ATYPICAL CLINICAL PRESENTATIONS OF COAGULASE-NEGATIVE STAPHYLOCOCCUS INFECTIONS

PhD Dissertation

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INTRODUCTION

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 [https://www.etymonline.com/word/staphylococcus]. *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.

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, one of the most abundant of which is *Staphylococcus epidermidis (S. epidermidis)*, which was first described by German microbiologist Friedrich Julius Rosenbach in 1884, who initially named it *S. albus* for the white colonies it formed on blood agar [http://www.whonamedit.com/doctor.cfm/1203.html]. 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.

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 [Otto 2014]. This is achieved by combating proliferation of other pathogenic species, such as *S. aureus*, by producing enzymes and antimicrobial factors that inhibit their growth [Iwase et al., 2010; Zipperer et al., 2016; Janek et al., 2016]. 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* [Eladli et al., 2018]. *S. epidermidis* is a common culprit in neonatal bloodstream infection (BSI) [Becker et al., 2014]; 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. Common species in humans include *Staphylococcus haemolyticus* (*S. haemolyticus*), *Staphylococcus capitis (S. capitis),* including subsp. *urealyticus, Staphylococcus auricularis (S. auricularis)* [Becker et al., 2014], and *Staphylococcus hominis* subsp. *hominis* and

novobiosepticus (*S. hominis*) [Becker et al., 2014; Severn et al., 2022]. Species involved in urinary tract infections (UTI) include *Staphylococcus caprae (S. caprae)* [Becker et al., 2014] and *Staphylococcus saprophyticus* subsp. *saprophyticus (S. saprophyticus*), which is involved in acute urethritis [Ehlers et al., 2023]. *Staphylococcus lugdunensis (S. lugdunensis)* may cause endocarditis of the native heart valves, as well as wound infections [Becker et al., 2014]. *Staphylococcus warneri (S. warneri)* infection may lead to septic arthritis*, and Staphylococcus schleiferi (S. schleiferi)* may lead to BSI and wound infections [Becker et al., 2014]. 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 [Becker et al., 2014; Zeman et al., 2017]. 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 [Santoiemma et al., 2020; Ramnarain et al., 2019], 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 [Zakrzewska-Czerwińska et al., 1995], these species are more often found in animals [Becker et al., 2014].

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 are mainly the self-produced extracellular glycosaminoglycan polysaccharide intercellular adhesin (PIA) [Mack et al., 1996], which protects and allows them to prosper in a secluded environment, usually on the surface of plastic devices such as prostheses and intravenous catheters [Hedin,1993]. Biofilms are encoded by various forms of the intracellular adherence (ica) operon [Heilmann et al., 1996], including icaA, icaD (a helper protein) [Gerke et al., 1998], and icaB (surface protein) [Vuong et al., 2004], as well as the accumulation-associated protein (*Aap*) [Hussain et al., 1997]. Virulence factors for *S. saprophyticus* include urease, S. *saprophyticus* surface-associated protein (Ssp), and autolysin adhesin (Aas) [Sakinc et al., 2005]. There have also been genomic studies indicating the possibility of gene transfer between *Staphylococcus* species, which encode for antibiotic resistance and virulence factors [Otto, 2009]. *Staphylococcus epidermidis* is sensitive to the antibiotic novobiocin, which has been widely used to differentiate it from the novobiocin-resistant *S. saprophyticus* [Levinson, 2010]. *Staphylococcus epidermidis* strains are also widely resistant to commonly-used antibiotics today, such as methicillin, tetracyclines, aminoglycosides, fluoroquinolones, and sulfonamides [Otto, 2009]. The gene that allows for methicillin resistance

in staphylococci is “mecA”, which codes for penicillin-binding protein (PBP2a) [Najar-Peerayeh et al., 2014]. Studies have shown that not only is *S. epidermidis* a reservoir for mecA, but also mediates horizontal gene transfer to other staphylococci [Cheung et al., 2010].

