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ATYPICAL CLINICAL PRESENTATIONS OF COAGULASE-NEGATIVE STAPHYLOCOCCUS INFECTIONS

PhD Dissertation

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List of Abbreviations

Aap protein	Accumulation-associated protein
Aas	Autolysin adhesin
AMD	Age related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
ARMOR	Antibiotic Resistance Monitoring in Ocular Microorganisms
BCVA	Best corrected visual acuity
BRAO	Branch retinal artery occlusion
BSI	Bloodstream infection
CME	Cystoid macular edema
CoNS	Coagulase-negative staphylococcus
CRVO	Central retinal vein occlusion
CSCR	Central serous chorioretinopathy
DME	Diabetic macular edema
DNA	Deoxyribonucleic acid
ERM	Epiretinal membrane
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EVS	Endophthalmitis Vitrectomy Study
GI	Gastrointestinal
HM	Hand motions
ica operon	Intracellular adherence operon
IOP	Intraocular pressure
LASIK	Laser Assisted In Situ Keratomileusis
LP	Light perception
MALDI-TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
mecA gene	Methicillin-resistance gene
NICU	Neonatal intensive care unit
NPDR	Non-proliferative diabetic retinopathy

OEK	Országos Epidemiológiai Központ (National Centre of Epidemiology, Hungary)
PBP2a protein	Penicillin-binding protein 2a
PFGE	Pulsed-field gel electrophoresis
PIA	Polysaccharide intercellular adhesin
PKP	Penetrating keratoplasty
PPV	Pars plana vitrectomy
SBA	Sheep blood agar
SOD	Superoxide dismutase
sodA gene	Superoxide dismutase gene A
Ssp	S. *saprophyticus* surface-associated protein
STI	Sexually transmitted infections
T/I	Vitreous tap and injection of intravitreal antibiotics
UPGMA	Unweighted pair group method with arithmetic mean
UTI	Urinary tract infection
VA	Visual acuity

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1. Introduction

1.1. *Staphylococcus*

Bacteria from the Staphylococcus genus are Gram-positive cocci belonging to the Staphylococcaceae family of the Bacillales order, obtaining their name from the spherical, grape-like clusters that they form when viewed microscopically. They were first described as such by renowned Scottish bacteriologist Alexander Ogston in the early 1880s.[1] *Staphylococcus* species are catalase-positive, facultative anaerobes, meaning that they can grow in both anaerobic and aerobic conditions. There are several biochemical tests that may be used to identify and further classify *Staphylococci*, of which one of the most notable is their ability to produce the blood-clotting enzyme, coagulase.

1.2. Coagulase-negative staphylococcus (CoNS)

Coagulase-negative staphylococci (CoNS) are a group of *Staphylococcus* that do not produce coagulase, which differentiates them phenotypically from coagulase-positive staphylococci, such as the well-known *Staphylococcus aureus (S. aureus)*. There are several species of CoNS relevant to human infections (Table 1), one of the most abundant of which is *Staphylococcus epidermidis (S. epidermidis)*, which was first described by German microbiologist Anton Julius Friedrich Rosenbach in the 1880s, who initially named it *S. albus* for the white colonies it formed on blood agar.[2] Coagulase-negative staphylococcus species can be differentiated from each other by biochemical and genomic tests, mainly based on their sensitivity to antibiotics and their virulence factor genes.

1.2.1. Coagulase-negative staphylococcus (CoNS) species

Coagulase-negative staphylococci have been shown to play a role in maintaining homeostasis of the human epithelial and mucosal microbiome.[3] This is achieved by combating proliferation of other pathogenic species, such as *S. aureus*, by producing enzymes and antimicrobial factors that inhibit their growth.[4–6] The distribution of CoNS species within the normal microbiome is not widely known, but one study has shown that 5.56% of the skin microbiome from 100 healthy subjects were *S. capitis*, 2.78% were *S. hominis*, 2.78% were *S. auricularis*, and 1.7% was *S. epidermidis.*[7]

S. epidermidis is a common culprit in neonatal bloodstream infection (BSI);[8] however, there are several other species of CoNS that are ubiquitous on mucosal and skin surfaces and may cause infections in humans. This is not an exhaustive list, as there are several species that mainly cause infections in animals. Extensive phylogenetic classification of Staphylococcus species has been described by Lamers et al. in 2012.[9] Common species in humans include *Staphylococcus haemolyticus* (*S. haemolyticus*), *Staphylococcus capitis (S. capitis),* including subsp. *urealyticus, Staphylococcus auricularis (S. auricularis),*[8] and *Staphylococcus hominis* subsp. *hominis* and *novobiosepticus* (*S. hominis*).[8,10] Species involved in urinary tract infections (UTI) include *Staphylococcus caprae (S. caprae)*[8] and *Staphylococcus saprophyticus* subsp. *saprophyticus (S. saprophyticus*), which is involved in acute urethritis.[11] *Staphylococcus lugdunensis (S. lugdunensis)* may cause endocarditis of the native heart valves, as well as wound infections[8]. *Staphylococcus warneri (S. warneri)* infection may lead to septic arthritis, *and Staphylococcus schleiferi (S. schleiferi)* may lead to BSI and wound infections.[8] Other less common species include *Staphylococcus saccharolyticus (S. saccharolyticus*), which causes spondylodiscitis; *Staphylococcus cohnii* subsp. *cohnii* and *urealyticus (S. cohnii),* which has been shown to cause BSI in patients with burns; and *Staphylococcus sciuri* subsp. *carnaticus, rodentium,* and *sciuri* (*S. sciuri*) which carry the mecA gene.[8,12] Rarer species include *Staphylococcus simulans (S. simulans) and Staphylococcus xylosus (S. xylosus)*. Although there have been studies that have shown that *Staphylococcus pasteuri (S. pasteuri*) has been isolated in patients with infective endocarditis and osteomyelitis [13,14], and that *Staphylococcus pulvureri (S. pulvureri, S.vitulinus*) has been isolated from humans and sick fowls and shown to cause septic arthritis of the hip,[15] these species are more often found in animals.[8] A list of CoNS species and their properties can be found in Table 1.

1.2.2. Virulence factors and antibiotic resistance

Virulence factors are properties of microbes that render them resistant to their environment and to agents used to neutralize them or reduce their activity. The main virulence factor in CoNS is biofilm formation, which is achieved by the self-produced extracellular glycosaminoglycan polysaccharide intercellular adhesin (PIA),[16] which protects and allows them to prosper in a secluded environment, usually on the surface of

plastic devices such as prostheses and intravenous catheters[17]. Biofilms are encoded by various forms of the intracellular adherence (ica) operon,[18] including icaA, icaD (a helper protein)[19], and icaB (surface protein),[20] as well as the accumulation-associated protein (Aap).[21] Virulence factors for *S. saprophyticus* include urease, S. *saprophyticus* surface-associated protein (Ssp), and autolysin adhesin (Aas).[22] There have also been genomic studies indicating the possibility of gene transfer between *Staphylococcus* species, which encode for antibiotic resistance and virulence factors.[23]

Staphylococcus epidermidis is sensitive to the antibiotic novobiocin, which has been widely used to differentiate it from the novobiocin-resistant *S. saprophyticus*.[24] *Staphylococcus epidermidis* strains are also widely resistant to commonly-used antibiotics today, such as methicillin, tetracyclines, aminoglycosides, fluoroquinolones, and sulfonamides.[23] The gene that allows for methicillin resistance in staphylococci is "mecA", which codes for penicillin-binding protein (PBP2a).[25] Studies have shown that not only is *S. epidermidis* a reservoir for mecA, but also mediates horizontal gene transfer to other staphylococci.[26]

1.2.3. Nosocomial and opportunistic infections

Coagulase-negative staphylococci, particularly *S. epidermidis* and *S. haemolyticus*, are a major group of bacteria responsible for nosocomial infections and worsening antibiotic resistance,[23,27,28] and are seen mainly on epithelial layers of the human body such as the epidermis of the skin and the epithelial mucosal linings of the gastrointestinal (GI) tract.[8] Although most infections caused by CoNS are rarely life-threatening, they may severely affect populations such as premature neonates who do not have a fully-developed immune system, and adults with compromised immunity. [8,29–31] This is especially true for those with intravenous and other indwelling catheters, as well as other prosthetic-devices.[31] Studies have suggested that CoNS may even translocate through intact GI mucosa into the bloodstream in premature neonates due to poorly developed innate immunity [32] or due to CoNS becoming more virulent [33].

Table 1. Most common species of CoNS in humans, in order of appearance in the text.

	Species	**Common locations and infections**	**Reference**
1	*S. epidermidis*	Skin (ubiquitous), nasopharyngeal mucosa; nosocomial infections and neonatal bacteremia, endophthalmitis	2, 8, 23
2	*S. haemolyticus*	Skin; nosocomial infections and neonatal bacteremia	8, 28
3	*S. capitis* Subsp. *capitis* Subsp. *urealyticus*	Scalp, forehead; neonatal bacteremia	8
4	*S. auricularis*	External ear canal; Neonatal sepsis	8
5	*S. hominis*	Inguinal and axillary skin; Neonatal BSI	8, 10
6	*S. saprophyticus*	Perineum; acute cystitis (e.g., urethritis, pyelonephritis, epididymitis, and prostatitis)	8, 11
7	*S. caprae*	Skin, nasal mucosa; acute cystitis	8
8	*S. lugdunensis*	Skin; wounds, native heart valve endocarditis	8
9	*S. warneri*	Skin, nasopharynx; Septic arthritis	8
10	*S. schleiferi*	Axillary skin; bacteremia, wounds	8
11	*S. saccharolyticus*	Forehead, skin; Spondylodiscitis	8
12	*S. cohnii* Subsp. *cohnii* Subsp. *urealyticus*	Skin; bacteremia in patients with burns	8
13	*S. sciuri* Subsp. *sciuri*	Skin; carrier of mecA gene	8, 12

	Subsp. *carnaticus* Subsp. *rodentium*		
14	*S. pasteuri*	Ubiquitous, on surfaces, food, meats; Infective endocarditis, osteomyelitis	8, 13, 14
15	*S. pulvereri (S. vitulinus)*	Fermented food, sick fowls; septic arthritis of the hip in humans	8, 15

2. Objectives

2.1. Hypothesis

Clinical laboratory diagnostics are readily available tools for guiding the treatment of common community-acquired and nosocomial infections. We hypothesize that these methods can help to determine the pathogenicity and outcomes of atypical CoNS infections in susceptible patient populations.

2.2. Aims and Objectives

Our aim is to investigate the use of clinical microbiological and laboratory diagnostic methods to detect and differentiate CoNS species in community-acquired and nosocomial infections, and to determine infection patterns, antibiotic susceptibility, and treatment outcomes.

To test the hypothesis, the following objectives were addressed:

a. In acute cystitis:
    - To identify characteristics of urinary tract infections (UTI) caused by *S. saprophyticus* in children and adults, including antibiotic resistance, and to determine patterns of *S. saprophyticus*-related UTIs in populations other than reproductive age women. Analysis of strains was performed using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass

Spectrometry (MALDI-TOF MS) and pulsed-field gel electrophoresis (PFGE).

b. In neonatal bloodstream infections:
    - To determine whether CoNS colonizing the GI tract in premature neonates may lead to bloodstream infection by identifying pathogenic CoNS species in the GI tract and blood cultures using MALDI-TOF MS and PFGE.
c. In endophthalmitis:
    - To determine the severity of CoNS endophthalmitis in adults, including clinical characteristics, outcomes, and treatment; using gene sequencing to identify pathogenic strains, and to determine antibiotic susceptibility of pathogenic CoNS strains.

3. Methods

3.1. Patients

Isolates and available clinical data were collected from two major University Hospital Centers: Semmelweis University in Budapest, Hungary, including Heim Pál Children's Hospital, and at the Charles T Campbell Microbiology Laboratory of the Eye and Ear Institute of Pittsburgh (Campbell Laboratory) at the University of Pittsburgh, in Pittsburgh, Pennsylvania, USA.

