questionable or unconfirmed; +, single cases; ++, occasional detection; +++, frequent detection; ++++ most common origin.

Comment [YV8]: What does this question mark represent?

Virulence factor in CONS:

CONS are seldom life-threatening except in immunocompromised patients as CONS do not produce aggressive virulence factors.[1]

Capsule:

Among CONS, capsule formation is frequent and they possess increased virulence compared to non-encapsulated variant strains. Slime may contain capsular polysaccharides, proteins and cell wall components. The capsule confers resistance to phagocytosis [26].

Slime: Glycocalyx is considered a slime layer when glycoprotein molecules are loosely attached with the cell wall. Slime material and biofilm formation has important role in colonization of uroepithelium and medical device- associated infections [27]. Slime has also been shown to inhibit the cell mediated immune response in vitro.

Biofilm:

Biofilm structures comprises mainly bacterial cells and an extracellular polymeric substance (EPS) provided by the polysaccharide intercellular adhesion (PIA) .PIA synthesis is associated with intercellular adhesion operon (ica ADBC) [28].

Biofilm provides

- protective environment to microorganisms
- quorum sensing(the exchange of genetic material between cells and intercellular communication)[29]
- the micro-organisms becomes more resistant to antibiotics and to host defense mechanisms.

.**Cytolytic toxins:**

Delta-toxin (PSM is produced by S. epidermidis . It forms pores in the cell membrane which leads to erythrocytes and other mammalian cells lysis. [25].

Production of Lantibiotics:

antibiotic-like peptides produced by commensal staphylococci are called lantibiotics and belongs to the class of cationic antimicrobial peptides (CAMPs) and are active against gram-positive bacteria. Lantibiotics production has role in bacterial interference on skin and mucous membranes. Type A lantibiotics induce pores in the cytoplasmic membrane. Lantibiotics produced by S.epidermidis are epidermin , Pep5, epilancin K7, epidermicin NI01, and epicidin 280 . Other species such as S. gallinarum (gallidermin), S. hominis (hominicin), and S. warneri (nukacin ISK-1)also show lantibiotic production.[25].

Siderophore:

Microorganisms produce low molecular weight (<1000D) chelating compounds called siderophore in their iron especially in free form. Siderophores are helpful to overcome host's non-specific defense mechanisms and thus helpful in survival within the host, [30].

Meiwes et al [31] has detected two iron binding compounds, staphyloferrin A and B which were highly hydrophilic and anionic.

Extracellular Enzymes:

CONS produces variety of enzymes and extracellular proteins such as proteases, lipases, phospholipases, esterase's, protein A, and fatty acid modifying enzymes. Protease are responsible for proteolytic inactivation of antibodies , platelet microbicidal proteins, and destruction of tissue protein which leads to increased invasiveness. S. epidermidis has two lipase genes involved in skin colonization [32].

Exopolymers:

Polysaccharide intercellular adhesin (PIA) and poly gamma-glutamate (PGA)s are produced by S. epidermidis.

Functions of PGA :

- protecting against neutrophill phagocytosis and antimicrobial peptides.
- important for survival in biofilm and as a commensal on the skin,
- during high salt concentrations it promotes growth by increase osmotolerance.

PIA has similar functions as PGA and also protects against complement deposition and immunoglobulins[33].

Table 5 shows various virulence factors of S. epidermidis.

Table 5. Important virulence factors of S. epidermidis [33].