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 [Otto, 2009; National Nosocomial Infections Surveillance System, 2004; Eltwisy et al., 2022], 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 [Becker et al., 2014]. 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 [Becker et al., 2014; Levy, 2007; Kristof et al., 2009; Giormezis et al., 2014]. This is especially true for those with intravenous and other indwelling catheters, as well as other prosthetic-devices [Giormezis et al., 2014]. Studies have suggested that CoNS may even translocate through intact GI mucosa into the bloodstream in premature neonates due to poorly developed innate immunity [Adeghate et al., 2020] or due to CoNS becoming more virulent [Groer et al., 2014].

OBJECTIVES

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.

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 Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and pulsed field gel electrophoresis (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.

METHODS

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 the University of Pittsburgh, in Pittsburgh, PA, 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.

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 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 [Http://Www.Eucast.Org/Clinical_breakpoints]. 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 using pulsed-field gel electrophoresis (PFGE) based on prior protocol by Tenover et al., 1995.

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 5,093 perianal, 4,022 pharyngeal surveillance samples, and 4,294 blood cultures obtained by the NICU were analyzed. Of the 4,294 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) that 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.

Endophthalmitis: Forty-two previously isolated strains of CoNS from 40 patients with 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.

Description of laboratory techniques

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) and Biolog GEN III microplates (Biolog, Hayward, CA, USA). Findings were analyzed with the Biolog Identification Systems Software (OOP 188rG Gen III Database v2.8).

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).

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. Our protocol was based on a prior method described by Bradford et al. [2006], and analysis was performed based on criteria described by Tenover et al. [1995]. 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, MO, USA). The DNA was digested at 25°C for 3 hours using SmaI enzyme (Promega, Madison, WI, 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, CA, 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, MO, USA), examined and photographed with UVItec (Pharmacia Biotech, Piscataway, NJ, 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. [1995], any isolates with >8% band similarity or with ≤6 band differences were regarded as clonally related.

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. 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.

Antibiotic Sensitivity Testing using the Disc Diffusion Method: Antibiotic resistance of CoNS isolates was tested in vitro using the disc diffusion method [Romanowski et al., 2021], and interpreted based on Clinical and Laboratory Standards Institute guidelines [Document M02-A12 and M100-S23]. Antibiotics were assumed to reach similar levels in the eye and serum. The susceptibility data obtained was analyzed according to the guidelines published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The following antibiotics were used for testing susceptibility: vancomycin, cephalosporins (cefazolin, ceftazidime, cefoxitin), fluoroquinolones (ofloxacin, ciprofloxacin, moxifloxacin), aminoglycosides (amikacin, gentamicin), and clindamycin.

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 wth $p<0.05$ were considered statistically significant.

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.

RESULTS

Demographics of acute cystitis caused by *S. 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. 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. 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.

Infections with *Staphylococcus saprophyticus*

S. saprophyticus was the main isolate in 66 subjects 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. It is also of interest to note that UTIs from *S. saprophyticus* followed a seasonal pattern. 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. With regards to treatment, *S. saprophyticus* showed a strong sensitivity to nitrofurantoin, fluoroquinolones, and except for one case, ampicillin as well. Of the 30 isolates analyzed with PFGE, 28 different genotypes were found.

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

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. 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 ($p<0.0002$).

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% ($n=19$). About seven percent (7.7%, $n=45$) of microbial strains isolated from the 588 positive blood samples contained Enterobacteriales species.

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. 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. 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.

PFGE dendrogram: 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.

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

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 endophthalmitis 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* was the third most common CoNS strain, accounting for 2.38% (*n*=1/42) of all isolated strains.

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). The cause of endophthalmitis for two of the samples could not be determined.

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). 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.

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.

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).

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). 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. Overall, intraocular pressure (IOP) was stable in all three cohorts of patients throughout the study period. 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).

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).

DISCUSSION

***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 [Szász et al., 2009; Raz et al., 2005]. In healthy individuals, *S. saprophyticus* is a resident of the GI tract, most commonly located in the rectum [Raz et al., 2005], and in the lower genital tract and the perineum in females [Levinson, 2010; Rupp et al., 1992; Widerström et al., 2012]. The 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 [Raz et al., 2005]. Any changes in the microbiome of the extragenital region may also predispose to S. saprophyticus-related UTIs [Raz et al., 2005]. 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 [Levinson, 2010]. 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 [Hedman et al., 1991].