Studies consisted of retrospective chart review of included patients where available, as well as prospective analyses of select clinical samples, as described in the subsections below.

3.1.1. Acute Cystitis

Retrospective analysis was performed on 10,022 CoNS strains isolated from 9,083 patients diagnosed with a UTI at Semmelweis University clinical locations and Heim Pál Children's Hospital in Budapest, Hungary over a one-year period (January 1st-December 31st, 2014). Data including the date of urine sample collection as well as patient age and gender were obtained. Patients were sorted into six age groups (0–4 years, 5–15 years, 16–24 years, 25–39 years, 40–59 years, 60–100 years). Matrix-assisted laser

desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used to phenotypically identify the species. The distribution of age and gender in UTIs caused by *S. saprophyticus* was determined, as well as the seasonal occurrence. Antibiotic susceptibility of *S. saprophyticus* was tested using the disc diffusion method, and was interpreted based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[34] All *S. saprophyticus* isolates (*n*=66) were stored at –80 °C in 25% glycerol for further analysis. Of these, 30 were randomly selected for genetic analysis pulsed-field gel electrophoresis (PFGE) based on prior protocol by Tenover et al.[35]

3.1.2. Neonatal Bloodstream Infection

Retrospective analysis was performed on 1,118 neonates hospitalized over 3 years (January 1st, 2013-December 31st, 2015) in two neonatal intensive care units (NICU) at Semmelweis University in Budapest, Hungary. Results from microbiological surveillance samples such as blood cultures, peritoneal fluid, and perianal and pharyngeal swabs were examined. A total of 5093 perianal, 4022 pharyngeal surveillance samples, and 4294 blood cultures obtained by the NICU were analyzed. Of the 4294 blood cultures, 449 were positive for CoNS species; however, only 390 CoNS-positive blood cultures had concurrent surveillance samples (perianal and pharyngeal swabs) available for analysis. Blood cultures with concurrent surveillance samples (*n*=390) which were positive for *S. epidermidis* or *S. haemolyticus* were further processed for species identification using MALDI-TOF MS and PFGE, and antibiotic susceptibility was tested. All strains were stored in glycerol-supplemented broth at −20°C until analysis.

3.1.3. Endophthalmitis

Forty-two previously isolated strains of CoNS from 40 patients with documented endophthalmitis diagnosed between August 1st, 2014, and August 31st, 2018, were selected from strains isolated at the Campbell Laboratory at the University of Pittsburgh. Samples were obtained from vitreous and/or aqueous samples. Only patients with CoNS endophthalmitis were studied. Retrospective review was performed with data including etiology of endophthalmitis, type of CoNS isolated, time to presentation, best corrected visual acuity (BCVA) at presentation and after treatment, clinical eye examination

findings at presentation, treatment instituted, and presence of other concurrent eye disease. The mean BCVA was recorded over the first 12 weeks following initial presentation. Patients were divided into groups based on presenting BCVA of hand motions (HM) or better, and light perception (LP) or worse. Additional analyses were performed to assess final BCVA in those who underwent various treatment forms, namely pars plana vitrectomy (PPV) and tap and injection of intravitreal antibiotics (T/I). Subgroup analysis of BCVA in patients with *S. epidermidis* endophthalmitis was also performed and compared in PPV and T/I groups.

3.2. Description of laboratory techniques

3.2.1. Identification and speciation of CoNS

The CoNS strains from endophthalmitis cases were initially identified using Gram and Giemsa staining after growth on trypticase soy agar with 5% sheep blood agar (SBA) BBL™, aerobic chocolate agar (BBL™), anaerobic chocolate agar (BBL™), Sabouraud dextrose agar with gentamicin (BBL™), and thioglycolate broth (BBL™) (Becton, Dickinson and Company, Sparks, MD, USA). This was followed by speciation using API Staph (BioMérieux, Chemin de L'Orme, Marcy-L'Etoile, France)[36] and Biolog GEN III microplates (Biolog, Hayward, CA, USA)[37] according to existing methods. Findings were analyzed with the Biolog Identification Systems Software (OOP 188rG Gen III Database v2.8).

3.2.2. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)

In our study, MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany) was used to phenotypically analyze pathogenic CoNS strains in the setting of acute cystitis and neonatal bloodstream infection. Smears were made from the bacterial samples of CoNS grown on culture media, and 70% formic acid and alpha-cyano-4-hydroxycinnamic acid matrix substance were added. These mixtures were then dried and placed in the spectrometer. The molecular mass of the samples (ratio of mass-to-charge) was later determined by their time-of-flight using the FlexAnalysis and FlexControl programs (Bruker).[32,38]

3.2.3. Pulsed-field gel electrophoresis (PFGE)

Genetic diversity of CoNS strains was analyzed using PFGE on isolates from urine samples in acute cystitis, and in neonatal blood cultures, perianal, and nasopharyngeal samples..[32,39] Our protocol was based on a prior method described by Bradford et al.[38] and analysis was performed based on criteria described by Tenover et al.[35] Briefly, after overnight incubation of CoNS strains at 37°C on blood agar culture plates, the bacterial isolates were collected, transferred onto a plug mold and lysed for DNA collection using lysostaphin (Sigma, St. Louis, Missouri, USA).

The DNA was digested at 25°C for 3 hours using SmaI enzyme (Promega, Madison, Wisconsin, USA), and subsequently loaded onto a gel for electrophoresis in 1% agarose (Bio-Rad, Hercules, California, USA). For this purpose, the CHEF-DR-II apparatus (Bio-Rad, Hercules, California, USA) was used in TBE buffer (1x Tris-borate-EDTA, pH: 8.3; Bio-Rad Hercules, California, USA). Electrophoresis was performed at 14°C for 21 hours with pulses between 5 to 60 seconds, at an angle of 120°, and voltage of 6 V/cm. Standardization of the first lane of each gel was achieved with Lambda DNA PFGE Marker (BioLabs, Budapest, Hungary).

After this step, the gels were stained with ethidium bromide solution (Sigma, St. Louis, Missouri, USA), examined and photographed with UVItec (Pharmacia Biotech, Piscataway, New Jersey, USA), and analyzed using Diversity Database software (version 2.2.0; Bio-Rad, Hercules, California, USA). Dendrograms were constructed with unweighted pair group method with arithmetic mean (UPGMA) clustering based on Dice coefficients (optimization and tolerance of 1%). As proposed by Tenover et al., any isolates with >8% band similarity or with ≤6 band differences were regarded as clonally related.[35]

3.2.4. Gene sequencing

DNA sequencing of CoNS strains isolated from endophthalmitis cases was also performed. Frozen isolates were thawed and cultured on SBA, and subsequently processed for DNA sequencing analysis using superoxide dismutase (SOD) gene A (sodA) as the target gene according to a previously reported protocol.[40] Namely, DNA chromosomes were extracted with QuickExtract™ DNA reagent (Lucigen, Middleton, WI, USA), followed by sodA gene sequencing using primers (Integrated DNA

Technologies, Coralville, IA, USA) and Taq DNA polymerase (New England Biolabs, Ipswich, MA, USA). DNA Sequencing was performed at the Genomic Core facility at the University of Pittsburgh, PA, USA.

3.2.5. Antibiotic Sensitivity Testing using the Disc Diffusion Method

Antibiotic resistance of CoNS isolates was tested[41] in vitro using the disc diffusion method, and interpreted based on Clinical and Laboratory Standards Institute guidelines.[42,43] Antibiotics were assumed to reach similar levels in the eye and serum.

The susceptibility data obtained from Semmelweis University samples were analyzed according to the guidelines published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[34]

The following antibiotics were used for testing susceptibility: vancomycin, cephalosporins (cefazolin, ceftazidime, cefoxitin), fluoroquinolones (ofloxacin, ciprofloxacin, moxifloxacin), aminoglycosides (amikacin, gentamicin), and clindamycin.[41]

3.2.6. Statistical Analysis

Significant differences between mean (+/- standard error of the mean) values of analyzed groups were calculated with unpaired *t*-tests (GraphPad QuickCalcs, GraphPad, San Diego, CA) and two-tailed *t*-tests (MATLAB 2021b & Simulink Student Suite, The MathWorks, Inc., USA). Data with $p<0.05$ were considered statistically significant.

3.2.7. Ethical Approval

The portion of the study performed at the Campbell Laboratory was approved by the Institutional Review Board of the University of Pittsburgh Medical Center, USA. The Laboratory Medicine Institute at Semmelweis University did not require ethical approval.

4. Results

4.1. Demographics of acute cystitis caused by *Staphylococcus saprophyticus*

Of 10,022 pathogens isolated from 9,083 patients diagnosed with UTIs in a 1-year period, *S. saprophyticus* was the third most common bacterium isolated (Table 2). Of these, 66 patients were shown to have *S. saprophyticus* UTIs (61 females and 5 males). Although *S. saprophyticus* was found in all female age-groups, it occurred most commonly in females aged 16–24 years and in males between 5–15 years of age (Table 2). Urinary tract infection caused by other microbes including *E. coli* and Enterobacteriaceae was more prevalent in patients under the age of 5 years and above the age of 40 years (Figure 1).

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Table 2. Age-dependent distribution of all UTI-causing microorganisms in males and females in 2014.

Microorganism	*E. coli*	*E. faecalis*	Klebsiella spp. (1)	*P. mirabilis*	*S. saprophyticus*	*P. aeruginosa*	Enterobacter spp.	Other Enterobacteria (2)	*S. agalactiae*	Yeasts	Others (3)	Total number of pathogens
Females												
Age 0–4	62,3%	6,7%	9,8%	6,7%	0,1%	6,8%	1,8%	3,2%	0,7%	0,1%	2,0%	1063
Age 5–15	67,8%	8,4%	7,0%	3,7%	0,7%	1,4%	2,1%	2,7%	2,2%	0,2%	3,9%	876
Age 16–24	50,5%	12,5%	4,4%	2,4%	7,4%	0,4%	0,4%	0,6%	5,2%	5,4%	10,7%	497
Age 25–39	42,5%	27,1%	6,6%	2,5%	1,2%	1,8%	1,9%	1,1%	7,0%	4,8%	3,6%	852
Age 40–59	42,0%	22,5%	10,4%	1,9%	0,4%	2,4%	1,4%	3,1%	5,3%	5,1%	5,5%	943
Age 60–100	43,2%	21,1%	10,2%	3,3%	0,1%	3,0%	2,6%	3,2%	2,6%	4,9%	5,8%	2155
Males												
Age 0–4	32,7%	26,5%	11,3%	8,4%	0,0%	9,0%	4,7%	4,7%	0,2%	0,3%	2,1%	978
Age 5–15	29,8%	24,7%	6,0%	7,7%	2,1%	10,2%	4,7%	9,4%	0,0%	0,9%	4,7%	235
Age 16–24	23,9%	27,4%	5,3%	1,8%	0,0%	10,6%	2,7%	4,4%	1,8%	4,4%	7,7%	113
Age 25–39	22,6%	39,1%	10,3%	1,5%	0,0%	2,7%	2,7%	4,2%	4,6%	0,0%	12,3%	261
Age 40–59	21,3%	35,6%	12,1%	2,2%	0,0%	7,4%	3,4%	5,3%	2,4%	3,1%	7,2%	677
Age 60–100	22,8%	30,2%	12,1%	4,0%	0,0%	9,3%	2,1%	5,3%	2,3%	5,0%	6,8%	1372

(1) Klebsiella spp. - Klebsiella pneumoniae, Klebsiella oxytoca. (2) Other Enterobacteria – Members of the Enterobacteriaceae Family, except Escherichia coli, Klebsiella spp., Enterobacter spp., and Proteus mirabilis. (3) Other – Other Gram-negatives, such as Pseudomonas spp.; other Gram-positives, such as Enterococcus spp.,

Streptococcus spp., Staphylococcus spp.; Ureaplasma urealyticum; Mycoplasma hominis; other less frequently encountered species.[39] Age is depicted in years. (Extracted from Adeghate J, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016 Mar; 63(1):57-67.)