Virulence factor	Gene	Function
Intercellular aggregation		
PIA (PNAG)	icaA,icaD,icaB, and icaC	Polysaccharide intercellular adhesion
Aap Bhp	Aap ,Bhp	Protein intercellular adhesion
Teichoic acids	Multiple biosynthetic genes	Components of the biofilm matrix
Protective exopolymers		
PIA	icaA,icaD,icaB, and icaC	Protects from IgG, AMPs, phagocytosis
PGA	capA,capB,capC and capD	Protects from AMPs and phagocytosis
Resistance to AMPs		
SepA protease	sepA	Involved in AMP degradation
Aps system	apsR, apsS, and apsX	senses AMPs and regulates AMP resistance mechanism
Toxins		

Virulence factor	Gene	Function
PSMs	psma,psmd,psme, hld	Pro-inflammatory cytolysins
Exoenzymes		
Glutamylendopeptidase GluSE and serine proteases SspA and Esp	sspA	Degrades fibrinogen and complement factor C5
Cysteine proteases SspB and Ecp	sspB	Possibly responsible for tissue damage
Other factors		
Staphyloferrins A and B	Sfna locus	Siderophores (iron acquisition)
SitA, SitB and SitC	sitA, sitB and sitC	Involved in iron uptake

Figure 1 shows scheme for identification of human CONS

Figure 1. Dichotomous key for identification of common human CONS[8]

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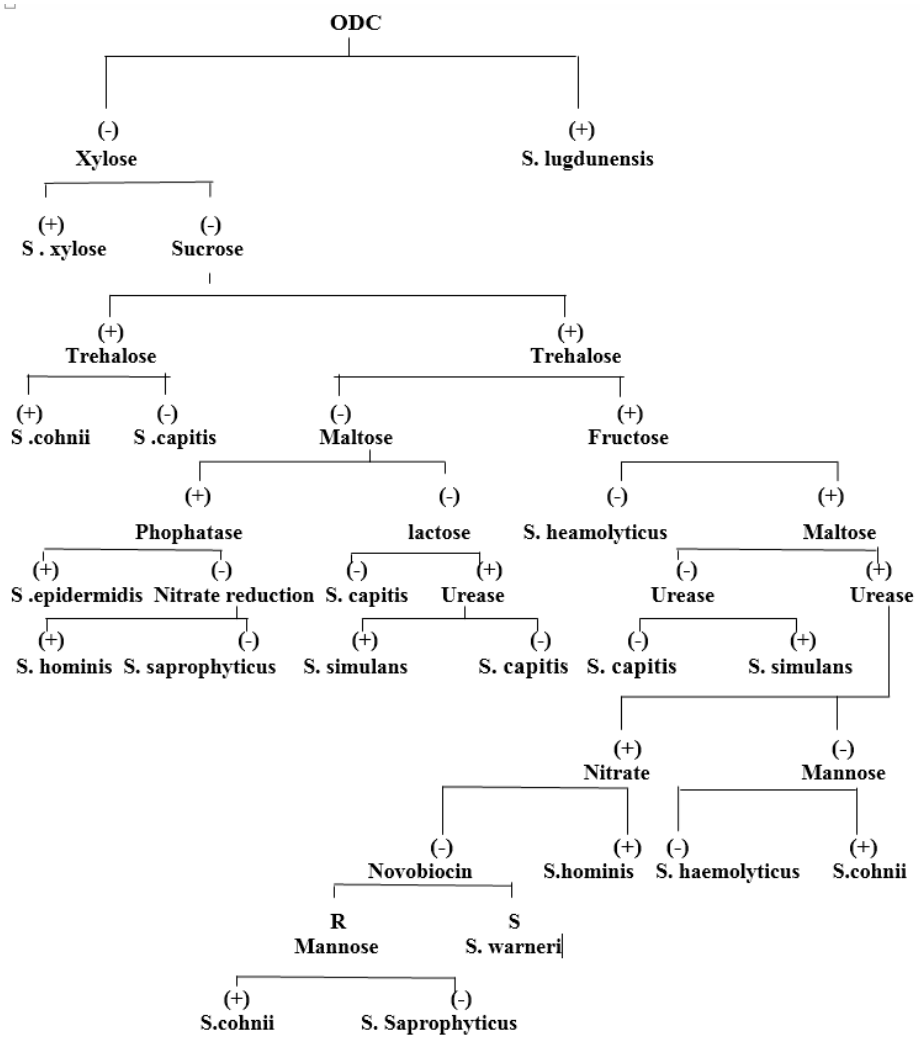
ODC
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S .capitis
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Maltose
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Fructose
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S. capitis
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S. hominis
S. saprophyticus
S. simulans
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Novobiocin
S.hominis
S. haemolyticus
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S. warneri
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S.cohnii
S. Saprophyticus