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 [Levinson, 2010]. *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 [Levinson, 2010]. Rare, but possible complications of *S. saprophyticus*-related UTIs include septicemia and endocarditis [Levinson, 2010].

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 [Jordan et al., 1980]. 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 [Eriksson et al., 2012]. Other bacteria have also been isolated from the urine samples in our study, including *E. faecalis*, a variety of Enterobacteriaceae strains, and *P. aeruginosa* [Adeghate et al., 2016]. 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 [Adeghate et al., 2016].

***S. saprophyticus*-related UTIs in males:** In our study, we also isolated *S. saprophyticus* from urine samples of males aged 5-15 years [Adeghate et al., 2016]. 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 [Raz et al., 2005]. Another possible mechanism may be increased sexual activity in males age of 15 years, which is a known risk factor for *S. saprophyticus*-related UTIs [Hedman, 1980].

Seasonal variation in *S. saprophyticus*-related UTIs: The findings of our study showed that the incidence of *S. saprophyticus* UTIs is much higher in the months of June, August, November, and January [Adeghate et al., 2016], which corroborates the findings of other studies indicating peaks in colonization with *S. saprophyticus* during summer and fall months [Raz et al., 2005]. 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 [Shah et al., 2007; Gatermann et al., 1997].

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 [http://www.oek.hu, Antibiotikum-rezisztencia]. 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 that examined nationally [Adeghate et al., 2016].

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 [Adeghate et al., 2020]. 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 [Shivanna et al., 2016]. 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 [Brady et al., 2005; Mireya et al., 2007; Von Dolinger de Brito et al., 2007].

Despite much investigation, the mechanisms by which resident CoNS bacteria in the GI tract induce bacteremia is unknown [Shi et al., 2017]. 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%) [Adeghate et al., 2020]. 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.

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 [Adeghate et al., 2020]. 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 [Shi et al., 2017].

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

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 [Adeghate et al., 2023]. 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 [Bannerman et al., 1997]. 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. [2018], 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.

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%) [Adeghate et al., 2023]. 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 [Lalwani et al., 2008]. However, Yannuzzi et al. [2018] reported a slightly higher number of patients who received intravitreal antibiotics (86%) and a lower number of patients who underwent PPV (14%).

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 [Adeghate et al., 2023]. This data appears to be lower than that reported in another study, where 82% of patients with CoNS-related endophthalmitis had a hypopyon [Lalwani et al., 2008]. 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. [1993] indicated that diagnosis of endophthalmitis is generally delayed due to lack of clinical signs that would otherwise guide a prompt diagnosis.

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 [The Endophthalmitis Vitrectomy Study Group, 1995 & 1996]. The average length of time from infection to presentation in our patients was 5 days [Adeghate et al., 2023]. This is much lower than the 13-day period reported by Lalwani et al [2008]. The importance of VA, as a guide, 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 [The Endophthalmitis Vitrectomy Study Group, 1995 & 1996]. 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 [Dib et al., 2020; Sousa et al., 2022; Tabatabaei et al., 2022]. 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 [Adeghate et al., 2023]. 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 [Adeghate et al., 2023]. 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 [Murad-Kejbouet al., 2014]. Schanzlin et al. [1980] suggested that low virulence pathogens should be considered in cases of chronic and persistent post-surgical inflammation of the eye.

Virulent transformation and antibiotic resistance in CoNS endophthalmitis: Inappropriate use of antibiotics may lead to antibiotic resistance in CoNS that transform into virulent strains [López et al., 2017]. 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%) [Asbell & DeCory, 2018]. 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 [López et al., 2017; Kato et al., 2022]. 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 [Speaker et al., 1991; Bausz et al., 2006].

Fluoroquinolones such as ciprofloxacin and gatifloxacin are effective in the management of CoNS endophthalmitis [Oliveira et al., 2007]; however, studies have shown that vancomycin and linezolid rather than fluoroquinolones are superior in the treatment of CoNS-related endophthalmitis [Harper et al., 2007]. In general, vancomycin is said to have the highest (100%) efficacy in the management of CoNS-related infection [Bispo et al., 2008; Melo et al., 2011; Melo et al., 2010; Kodatiet al., 2017], which is in accordance with more recent reports [Romanowski et al., 2021].