4.1.1. Infections with *Staphylococcus saprophyticus*

S. saprophyticus was the main isolate in 66 subjects with diagnosed with a UTI (61 female, 5 male). Although this pathogen was isolated in all female age groups (most commonly between 16 and 24 years), it was also commonly noted in female patients aged 25-39 years and males aged 5-15 years (Figure 1 and 2). It is also of interest to note that UTIs from *S. saprophyticus* followed a seasonal pattern (Figure 3). Most of the *S. saprophyticus*-related UTIs in our study occurred in the summer and winter seasons with major peaks observed in the months of June, August, November, and January (Figure 3). With regards to treatment, *S. saprophyticus* showed a strong sensitivity to nitrofurantoin, fluoroquinolones, and except for one case, ampicillin as well (Figure 4). Of the 30 isolates analyzed with PFGE, 28 different genotypes were found (Figure 5).

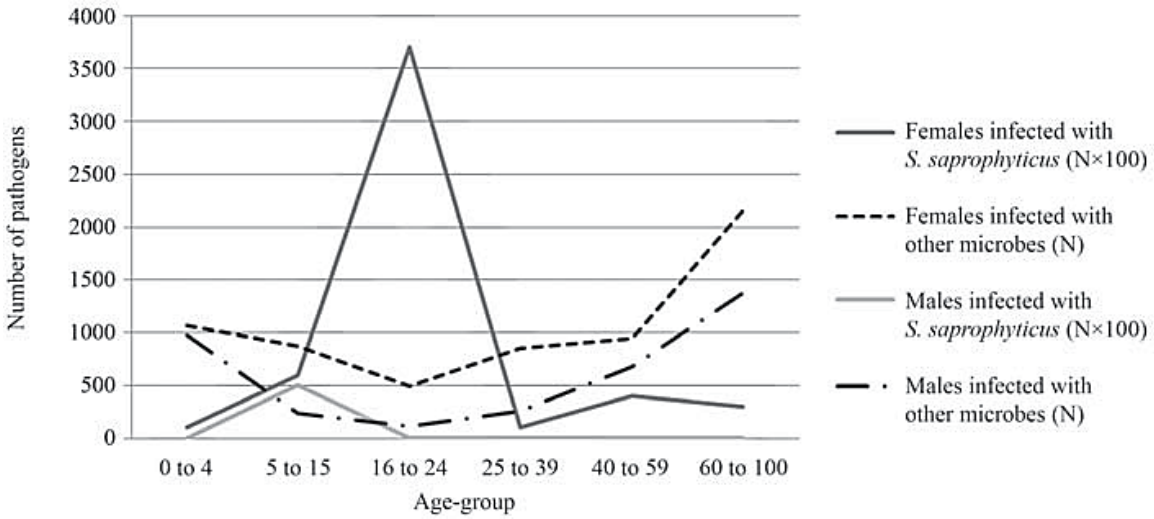

Figure 1. Age- and gender-dependent distribution of *Staphylococcus saprophyticus*-caused UTIs, compared to UTIs caused by other microorganisms.[39] Age is depicted in years. (Extracted from Adeghate J, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does

Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016 Mar; 63(1):57-67.)

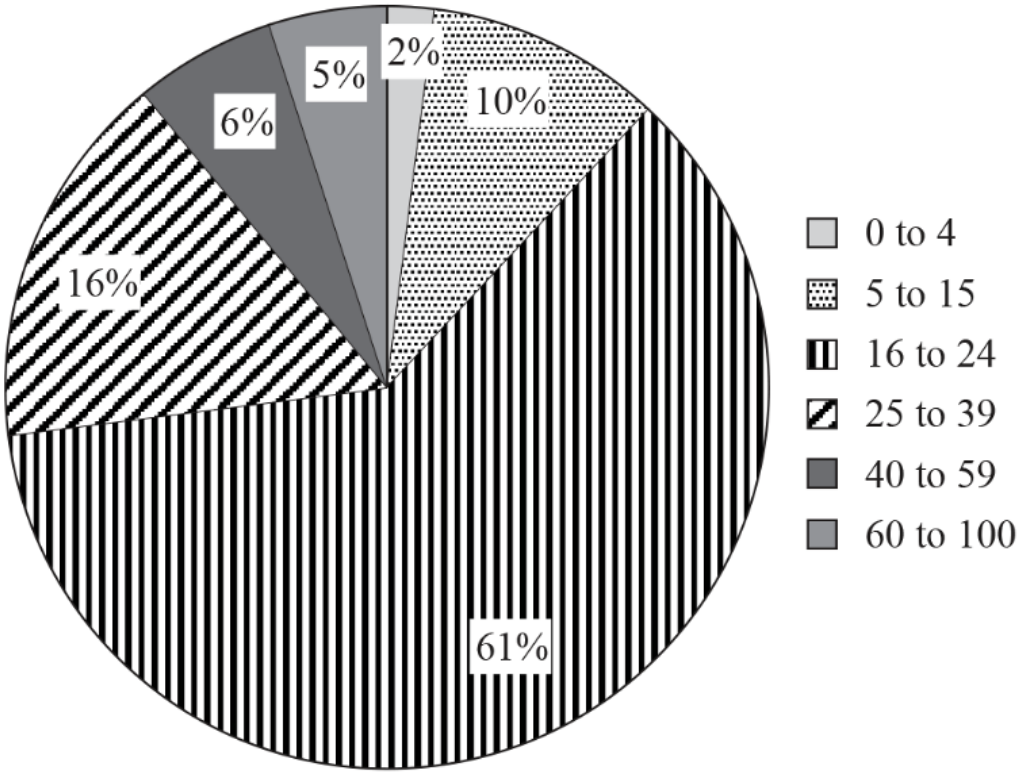

Figure 2. Age-dependency of *Staphylococcus saprophyticus*-related UTIs in female patients (n = 61).[39] Age is depicted in years. (Extracted from Adeghate J, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016 Mar; 63(1):57-67.)

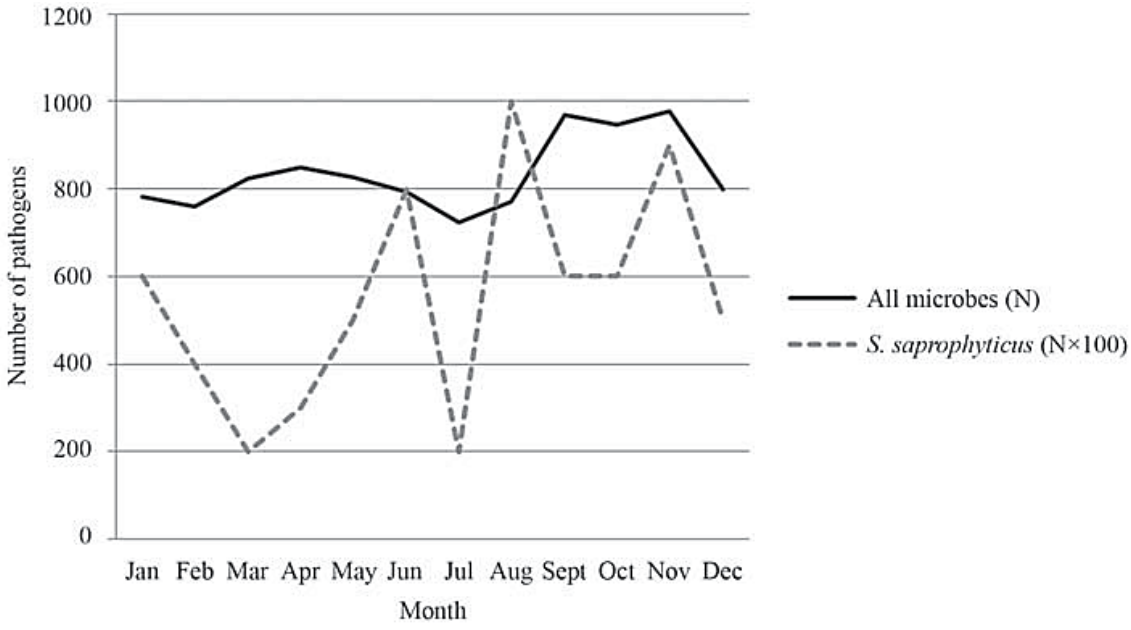

Figure 3. Seasonal distribution of all UTI-causing microorganisms in patients aged 0-100 years in 2014.[39] (Extracted from Adeghate J, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016 Mar; 63(1):57-67.)

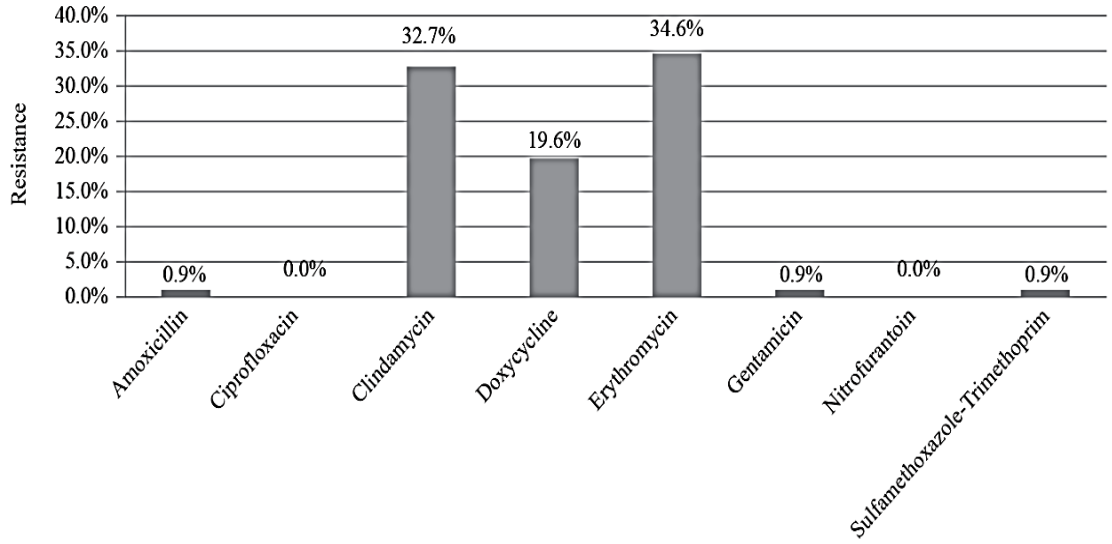

Figure 4. Antibiotic-resistance profile of *S. saprophyticus*. Resistance was tested with respect to Amoxicillin, Ciprofloxacin, Clindamycin, Doxycycline, Erythromycin,

Gentamicin, Nitrofurantoin and Sulfamethoxazole-Trimethoprim.[39] (Extracted from Adeghate J, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016 Mar; 63(1):57-67.)