Table 6 shows Various biochemical characteristics of CONS

Table 7.Biochemical characteristics of coagulase negative Staphylococci [34]

	Coagulase test									Carbohydrate fermentation test							
Species	**Slide**	**Tube**	**NV**	**Pol-B**	**PYR**	**Nit**	**VP**	**Ure**	**ODC**	**Glu**	**Mal**	**Su**	**La**	**Man**	**Mo**	**Xy**	**Tre**
S. epidermidis	_	_	S	R	_	+	+	+	V	+	+	+	V	_	+	_	_
S. saprophyticus subsp saprophyticus	_	_	R	S	_	_	+	+	_	+	+	+	V	v	_	_	+
S. haemolyticus	_	_	S	S	+	_	+	_	_	+	+	+	V	V	-	-	+
S. hominis subsp hominis	_	_	S	S	_	V	V	+	_	+	+	+	V	-	-	-	V
S. hominis subsp novobiosepticus	_	_	R	NA	_	V	V	+	_	+	+	+	V	-	-	-	-
S. lugdunensis	+	_	S	S/R	+	+	+	V	+	+	+	+	+	-	+	-	+
S. schleiferi subsp schleiferi	+	V	S	S	+	+	+	_	_	+	-	-	-	-	+	-	V
S. schleiferi subsp coagulans	V	+	S	NA	NA	+	+	+	NA	+	-	v	V	V	+	-	-
S. warneri	_	_	S	S	_	V	+	+	_	+	+	+	v	V	-	-	+
S. xylosus	_	_	R	S	V	V	V	+	_	+	+	+	v	+	+	+	+
S.intermedius			S	S	+	+	-	+	-	+	v	+	V	V	+	-	+
S.hyicus	-	V	S	R	-	+	-	V	-	+	-	+	+	-	+	-	+
S.cohnii subsp. Cohnii	-	-	R	S	-	-	V	-	-	+	V	-	-	V	V	-	+

Abbreviations:NV-Novobiocin,Pol-B- Polymyxin-B, Nit- Nitrate reduction test, Ure-Urease Production test, ODC- Ornithine Decarboxylase test, Glu-Glucose, Mal-Maltose, Su-Sucrose, La- Lactose, Man-Mannitol, Mo-Mannose, Xy-Xylose, Tre-Trehalose. V-Variable, R-Resistant, S-Susceptible, + Positive,- Negative

Molecular methods:

Genotypic methods have higher discriminatory power and are less laborious.[35,36].

Disadvantages:

1. Costly, expensive
2. Time consuming

Commercial identification systems:

Comment [YV10]: Other disadvantages of using molecular methods should be considered

With these commercial kits , identification of human CONS species can be possible with accuracy of 70->90%.For organism identification these kits use adaptations of standard bacteriologic identification tests , chromogenic enzyme substrate tests and modified carbohydrate fermentation tests.

Different systems available for identification of CONS are [34]

1. API Staph
2. BD Phoenix system
3. BD Phoenix ID-13 system
4. VITEK 2 ID-GP system
5. ID 32 STAPH system
6. Rapidec STAPH
7. API Staph- IDENT
8. MICROSCAN RAPID POS COMBO PANEL
9. STAF- SISTEM 18-R
10. STAPH-ZYM
11. MICROBIAL IDENTIFICATION SYSTEM

As there is addition of more discriminating tests and availability of growing data bases, the reliability of these commercial systems will continue to increase [34].

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Comment [YV11]: The bibliographic references should be more current since in the abstract it mentions: "Coagulase-negative staphylococci (CoNS) has gain more importance as pathogenic organism in recent years as causative organism for infections", however the most recent reference is from 2014.
The format of the references is varied, APA, Vancouver, etc.

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