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.

PUBLICATIONS

Publications related to the PhD thesis

A. 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]
2. **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. [Impact Factor: 2.471]
3. **Adeghate JO**, Yadav S, Kowalski RP, Juhasz E, Kristof K, Olsen KR, 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*. In Press. [Impact Factor: 4.200]
4. Kristóf K; **Adeghate J**; Iván M; Juhász E. Bakteriális fertőzések a szemészetben: kórokozóspektrum és antibiotikum-rezisztencia egy harmadik ellátási szintű laboratóriumban. *Szemészet.* 2018; 155(4):186-187. [Impact Factor: 0]

B. 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.

C. Scientific Conferences Attended

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

Publications not related to the PhD thesis

A. 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]
2. Kántor O, Mezey Sz, Adeghate J, Naumann A, Nitschke R, Énzsöly A, Szabó A, Lukáts Á, Németh J, Völgyi B. Calcium buffer proteins are selectively expressed by neurons of the human retina. *Cell and Tissue Research.* 365(1):29-50, 2016. [Impact Factor: 2.787]
3. Hark L, Katz LJ, Acito M, **Adeghate J**, Henderer J, Okudolo J, Malik K, Molineaux J, Burns C, Eburuoh R, Bennett TH, Zhan T, Haller JA. Philadelphia Telemedicine Glaucoma Detection and Treatment Study: Ocular Findings at Two Health Centers. *Journal of Health Care for the Poor and Underserved. 29(4):1400-1415, 2018.* [Impact Factor: 0.966]
4. Hark LA, Madhava M, Radakrishnan A, Anderson-Quiñones C, Robinson D, **Adeghate J**, Silva S, Zhan T, Adepoju T, Dave Y, Fudemberg SJ. Impact of a Social Worker in a Glaucoma Eye Care Service: A Prospective Study. *Health and Social Work. 44(1):48-56, 2019.* [Impact Factor: 1.226]
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6. Hark LA, Radakrishnan A, Madhava M, Anderson-Quiñones C, Fudemberg S, Robinson D, Myers JS, Zhan T, **Adeghate J**, Hegarty S, Leite S, Leiby BE, Stempel S, Katz LJ. Awareness of ocular diagnosis, transportation means, and barriers to ophthalmology follow-up in the Philadelphia Telemedicine Glaucoma Detection and Follow-up Study. *Soc Work Health Care.* 2019 Aug;58(7):651-664. [Impact Factor: 0.982]
7. Dow ER, **Adeghate JO**, Coombs PG, Gupta Patel M, D'Amico DJ, Kiss S. Fellow-Eye Conversion and Treatment in Exudative Age-Related Macular Degeneration. *Journal of VitreoRetinal Diseases*. 2019;3(6):438-444. [Impact Factor: 0]
8. Hark LA, **Adeghate J**, Katz LJ, Ulas M, Waisbourd M, Maity A, Zhan T, Hegarty S, Leiby BE, Pasquale LR, Leite S, Saaddine JB, Haller JA, Myers JS. Philadelphia Telemedicine Glaucoma Detection and Follow-Up Study: Cataract Classifications Following Eye Screening. *Telemed J E Health.* 2020 Aug;26(8):992-1000. [Impact Factor: 0]