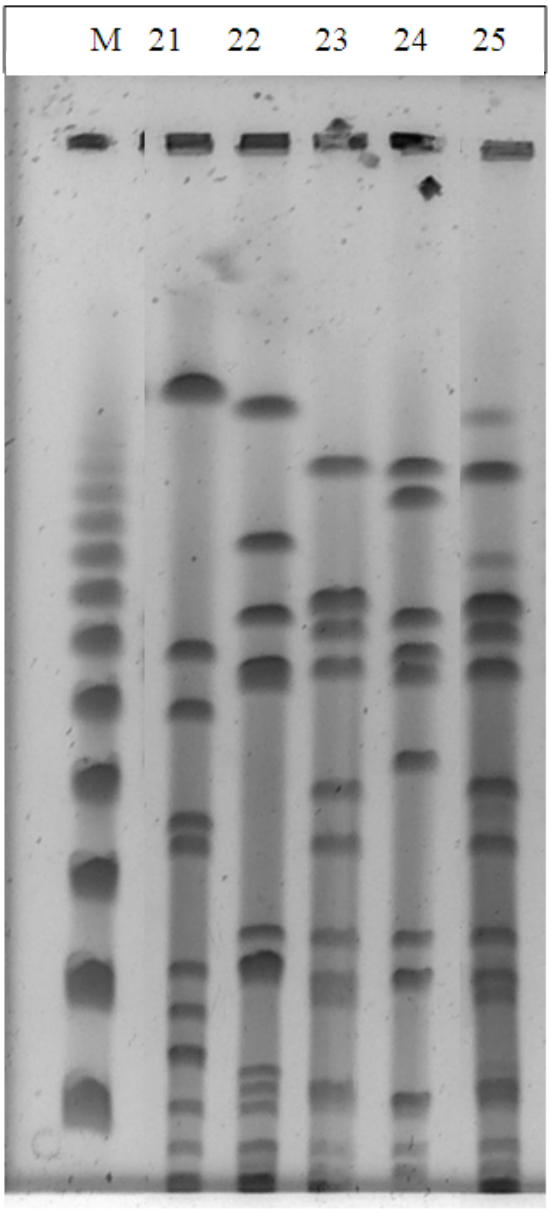

Figure 5. Representative PFGE fingerprints showing 5 varying genotypes of *S. saprophyticus* isolates from our study. M: Lambda Ladder.

4.2. Locations of CoNS colonies, their genetic profiles and transformation into virulent pathogens in neonates

4.2.1. Localization of CoNS colonies in bacteremic neonates

Coagulase-negative staphylococci were isolated from 1885 (37%) of the perianal specimens and 1619 (40.3%) of the pharyngeal specimens (Figure 6). Of these, CoNS were isolated from 216 blood cultures (11.5%) from neonates with CoNS-positive perianal samples, and 174 blood cultures (10.7%) from neonates with CoNS-positive pharyngeal samples. Interestingly, the number of neonates with bacteremia after CoNS colonization was significantly higher when compared to the bacteremia acquired after Enterobacteriales species colonization (p<0.0002) (Table 3).

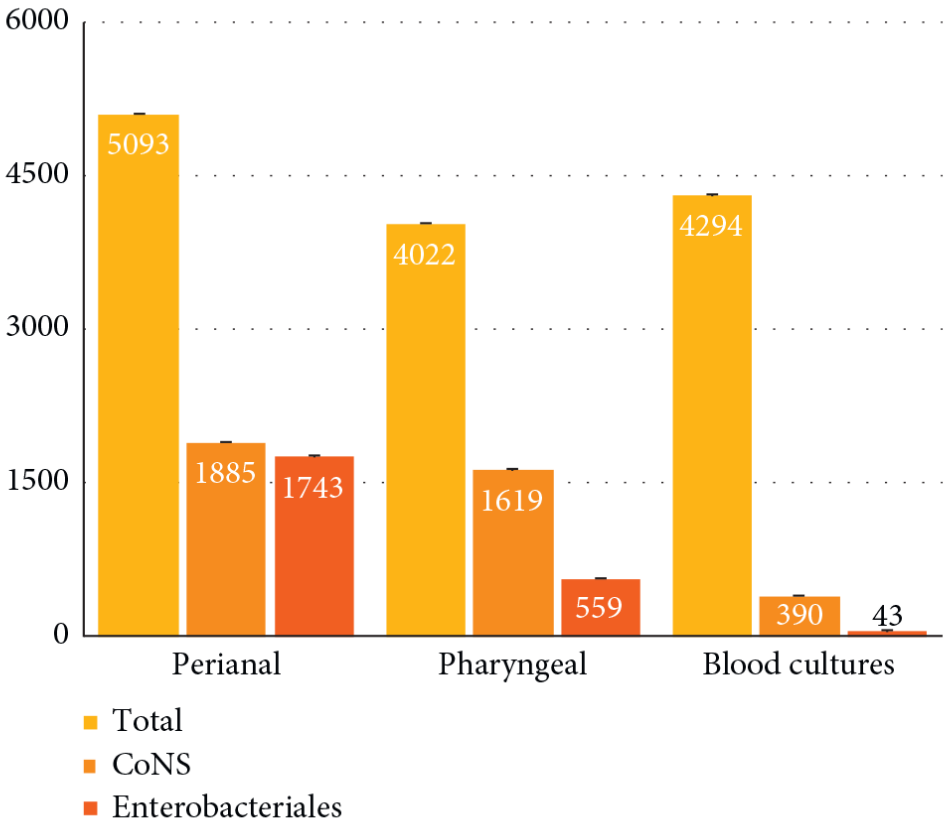

Figure 6. Total number of perianal, pharyngeal, and blood culture samples collected over 3 consecutive years (first column of each group). Of these, the number of cultures positive for CoNS and Enterobacteriales species is depicted in the second and third columns of each group, respectively. From 1118 neonates, a total of 5093 perianal samples, 4022

pharyngeal surveillance samples, and 4294 blood cultures were obtained. CoNS were isolated from 1885 (37%) of the perianal samples and 1619 (40.3%) of the pharyngeal samples. Enterobacteriales species were isolated from 1743 (34.2%) perianal samples and 559 (13.9%) pharyngeal samples. Of the 1885 CoNS-positive perianal samples and 1619 CoNS-positive pharyngeal samples, 216 and 174 blood cultures were positive for CoNS, respectively (*n*=390). Similarly, of the 1743 Enterobacteriales species-positive perianal samples and 559 Enterobacteriales species-positive pharyngeal samples, 34 and 9 blood cultures were also positive for Enterobacteriales species, respectively (*n*=43).[32] (Extracted from Adeghate JO, Juhász E, Iván MÁ, Pongrácz J, Kristóf K. Similar Strains of Coagulase-Negative Staphylococci Found in the Gastrointestinal Tract and Bloodstream of Bacteremic Neonates. Can J Infect Dis Med Microbiol. 2020 Jul 21; 2020:3509676.)

Table 3. Distribution of coagulase-negative staphylococci (CoNS) and enterobacterial bacteremia based on positive perianal and pharyngeal surveillance cultures over 3 consecutive years (%) (p<0.0002).[32]

Year	Type of culture (CoNS)	CoNS bacteremia (%)	Enterobacterial bacteremia (%)	Type of culture (Enterobacteria)
2013	Perianal (*n* = 608)	7.9	1.1	Perianal (*n* = 379)
	Pharyngeal (*n* = 475)	8.2	0.0	Pharyngeal (*n* = 125)
2014	Perianal (*n* = 635)	11.0	1.8	Perianal (*n* = 501)
	Pharyngeal (*n* = 548)	10.0	0.0	Pharyngeal (*n* = 145)
2015	Perianal (*n* = 642)	15.3	2.4	Perianal (*n* = 863)
	Pharyngeal (*n* = 596)	13.4	3.1	Pharyngeal (*n* = 289)
	Total perianal: 1885	34.2	5.3	Total perianal: 1743
	Total pharyngeal: 1619	31.6	3.1	Total pharyngeal: 559

(Extracted from Adeghate JO, Juhász E, Iván MÁ, Pongrácz J, Kristóf K. Similar Strains of Coagulase-Negative Staphylococci Found in the Gastrointestinal Tract and Bloodstream of Bacteremic Neonates. Can J Infect Dis Med Microbiol. 2020 Jul 21; 2020:3509676.)

4.2.2. Distribution of CoNS in positive blood cultures

A total of 588 blood cultures contained microbial pathogens. A large majority of these were CoNS (76.4%; *n*=449). The CoNS species observed in blood cultures were distributed as follows: *S. epidermidis* (54.6%, *n*=245); *S. haemolyticus* (23.2%, *n*=104); *S. hominis* (14.3%, *n*=64); *S. warneri* (2.4 %, *n*=11); and *S. capitis* (1.3%, *n*=6). Other

species comprised the remaining 4.2% (*n*=19) (Figure 7a). About seven percent (7.7%, *n*=45) of microbial strains isolated from the 588 positive blood samples contained Enterobacteriales species (Figure 7b).

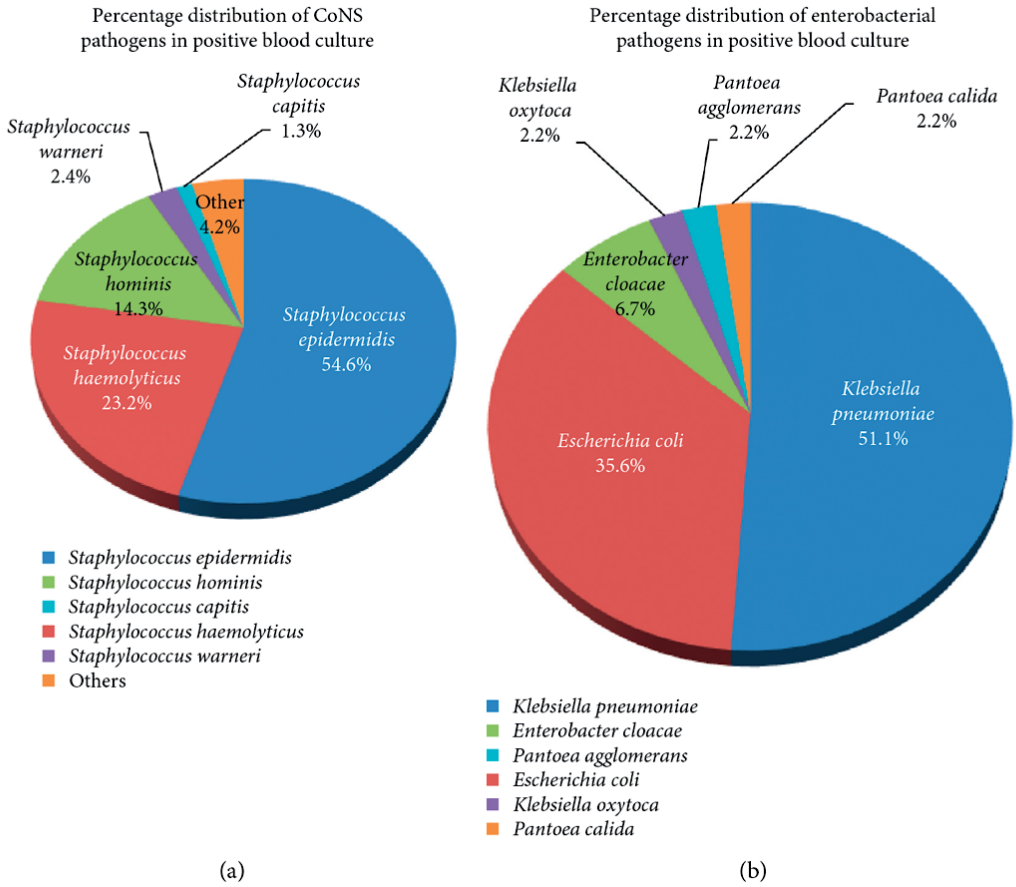

Figure 7. The percentage distribution of CoNS species (a) and Enterobacteriales species (b) in positive blood cultures of neonates.[32] (Extracted from Adeghate JO, Juhász E, Iván MÁ, Pongrácz J, Kristóf K. Similar Strains of Coagulase-Negative Staphylococci Found in the Gastrointestinal Tract and Bloodstream of Bacteremic Neonates. Can J Infect Dis Med Microbiol. 2020 Jul 21; 2020:3509676.)

4.2.3. Characterization of microbial pathogens in neonates

MALDI-TOF MS and PFGE were used to analyze CoNS strains retrieved from positive blood cultures in bacteremic neonates. This analysis showed that the isolates from positive blood cultures were markedly similar to the strains obtained from the pharyngeal

and perianal samples (Figures 8a-d). The molecular mass of *S. epidermidis* and *S. haemolyticus* strains obtained from positive blood cultures displayed marked similarity to the proteins of *S. epidermidis* and *S. haemolyticus* strains isolated from both pharyngeal and perianal specimens. Moreover, the molecular masses of proteins of the bacteremia-causing strains were different from those isolates retrieved from healthy neonates (Figure 8e). These findings indicate that there may be a difference in virulence between pathogenic and non-pathogenic variants of CoNS strains located in the GI tract, which may be causative of bacteremia in premature neonates.

DOI:10.14753/SE.2024.2974

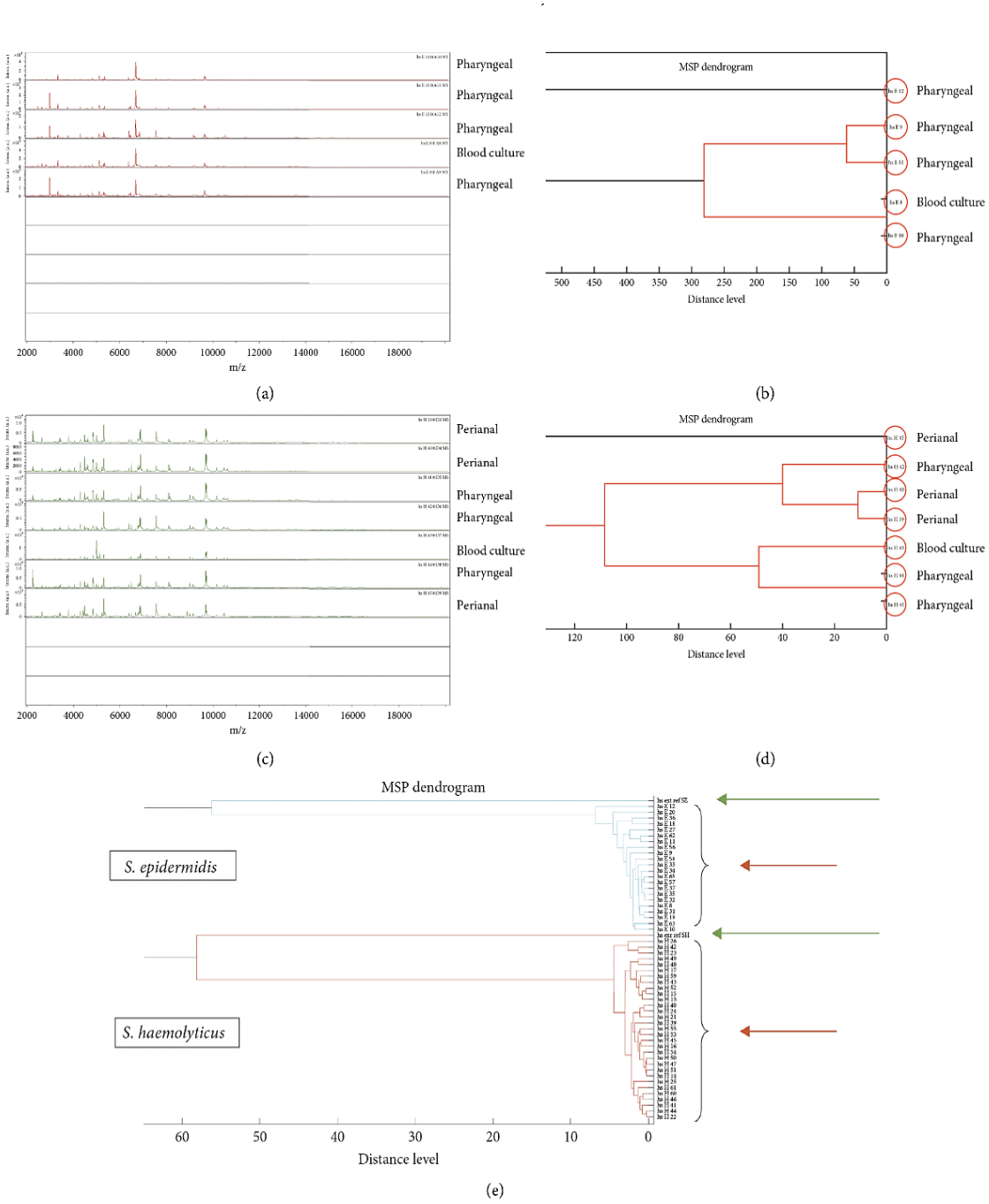

Figure 8. MALDI-TOF MS analysis (a) and representative dendrogram (b) of *S. epidermidis* strains isolated from a positive blood culture and 4 pharyngeal samples in a symptomatic neonate (*n*=1). MALDI-TOF MS analysis (c) and representative dendrogram (d) of *S. haemolyticus* strains isolated from a positive blood culture, 3 pharyngeal samples, and 3 perianal samples in a symptomatic neonate (*n*=1). Note the similarity in the graphs and dendrograms comparing pharyngeal, perianal, and blood

culture strains (a-d). Main spectra dendrogram (e) of mass spectrum profiles of 23 *S. epidermidis* and 31 *S. haemolyticus* strains isolated from positive blood cultures, pharyngeal samples, and perianal samples from symptomatic neonates (short red arrows) was compared to 1 *S. epidermidis* and 1 *S. haemolyticus* strain from healthy neonates (long green arrows). In (a) and (c), the x-axis depicts the mass-to-charge ratio in m/z, while the y-axis depicts the intensity of the spectra in arbitrary units (a.u.).[32] (Extracted from Adeghate JO, Juhász E, Iván MÁ, Pongrácz J, Kristóf K. Similar Strains of Coagulase-Negative Staphylococci Found in the Gastrointestinal Tract and Bloodstream of Bacteremic Neonates. Can J Infect Dis Med Microbiol. 2020 Jul 21; 2020:3509676.)

4.2.4. PFGE dendrogram

The PFGE dendrogram and fingerprints of the isolates that were examined are shown in Figure 9. The genotype of the *S. epidermidis* strains isolated from positive blood culture of bacteremic premature neonates was different from those obtained from pharyngeal and perianal samples. In contrast, the genotype of *S. haemolyticus* strains isolated from the pharyngeal and perianal samples was identical to that isolated from the blood cultures of neonates with bacteremia. The genetic configuration of bacteria isolated from healthy neonates was similar to those found in positive blood cultures, but not identical. The dendrograms obtained from the PFGE and MALDI-TOF MS procedures displayed significant similarity.

DOI:10.14753/SE.2024.2974

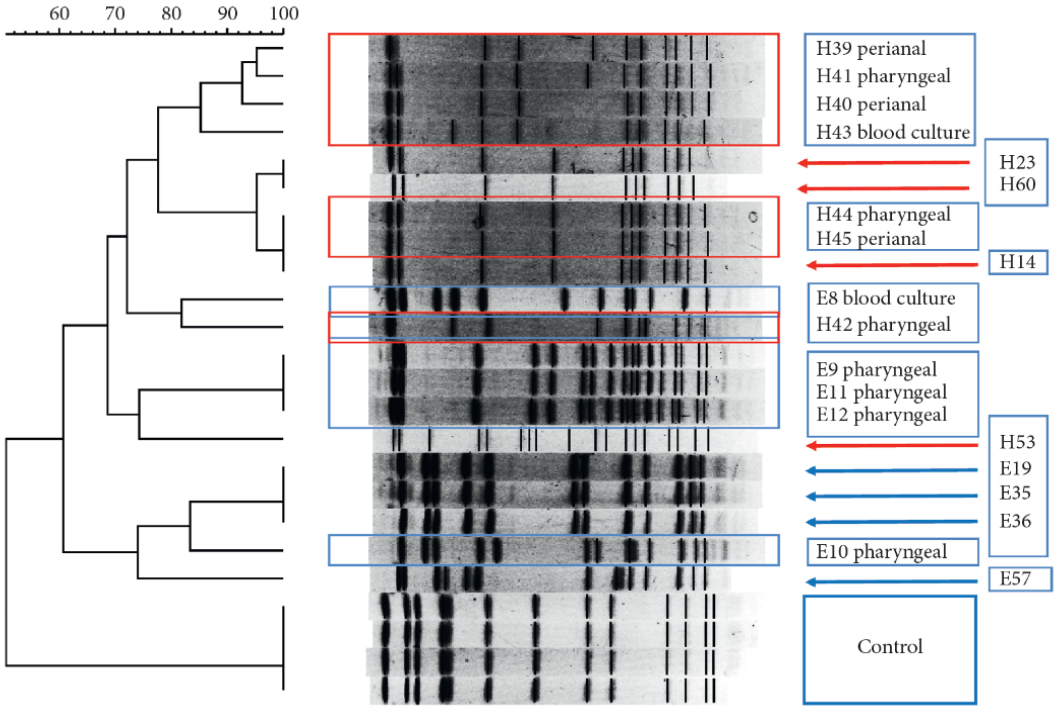

Figure 9. PFGE dendrogram and fingerprints of 5 *S. epidermidis* and 7 *S. haemolyticus* strains isolated from positive blood cultures, pharyngeal samples, or perianal samples from two symptomatic neonates, and 4 *S. epidermidis* and 4 *S. haemolyticus* strains isolated from healthy neonates (control). One random specimen was used as a control for testing the validity of the PFGE results.[32] (Extracted from Adeghate JO, Juhász E, Iván MÁ, Pongrácz J, Kristóf K. Similar Strains of Coagulase-Negative Staphylococci Found in the Gastrointestinal Tract and Bloodstream of Bacteremic Neonates. Can J Infect Dis Med Microbiol. 2020 Jul 21; 2020:3509676.)

4.3. CoNS-related infections in endophthalmitis: clinical characteristics, treatment, and outcomes

4.3.1. Distribution of CoNS species in ophthalmic patients

A total of 42 ophthalmic samples including vitreous (*n*=15), aqueous (*n*=9), both aqueous and vitreous (*n*=15), and other intraocular structures (1 intraocular foreign body, 1 vitreous and lens, 1 unknown), from 40 patients with confirmed CoNS endophthalmitis

between August 1st, 2014, and August 31st, 2018, were examined. *S. epidermidis* was the most common isolate of these ocular samples (92.85%; *n*=39/42). This was followed by *S. lugdunensis* which consisted *of* 4.76% (*n*=2/42) of all isolates, while *S. haemolyticus* stands as the third most common CoNS strain, accounting for 2.38% (*n*=1/42) of all isolated strains.

4.3.2. Clinical perspectives of endophthalmitis

In this cohort of patients, the main etiologies of endophthalmitis were post-cataract surgery in 45% (*n*=18/40) of cases; intravitreal anti-vascular endothelial factor (anti-VEGF) injections in 35% (*n*=14/40); trauma, glaucoma surgery, or recurrence in 5% (*n*=2/40); and post corneal transplant and combined glaucoma-cataract surgery in 3% (*n*=1/40) (Figure 10). The cause of endophthalmitis for two of the samples could not be determined.