9. Kalász H, Szimrók Z, Karvaly G, **Adeghate J**, Tekes K. Pharmacokinetics of two chlorine-substituted bis-pyridinium mono-aldoximes with regenerating effect on butyrylcholinesterase. *Molecules.* 2020, 25(5): 1250. [Impact Factor: 4.412]
10. Kalász H., Karvaly G, Szimrók F, Szabó D, Milánkovits M, Keglevich A, **Adeghate J**, Darvas F, Kuca K, Musilek K, Tekes K. Pharmacokinetics of a mono-pyridinium-mono-aldoxime (K-347), a potential antidote in organophosphate poisoning. (2020) *Open Medicinal Chemistry Journal.* 14: 99-107. [Impact Factor: 0]
11. Han Y, Routray A, **Adeghate JO**, MacLachlan RA, Martel JN, Riviere CN. (July 27, 2021). Monocular Vision-Based Retinal Membrane Peeling with a Handheld Robot. ASME. *J. Med. Devices.* September 2021; 15(3): 031014. [Impact Factor: 0.743]
12. **Adeghate JO**, D'Souza C, Kántor O, Tariq S, Souid A-K, Adeghate E. Early (5-Day) Onset of Diabetes Mellitus Causes Degeneration of Photoreceptor Cells, Over-expression of Incretins, and Increased Cellular Bioenergetics in Rat Retina. *Cells.* 2021; 10:1981. [Impact Factor: 7.666]
13. Kalász H, Tekes K, Bátor G, **Adeghate J**, Adeghate E, Darvas F, Fűrész J, Karvaly G. Investigation of the Experimental Pharmacokinetics of the Bis-Chlorinated Bispyridinium Mono-aldoxime Cholinesterase Reactivator K-868 in Rats. *Open Medicinal Chemistry Journal.* 2021; 15:17-27. [Impact Factor: 0]
14. Mahgoub MO, Ali II, **Adeghate JO**, Tekes K, Kalász H, Adeghate EA. An Update on the Molecular and Cellular Basis of Pharmacotherapy in Type 2 Diabetes Mellitus. *Int. J. Mol. Sci.* 2023; 24(11):9328. [Impact Factor: 5.600]
15. **Adeghate J**, Goldburg SR, Kaden TR. An Intraocular Spectacle. *Ophthalmol Retina.* 2023 May 17: S2468-6530(23)00158-6. [Impact Factor: 4.500]
16. **Adeghate JO**, Bonhomme GR, Indermill C, Taylor SL, Rocha M, Moghadam-Kia S, Errera MH. Retinal neovascularization in Susac's syndrome: A rare imaging finding. Oman J Ophthalmol. 2023 Oct 18;16(3):570-572.
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B. Reviews

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2. **Adeghate J**, Nurulain S, Tekes K, Fehér E, Kalász H, Adeghate E. Novel biological therapies for the treatment of diabetic foot ulcers. *Expert Opinion on Biological Therapy*. 17(8):979-987, 2017. [Impact Factor: 3.974]
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5. Lazar E, Sherzai A, **Adeghate J**, Sherzai D. Gut dysbiosis, insulin resistance and Alzheimer's disease: review of a novel approach to neurodegeneration. *Frontiers in Bioscience-Scholar.* 2021. 13(1); 17-29. [Impact Factor: 0]

C. Book Chapters

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D. Abstracts

1. **Adeghate J**, D'Souza C, Kántor O, Tariq S, Adeghate E. The pattern of distribution of incretins in diabetic rat retina. HMAA Füred, Balatonfüred, Hungary. 27; 2016.
2. Kalász H, **Adeghate J**, Tekes K. Whole body autography: valuable and impressive image technique for location and pharmacokinetics of drugs in the body. Recent Advances in Diabetes Mellitus and its Complications Symposium in Honor of Professor Tibor Donáth's 90th Birthday. Budapest, Hungary. 2016.
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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6. **Adeghate J**, Port A, Papworth-Jones N, Sun G. Factors influencing attendance at an integrated vision screening program: Survey responses reflecting distance, demographics, and the decision to seek eye care. Annual Meeting of the American Public Health Association (APHA). Atlanta, GA, USA. 2017.
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13. **Adeghate J**; Fisher R; Wen H; Davoli K; Epperly MW; Huq MS; Wipf P; Sahel JA; Greenberger JS; Eller AW. A Novel Agent in Prevention of Acute Radiation Toxicity in the Mouse Retina. Invest. Ophthalmol. Vis. Sci. 2021;62(8): 3290.
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19. **Adeghate J.** Importance of diabetic retinopathy screening in the primary care setting. Hungarian Medical Association of America Annual Meeting, Sarasota, FL, USA. 2023.

20. **Adeghate J,** Goldburg S, Kaden T. Mystery Case. Atlantic Coast Retina Club, New York, NY, USA. 2024.