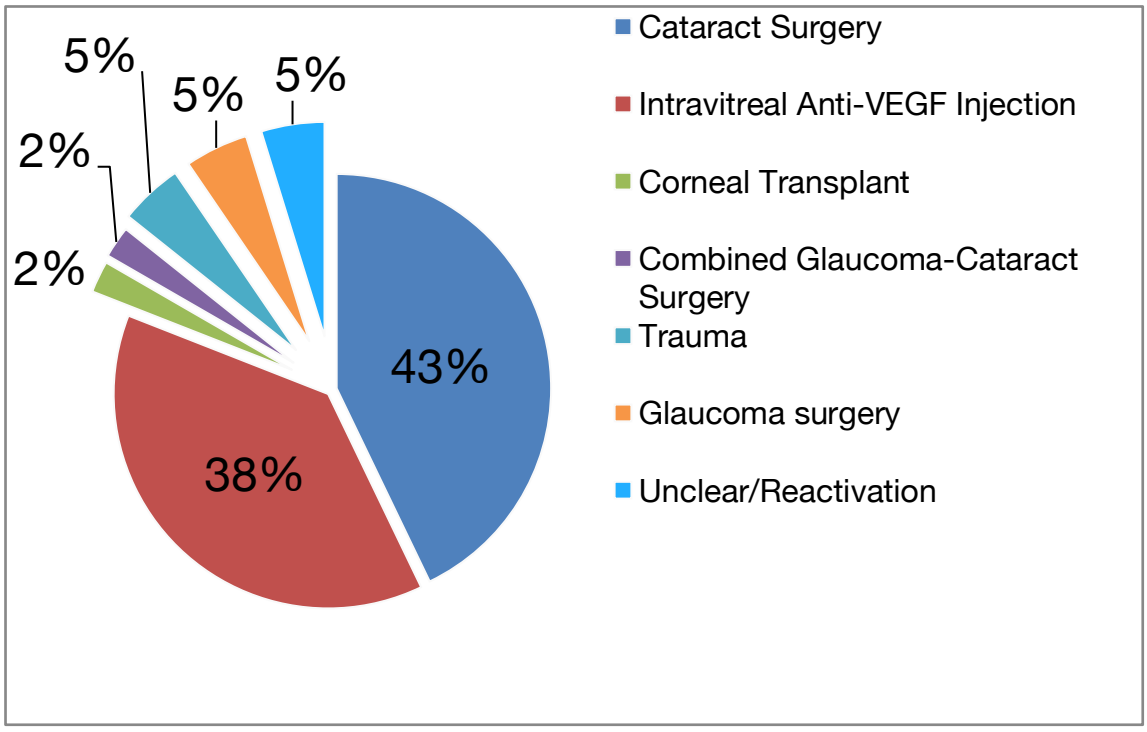

Figure 10. Causes of endophthalmitis in the study population. Note that cataract extraction (45%) and intravitreal anti-VEGF injection (35%) accounted for the most frequent etiologies of endophthalmitis in our study.[44] (Adapted from Adeghate JO, Yadav

S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

4.3.3. Intravitreal antibiotics versus pars plana vitrectomy for CoNS endophthalmitis

Out of the total 42 isolates, 74% of samples were collected from subjects treated with intravitreal antibiotics (*n*=31/42); 24% from patients who underwent PPV (*n*=10/42); and 2% from subjects with other modes of treatment (antibiotics, topical or oral steroids) (*n*=1/42) (Figure 11). Intravitreal antibiotic injections utilized included the following: vancomycin (1mg/0.1ml), amikacin (400mcg/0.1ml), and ceftazidime (2.25mg/0.1ml). The 2 patients with *S. lugdunensis* and 1 patient with *S. haemolyticus* endophthalmitis all had intravitreal injection of antibiotics only. In contrast, of the samples positive for *S. epidermidis*, 10 were obtained from subjects treated with PPV and 29 with intravitreal injection of antibiotics (Table 4).

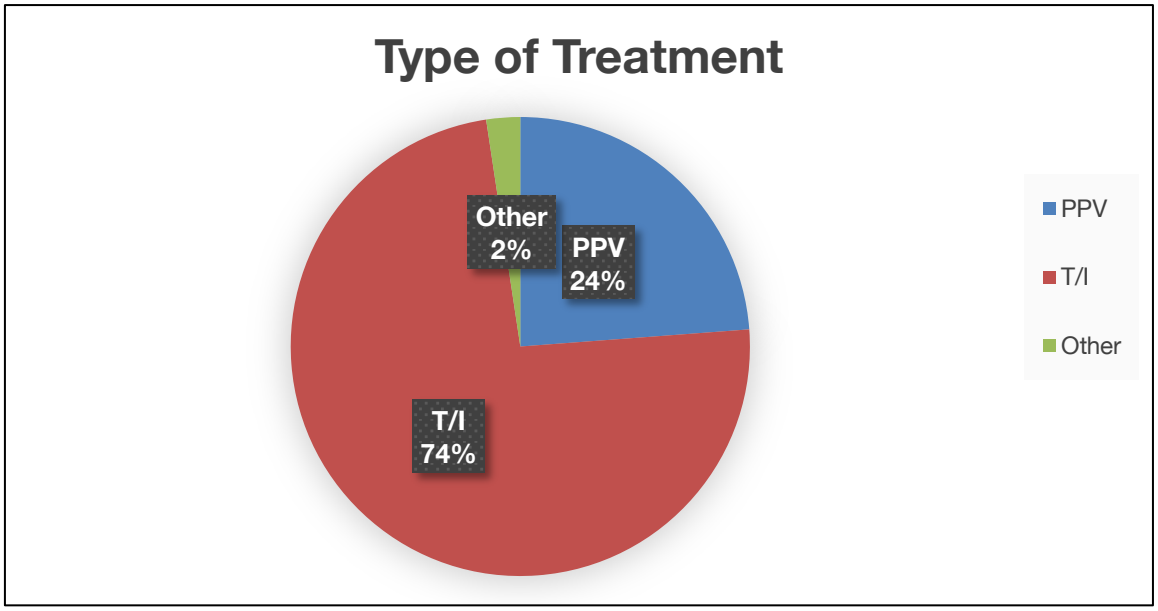

Figure 11. Type of treatment undergone by endophthalmitis patients. Note that most patients underwent vitreous tap and injection of intravitreal antibiotics (T/I) (74%),

followed by pars plana vitrectomy (PPV) (24%) and other interventions (2%) including topical antibiotics, and topical or oral steroids.[44] (Adapted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

Table 4. Type of treatment based on CoNS strain (%).

	PPV	T/I
S. epidermidis	10	29
S. haemolyticus	0	1
S. lugdunensis	0	2

Table 4. Type of treatment based on CoNS strain. PPV: pars plana vitrectomy, T/I: tap and injection of intravitreal antibiotics.[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

4.3.4. Ocular findings associated with CoNS-related endophthalmitis

Several ocular findings were observed in CoNS-related endophthalmitis. These include inflammation of the anterior chamber in 97.5% of subjects (*n*=39/40), hypopyon in 65% (*n*=26/40); hazy view to the fundus noted in 75% of patients (*n*= 30/40) and vitritis seen in 55% (*n*=22/40) of patients (Table 5).

Table 5. Associated Eye Exam Findings.		
List of associated exam findings	**% patients (*n*=40)**	**%**
Anterior chamber inflammation (cells >0.5+)	39	97.5%
Hazy view of fundus	30	75%
Hypopyon	26	65%
Vitritis	22	55%
Corneal edema	12	30%

Table 5. Anterior chamber inflammation (cells in anterior chamber ≥0.5+), hazy view of the fundus, hypopyon and vitritis were the most common exam findings in patients who presented with CoNS endophthalmitis.[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

4.3.5. Visual outcomes in CoNS-related endophthalmitis

The visual outcomes of patients with CoNS-related endophthalmitis were examined based on the initial visual acuity (VA) and mode of treatment. The average final LogMAR VA in eyes with a presenting vision of hand motions (HM) or better were comparable in both the PPV and T/I-treated cohort of patients (0.87 vs 0.90, respectively, p=0.94). However, patients with light perception (LP) or poorer vision at presentation with endophthalmitis had a more favorable clinical outcome after PPV compared to those who underwent T/I (0.37 versus 2.30, respectively; p<0.0012).

Analysis of patients with *S. epidermidis* endophthalmitis showed that the average final VA between PPV and T/I eyes was significantly improved compared to presenting VA in both groups. The improvement was from LogMAR 1.11 to 0.49 after PPV, and from

1.39 to 0.44 in the T/I group (p=0.0113 and p<0.001, respectively). There was no significant difference in the final BCVA between the two cohorts of patients (p=0.72) (Table 6).

Table 6. Final visual acuity by treatment method.

	Mean Final VA		
Mean Initial VA	**PPV**	**T/I**	***p*-value**
LP or worse (*n*=7)	0.3701 (*n*=4)	2.1215 (*n*=3)	0.0003
HM or better (*n*=34)	0.8722 (*n*=6)	0.8926 (*n*=28)	0.9544

Table 6. The final VA in the eyes of patients presenting with light-perception (LP) or worse VA was better after pars plana vitrectomy (PPV) when compared to eyes treated with vitreous tap and intravitreal antibiotics injection (T/I). Eyes with VA recorded as hand motions (HM) or better had no difference in final VA after PPV or T/I.[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

4.3.6. Visual outcomes based on CoNS species and treatment

The average time of follow-up (initial & final VA) in this cohort of patients was two years (716 days, ranging between 2 to 2,342 days). The average period from start of infection to presentation was 4.94 days (ranging between 2 to 10 days). Data was presented for 16 of 40 patients over the course of 12 weeks following presentation. The mean VA at presentation was LogMAR 1.985 (20/2000; equivalent to HM). In general, the VA was better over a period of three months after the onset of CoNS endophthalmitis in all patients treated with either PPV or T/I. The mean final VA at 12 weeks was 0.906 (20/160).

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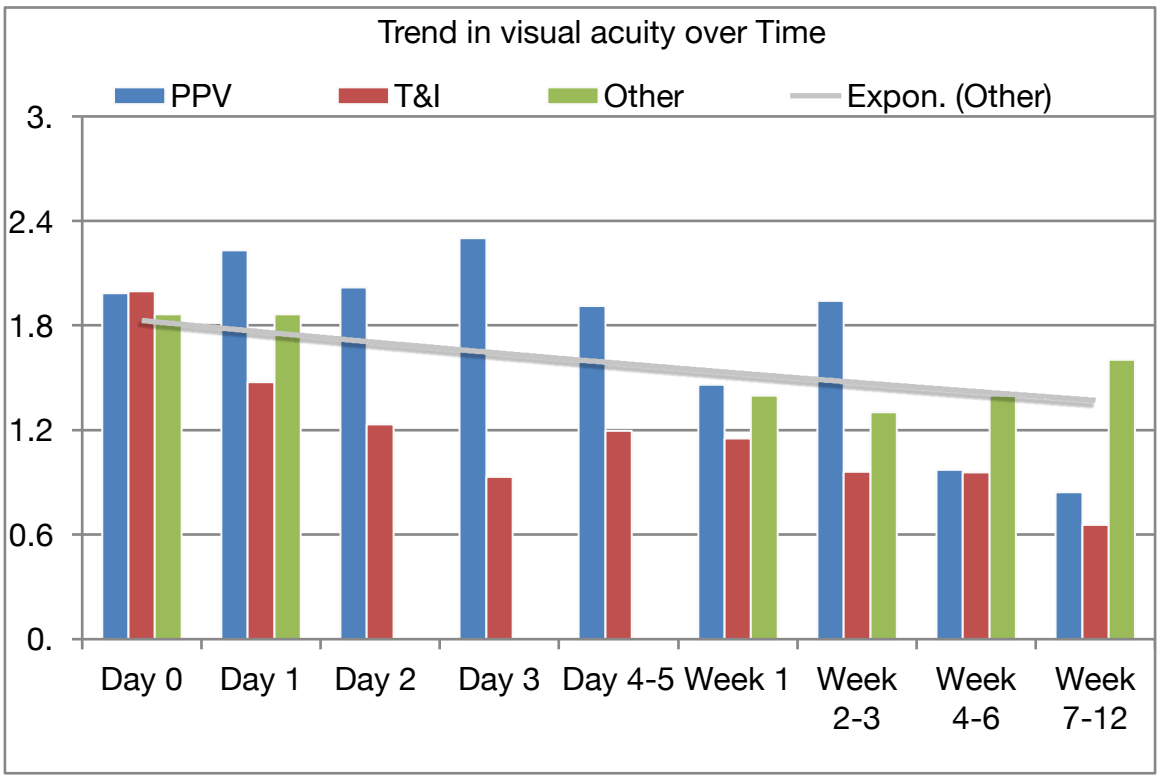
However, a worsening trend in VA over 12 weeks was seen in the only patient who was not treated with either PPV or T/I, but with topical antibiotics, topical steroids, or oral steroids (Figure 12a). Overall, intraocular pressure (IOP) was stable in all three cohorts of patients throughout the study period (Figure 12b). There was no significant difference in the final VA after PPV versus T/I (p=0.3453). In addition, there was no significant difference between mean final VA in subjects with *S. lugdunensis* compared to *S. epidermidis* endophthalmitis (p=0.8347) (Table 7).

(a)



(b)

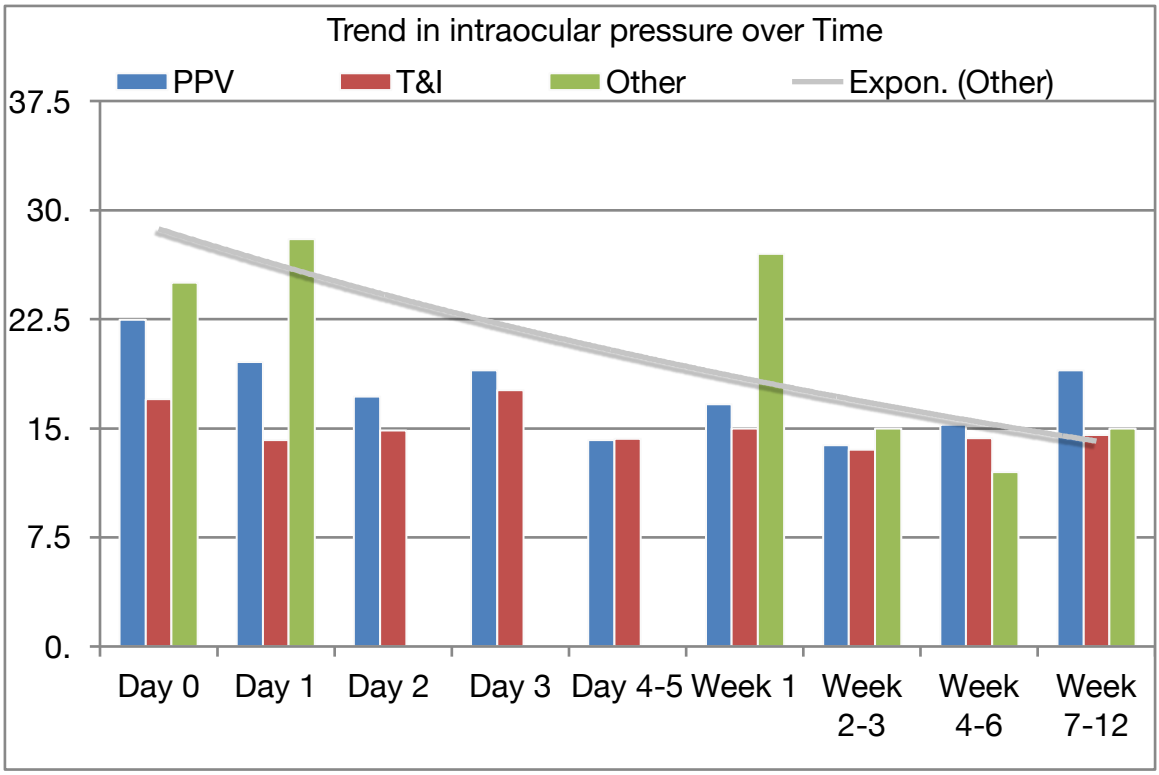


Figure 12a & 12b. Visual acuity (VA) and intraocular pressure (IOP) trends over time, distributed by treatment type: pars plana vitrectomy (PPV; blue), tap and intravitreal antibiotic injection (T&I; red), other treatments (topical antibiotics, and topical or oral steroids; green). Note that in both PPV and T&I groups, VA improved over the course of 12 weeks after the onset of endophthalmitis (a), and IOP decreased over the course of 12 weeks after onset of endophthalmitis (b).[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

Table 7. Comparison of initial and final visual acuity in patients with *S. epidermidis* endophthalmitis undergoing PPV vs. T/I.			
	Mean initial VA	**Mean Final VA**	***p*-value**
PPV (*n*=10)	1.965	0.6714	0.0008
T/I (*n*=29)	1.9625	0.9429	<0.001
***p*-value**		0.3512	

Table 7. There was a significant improvement between initial and final VA in both pars plana vitrectomy (PPV) and intravitreal antibiotics (T/I) groups; however, neither was superior to the other (p=0.3512). VA: visual acuity.[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

4.3.7. Co-existing ocular disease in CoNS endophthalmitis

The most prevalent eye disease associated with CoNS endophthalmitis included the following: age-related macular degeneration (AMD; n=11/42, 26.2%); primary and secondary glaucoma (n=7; 16.7%), diabetic retinopathy or maculopathy (n=7/42, 12.5%), and epiretinal membranes (n=5/42, 11.9%). There were no associated eye comorbidities in 19% of cases (n=8/42) (Table 8).

Table 8. Co-existing ocular conditions.		
List of Ocular conditions	**Number of patients (*n*=42)**	**%**
Exudative AMD and dry AMD	11	26.2%
None	8	19.0%
Primary and Secondary Glaucoma	7	16.7%
Diabetic retinopathy (NPDR), Diabetic maculopathy (DME)	6	14.3%
ERM	5	11.9%
Pseudophakia	3	7.1%
History of Refractive Surgery (e.g., LASIK)	3	7.1%
Cataract	2	4.8%
Choroidal nevi or scars	2	4.8%
Vascular retinal disease: CRVO with CME, BRAO	2	4.8%
Eye Trauma	2	4.8%
Diabetes Mellitus without complications	1	2.4%
Unspecified CME	1	2.4%
Corneal dystrophy	1	2.4%
History of Corneal Transplant (e.g., PKP)	1	2.4%
CSCR	1	2.4%
Amblyopia	1	2.4%

Table 8. Most of the patients had the following co-existing ocular diseases before developing endophthalmitis: age-related macular degeneration (AMD), glaucoma, non-proliferative diabetic retinopathy (NPDR), diabetic macular edema (DME), and epiretinal membranes (ERM). Other abbreviations include LASIK: laser assisted in situ

keratomileusis, CRVO: central retinal vein occlusion, CME: cystoid macular edema, BRAO: branch retinal artery occlusion, PKP: penetrating keratoplasty, and CSCR: central serous chorioretinopathy.[44] (Extracted from Adeghate JO, Yadav S, Kowalski RP, Juhász E, Kristóf K, Olsen KR, Bergren RL, Knickelbein JE, Chhablani J, Martel JN, Anetakis A, Dansingani KK, Rosin B, Gallagher DS, Prensky C, Eller AW, Friberg T, Sahel JA, Errera MH. Coagulase-negative staphylococcal endophthalmitis: clinical severity and outcomes based on speciation. Can J Ophthalmol. 2023 Jun 13:S0008-4182(23)00175-8.)

5. Discussion

5.1. *S. saprophyticus*-related UTIs

S. saprophyticus is a common microbe responsible for urinary tract infections (UTIs), particularly acute cystitis in young females, and its antibiotic resistance capabilities are well-known.[45,46] In healthy individuals, *S. saprophyticus* is a resident of the GI tract, most commonly located in the rectum,[46] and in the lower genital tract and the perineum in females.[24,47,48] he predisposition of young females for *S. saprophyticus* UTIs is proposed to be related to a potential reservoir for infection allowing for higher rate of colonization in this group.[46] Any changes in the microbiome of the extragenital region may also predispose to *S. saprophyticus*-related UTIs.[46] Less commonly, *S. saprophyticus* can cause cystitis in males, and conditions that may increase the probability of this is obstruction of the urinary tract or the presence of urinary catheters. [24] Other factors that could enhance *S. saprophyticus*-related UTIs include sexual activity, which may enable translocation of the bacterium from the perineum to the urethra; the use of public baths; and handling and eating of certain meats.[49]

The mechanism by which *S. saprophyticus* colonizes the urinary tract is not definitively known, but it was proposed that the bacteria ascend proximally along the urothelium of the urinary tract causing cystitis and more severe UTIs, such as acute pyelonephritis.[24] *S. saprophyticus*-related UTIs are mostly associated with symptoms such as dysuria, pollakiuria, hematuria, pyuria, and back pain, in contrast to other bacterial pathogens such as E. coli and Proteus spp., which may cause asymptomatic infections. [24] Rare but

possible complications of *S. saprophyticus*-related UTIs include septicemia and endocarditis.[24]

The findings of our study corroborate reports of other research groups showing that *S. saprophyticus* is the most common bacterium isolated from the urine of young and sexually active females with UTIs.[50] Our study showed *S. saprophyticus* as the most commonly isolated bacterium from urinary samples of women aged 16-24 years and 25-39 years, as previously reported.[51] Other bacteria have also been isolated from the urine samples in our study, including E. faecalis, a variety of Enterobacteriaceae strains, and P. aeruginosa.[39] Overall, UTIs were most prevalent in infants (ages 0-4 years) and in the elderly population (60-100 years), suggesting a link between reduced immune system function and susceptibility to UTIs.[39]

5.1.1. *S. saprophyticus*-related UTIs in males

In our study, we also isolated *S. saprophyticus* from urine samples of males aged 5-15 years.[39] A possible explanation for this finding is that in this age group in males, the distal GI tract is in close proximity to the genital tract, enabling ascension of *S. saprophyticus* within the urinary tract, supporting the reservoir theory previously discussed.[46] Another possible mechanism may be increased sexual activity in males age of 15 years, which is a known risk factor *S. saprophyticus*-related UTIs.[50]

5.1.2. Seasonal variation in *S. saprophyticus*-related UTIs

The findings of our study showed that the incidence of *S. saprophyticus* UTIs was much higher in the months of June, August, November, and January,[39] which corroborates the findings of other studies indicating peaks in colonization with *S. saprophyticus* during summer and fall months.[46] Interestingly, this seasonal occurrence of *S. saprophyticus* UTIs is similar to that of sexually transmitted infections (STIs), which suggests that *S. saprophyticus* infections may occur concurrently with STIs.[52,53]

5.1.3. Treatment and antibiotic resistance of *S. saprophyticus*

Several antibiotics are used to successfully treat UTIs caused by *S. saprophyticus*, including fluoroquinolones (ciprofloxacin), amoxicillin, macrolides (erythromycin, clindamycin), tetracyclines (doxycycline), aminoglycosides (gentamicin), nitrofurantoin,

and sulfamethoxazole-trimethoprim. Although there are differences between our resistance results compared to that of the National Center for Epidemiology (OEK), there was no evidence in our study that *S. saprophyticus* is resistant to any of these antibiotics.[54] The differences between the resistance data in our study to those of the OEK include a higher resistance to amoxicillin and lower resistance to clindamycin in our study, which is likely due to our smaller patient population than examined nationally.[39]

5.2. Presumed translocation of CoNS into the bloodstream from the GI tract in premature neonates

CoNS isolates from blood and surveillance cultures of 1,118 neonates were analyzed using MALDI-TOF MS and PFGE to determine whether the genetic profiles of CoNS found in blood of septicemic neonates were similar to those obtained from either pharyngeal or perianal colonies.[32]

Reports have in fact shown that CoNS may cause bloodstream infection (BSI) in premature neonates, and these otherwise benign microorganisms may reach the bloodstream after proliferating on indwelling catheters, prostheses, and other medical devices.[55] In our study, CoNS accounted for more than 75% of all bacteria isolated from blood cultures of the investigated neonates. This observation agrees with many other studies, which have reported that 50-66% of microbes isolated from the blood of septic neonates were CoNS.[56–58]

Despite much investigation, the mechanisms by which resident CoNS bacteria in the GI tract induce bacteremia is unknown.[59] In our study, although many enterobacteria colonized the GI tract, only a small fraction were isolated from blood cultures of bacteremic neonates (1.6-2.0%).[32] In contrast, 10.7-11.5% of CoNS colonies populating the GI tract were shown to cause BSIs. This demonstrates that the ability of CoNS to become pathogenic may be higher than that of other colonizing bacteria such as Enterobacteriales species. The mechanism by which this transformation occurs needs to be further elucidated to help in the prevention of CoNS-related neonatal sepsis.

5.2.1. Characterization of microbial pathogens in neonates

In our study, MALDI-TOF MS showed that the molecular mass of *S. epidermidis* and *S. haemolyticus* proteins from the blood cultures of selected neonates displayed significant

resemblance to those obtained from the perianal and pharyngeal colonies of the same neonates.[32] In addition, the genetic profile of the *S. haemolyticus* strains isolated from a symptomatic neonate displayed similar PFGE genotypes. This indicates that the samples obtained from pharyngeal and perianal colonies in bacteremic neonates were genetically similar to those obtained from blood cultures, implying causality between GI colonization with CoNS and subsequent bacteremia. We also found that the molecular mass and genome of *S. epidermidis* and *S. haemolyticus* isolates in affected neonates were different from those obtained from healthy neonates without bacteremia, indicating that these strains may have different genetic profile.

Our findings suggest that CoNS may have a higher ability to transform into an invasive pathogen from a non-pathogenic state in the GI tract and is perhaps more likely to occur in susceptible populations. The low potential of enterobacterial gut colonies to cause bacteremia may also point to a protective role of this species in neonates. Previous reports have in fact shown that Enterobacteriales species colonizing the gut may play a significant role in the protection and maintenance of homeostasis within the GI tract.[59]

5.3. CoNS infections in patients with endophthalmitis: clinical characteristics, treatment, and outcomes

5.3.1. Distribution of CoNS species in ophthalmic patients

S. epidermidis was the most commonly isolated CoNS in this group of patients with acute endophthalmitis (92.9%), followed by *S. lugdunensis* and *S. haemolyticus* contributing to about 5% of the remaining CoNS strains.[44] This observation corroborates reports which indicate that *S. epidermidis* accounts for 82% of microbial isolates and *S. lugdunensis* forming around 6% of all pathogenic isolates from endophthalmitis specimens.[60] In our study, a large number of the patients had endophthalmitis secondary to cataract surgery (45%), followed by intravitreal anti-VEGF injections performed for exudative AMD (35%), trauma (5%), glaucoma surgery (5%) and penetrating keratoplasty (3%). These results also agree with those of Yannuzzi et al., who in a study of endophthalmitis reported that post-cataract surgery endophthalmitis is the most prevalent etiology of endophthalmitis (49%), while intravitreal injections are responsible in 22%, trauma in

8%, glaucoma surgery in 7% and penetrating keratoplasty in 5% of cases with acute endophthalmitis.[61]

5.3.2. Treatment of CoNS species in ophthalmic patients

Most patients we studied were managed with intravitreal antibiotic injections (75%), while much fewer were treated with pars plana vitrectomy (PPV) (25%).[44] This treatment pattern corroborates with another retrospective study completed more than 10 years ago, in which out of 73 eyes, 74% of subjects were treated with intravitreal antibiotic injections, and 26% with PPV.[62] However, Yannuzzi et al. reported a slightly higher number of patients who received intravitreal antibiotics (86%) and a lower number of patients who underwent PPV (14%).[61]

5.3.3. Clinical perspectives of CoNS-related endophthalmitis

More than 97% of patients with CoNS-related endophthalmitis in our study had inflammation in the anterior chamber of the eye, and 65% had a visible hypopyon.[44] This data appears to be lower than that reported in another study, where 82% of patients with CoNS-related endophthalmitis had a hypopyon.[62] In addition, 55% of patients in our study had vitritis. Early recognition of these associated findings may help in timely diagnosis and treatment of CoNS-related endophthalmitis. Ormerod et al. indicated that diagnosis of endophthalmitis is generally delayed due to lack of clinical signs that would otherwise guide a prompt diagnosis.[63]

5.3.4. Visual outcomes in CoNS-related endophthalmitis

The degree of visual acuity (VA) loss largely depends on the severity of infection at initial presentation, as well as the type of treatment instituted.[64,65] The average length of time from infection to presentation in our patients was 5 days.[44] This is much lower than the 13-day period reported by Lalwani et al.[62] The importance of VA in the management of CoNS-related endophthalmitis has been described by the Endophthalmitis Vitrectomy Study (EVS), notably in the treatment for acute post-cataract surgery endophthalmitis.[64,65] With the introduction of small-gauge vitrectomy, preferred practice patterns have changed, and the benefits of early PPV as the first line

of treatment have been suggested.[66–68] In contrast to literature reports, our study did not find any observation that early PPV led to marked augmentation in vision when compared to presentation (LogMAR 1.11 to 0.49 in PPV, and LogMAR 1.39 to 0.44 in T/I eyes) (p=0.72). However, we did find that in patients with *S. epidermidis* endophthalmitis, intravitreal injection of antibiotics (T/I) may have similar outcomes compared to PPV, thus potentially reducing the burden of treatment and costs associated with PPV.[44] Our study also showed that, in accordance with the EVS study, patients with HM vision or better were able to benefit from T/I, while patients with LP vision or worse benefited from PPV performed in the early course of the disease.[44] These observations suggest that PPV may be more beneficial in subjects with severe endophthalmitis with poor VA at presentation, or in selected cases of *S. epidermidis* endophthalmitis. Additional study is warranted to investigate the visual outcomes of endophthalmitis caused by *S. haemolyticus* or *S. lugdunensis*, the latter which has been reported to lead to atypical and serious infection.[69] Schanzlin et al. suggested that low virulence pathogens should be considered in cases of chronic and persistent post-surgical inflammation of the eye.[70]

5.3.5. Virulent transformation and antibiotic resistance in CoNS endophthalmitis

Inappropriate use of antibiotics may lead to antibiotic resistance in CoNS that may transform into virulent strains.[71] A 2018 report from the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study observed that 39% of CoNS are resistant to multiple drugs, and that multidrug resistance is more likely associated with methicillin-resistant CoNS (72.8%) than methicillin-sensitive CoNS (7.6%).[72] Several investigations have shown a beneficial effect of prophylactic antibiotics prior to or during cataract surgery to prevent postoperative endophthalmitis; however, there is currently no consensus on this practice.[71,73] The current worldwide consensus among ophthalmic surgeons for reducing the incidence of postoperative endophthalmitis is the application of 10% povidone-iodine solution to the periocular region, and 5% povidone-iodine solution to the ocular surface prior to surgery. [74,75]

Fluoroquinolones such as ciprofloxacin and gatifloxacin are effective in the management of CoNS endophthalmitis;[76] however, studies have shown that vancomycin and linezolid

rather than fluoroquinolones are superior in the treatment of CoNS-related endophthalmitis.[77] In general, vancomycin is said to have the highest (100%) efficacy in the management of CoNS-related infection,[78–81] which is in accordance with more recent reports.[41]

6. Conclusions

In our studies, we demonstrated that the occurrence of *S. saprophyticus* infections depends highly on the studied population, and that predisposing factors such as age, gender, clinical progression, and even seasonal changes may influence the incidence of infection. *S. saprophyticus* is a urinary pathogen that is a major cause of acute cystitis not only in women of reproductive age, but also in other age and gender groups. *S. saprophyticus* isolates show highly variable genetic characteristics due to differing sources of infection. Fortunately, antibiotic resistance does not pose an issue in the treatment of UTIs caused by this bacterium, as most genetic variants have been shown to possess high sensitivity to commonly used antibiotics.

Similarly, CoNS bacteremia is responsive to the currently used antibiotics, but premature neonates can be severely affected by these infections. Our findings suggest an association between *S. epidermidis* and *S. haemolyticus* strains in the GI tract and those found in the bloodstream in bacteremic neonates, indicating that GI CoNS may undergo malignant transformation and translocate through the GI mucosa. This is incredibly important in our understanding of continued surveillance of premature neonates as a population susceptible to nosocomial infections.

Due to their abundance on the ocular surface, CoNS are common causative microbes in endophthalmitis. Most cases of CoNS endophthalmitis occur after cataract surgery and intravitreal injections for macular degeneration. The findings of the Endophthalmitis Vitrectomy Study (EVS) stand true today as they did in the late 1990s, indicating that severe cases benefit from early operative intervention, while less severe cases benefit similarly from intravitreal injections alone. Ultimately, clinical findings may not always be apparent, therefore heightened suspicion is necessary in atypical cases.

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7. Summary

Background: Coagulase-negative staphylococci (CoNS) belong to the normal microbiome; however, they may cause opportunistic infections in neonates and adults with compromised immune systems. **Aims and objectives:** We aimed to investigate the unusual presentations of CoNS in various organ systems. **Methods:** CoNS strains isolated from urine, blood cultures, and perianal and pharyngeal samples were investigated using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and pulsed-field gel electrophoresis. Additional molecular identification and genetic analysis of CoNS strains was performed on vitreous and aqueous samples of patients with CoNS-related endophthalmitis. **Results and Discussion:** *S. saprophyticus* affected atypical patient populations such as young males. The molecular mass and genetic profile of CoNS isolates from blood cultures and the GI tract of bacteremic neonates showed marked similarity. Severe endophthalmitis benefitted from early vitrectomy over intravitreal injections, while *S. epidermidis* endophthalmitis cases appeared to benefit similarly from vitrectomy and intravitreal antibiotic injections. Antibiotic resistance is not an issue in treatment of CoNS-related infections. **Conclusion:** Despite being part of the commensal microbiome of the skin, CoNS may become virulent pathogens causing significant disease in multiple organ systems in patients of all ages.

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9. Bibliography of the candidate's publications

9.1. Publications related to the PhD thesis

9.1.1. Full-length articles

1. **Adeghate J**, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. *Acta Microbiol Immunol Hung.* 2016 Mar; 63(1):57-67. [Impact Factor: 0.921]

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9.1.2. Abstracts

1. **Adeghate J**, Juhász E, Pongrácz J, Rimanóczy É, Kristóf K. *Staphylococcus saprophyticus* – Csak fiatal nők húgyúti fertőzéseinek kórokozója vagy kereshető a szerepe más betegpopulációkban is? [English title: *Staphylococcus saprophyticus* – Does it cause urinary tract infections only in young women, or are other patient populations also affected?]. *Orvosképzés, Budapest, Hungary.* 91: 198; 2016.

9.1.3. Scientific Conferences Attended

1. Semmelweis University Students' Scientific Conference, February 10-12, 2016. Budapest, Hungary. Received 3rd place prize for candidate's presentation.

9.2. Publications not related to the PhD thesis

9.2.1. Original, peer-reviewed articles

1. Supák D, **Adeghate J**, Baranyai É, Cseh K, Melczer Zs. Elevated serum acylated (biologically active) ghrelin and resistin levels associate with pregnancy-induced weight gain, insulin resistance and anthropometric data in the fetus [Emelkedett szérum acilált ghrelin- és resistinszintek összefüggése a terhességi testsúllyal, az inzulinrezisztenciával és a magzat antropometriai paramétereivel - *Magyar Nőorvosok Lapja* - In Hungarian]. *Journal of the Hungarian Society of Obstetricians & Gynaecologists*. 77 (5): 6-14, 2014. [Impact Factor: 0]

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9.2.3. Book Chapters

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9.2.4. Abstracts

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3. **Adeghate J**, Port A, Papworth-Jones N, Sun G. Who should we be screening for eye disease? The impact of demographic and socioeconomic background on attendance and referral patterns at an integrated vision screening program. Invest. Ophthalmol. Vis. Sci. 2017;58(8):5079.

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