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INFECTIVE ENDOCARDITIS: AETIOLOGY, CLINICAL FEATURES, PRINCIPLES OF TREATMENT AND PREVENTION

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Abstract

Infective endocarditis (IE) is characterized by pathogen colonization and endocardium invasion, causing the formation of vegetations - amorphous aggregates, composed of platelets, fibrin, microorganisms and inflammatory cells. IE microbiological aspects are variable from country to country, reason for which, the purpose of this review was to integrate some original data concerning the etiology and antimicrobial resistance markers in microbial strains isolated from infections occurred in patients with underlying cardiovascular diseases in the general microbiological picture IE (i.e. diagnosis, etiology and treatment). In our hospital, the etiology of positive blood cultures and prosthetic devices associated infections occurred in patients with cardiovascular diseases is dominated by Gram-positive cocci, especially S. aureus and coagulase-negative staphylococci (CNS), followed by Gram-negative fermentative and non-fermentative bacilli. The major concerns regarding the resistance markers of the isolated strains are the methicillin and macrolides lincosamides streptogramines resistance exceeding 50%, both in S. aureus and CNS and the aminoglycosides high level resistance (30%) in E. faecium strains.

Keywords *Infective endocarditis (IE); etiology and antimicrobial resistance markers; prosthetic devices associated infections*

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Infective endocarditis

Infective endocarditis (IE) is characterized by pathogen colonization and endocardium invasion, causing the formation of vegetations - amorphous aggregates, composed of platelets, fibrin, microorganisms and inflammatory cells. The most common injuries occur in the valvular endocardium, but they also can be located in the septal wall, cordage tendon or mural endocardium. Infection localized in the arterial endothelium in coarctation of the aorta or arterial channel is called infectious endarterita. Although fungi, chlamydiae, rickettsiae, may be involved in its appearance, the most common is the bacterial etiology, so, in the past, a common name of the disease was bacterial endocarditis. IE is a serious disease with a mortality of ~ 20-25% despite actual medical and surgical treatment (2).

Incidence. IE incidence is variable from country to country, but the differences could result from diverse methodological approaches between studies. The incidence is between 1.7-6.2 cases / 100,000 persons / year, increasing with age. The increased incidence is reported for IV drug users. The disease has a male preponderance, the gender ratio being 2: 1, and the average age of occurrence is between 47-69 (5,6). 70-

75% of IE cases, occur in people with predisposing heart lesions (rheumatic valvular and congenital heart disease, degenerative valvular lesions, prosthetic valves, invasive procedures with risk of bacteremia), immunosuppression, diabetes, poor dental hygiene, prolonged hemodialysis. The bacterial profile changed with the changing spectrum of lesions – the streptococci, the most common cause predisposing to IE, being replaced by staphylococci, especially *Staphylococcus aureus*. Microorganisms that are transient in circulation (transient bacteremia) colonize preexisting thrombus; this is the stage of transition from the nonbacterial endocarditis to infective endocarditis. Besides this transitional movement for IE appearance, enough bacterial inoculum and virulence factors are required. Most cases of transient bacteremia are short and have no consequences. They meet frequently during daily activities, such as brushing teeth. In most cases the bacteria are removed by different immune systems before joining the endocarditic nidus. Once adhered to the vegetation surface, microorganisms trigger further activation and monocytes adherence, local production of cytokines, further attracting platelets, fibrin accelerated storage and progressive growth of vegetation. With the multiplication of bacteria, microorganisms are gradually covered by successive layers of platelets and fibrin, are protected by neutrophils. Over 90% of the vegetation' microorgansims are metabolically inactive, due to low local concentrations of nutrients and are less susceptible to antibiotics that interfere with bacterial cell wall synthesis. Endothelial injury may occur in the areas of impact (high velocity jets of blood). According to the Venturi effect, when a fluid is flowing through a incompressible tube, when passing through a narrow area the velocity increases along with decreasing pressure. Thus, bacteria and fibrin thrombus composed of platelets appear on the low pressure side. In atrioventricular regurgitation the vegetation appears on the atrial side, while in semilunar valve regurgitation on ventricular side. In ventricular septal defects, it occurs in the vegetation of low pressure - typically represented by the right ventricle. Pathogenesis of intracardiac devices is similar (6,7,8). Initially, they are not endothelised and act as the training place for fibrin thrombi and platelets. Vegetation interfering with the normal function of heart valves by preventing valvular perforation or cordage rupture, is actually leading to worsening of heart defects and heart failure (9, 10). The infection can spread to nearby structures including valvular ring, adjacent myocardium, conduction system, producing abscesses, fistulas, impaired driving. In prosthetic endocardites, paravalvular tissue invasion is more common, leading to formation of abscess and dehiscence of the prosthesis. Spontaneous vegetation colonization, associated with different medical procedures may led to bacteraemia. It can be caused by extracardiac infections (e.g. pneumonia, pyelonephritis), but most often originates in dental infections, produced by dental extractions or other maneuvers that require gum microlesions or common tasks such as brushing or mastication. Invasive maneuvers, the rigid tube bronchoscopy, colonoscopy, interventions in the field of gastroenterology, gynecological or urological especially, in the presence of infections (urinary tract biopsy / prostate, esophageal dilatation or sclerotherapy, biliary tract instruments) has the potential to induce bacteraemia. Injury skin has a different potential to induce bacteraemia generally lower than dental extractions (1). Clinical manifestations vary from minimal symptoms to the fulminant heart failure, depending on preexisting valve damage, virulence factors of the involved microorganism and the host response. Poor correlation between clinical manifestations and type of germs involved in IE do to old calassification (from acute IE - generally free valves, caused by highly virulent germs as *S. aureus*, with rapid clinical course in days-weeks to valvular destruction, metastatic infection, and subacute death - the slow evolution of weeks-months, usually produced by *Streptococcus* species), led to quit this classification (2). Current terminology addresses to valvular status (native valves, prosthetic valves -early and late EI- and EI associated with intracardiac devices), involved microorganism, affected valve, disease activity (active or healed EI) and recurrence (relapse or reinfection) (1).

About three quarters of the native valve endocarditis appear on a preexisting lesion. The most common injuries associated with them is mitral valve prolapse with mitral regurgitation - ~ 30% of IE native valve (reflecting the large proportion of this valvular heart disease in the population, the injury itself being associated with low-moderate risk of IE), followed by degenerative aortic disease in the elderly. Rheumatic lesions are counting for <20% of congenital heart diseases and are responsible for 10-20% of cases. In this case the most common injury is the bicuspid aortic valve, followed by patent ductus arteriosus, VSD, aortic coarctation, Fallot tetralogy. Atrial septal defect (ostium secundum) is not associated with increased risk of IE. Obstructive hypertrophic cardiomyopathy is responsible for <5% of cases of EI on native valves, the lesion being located in the mitral valve (6). Microorganisms involved in occurrence in adults IE, are species of streptococci, staphylococci, enterococci, HACEK group bacteria (3) and gram- negative bacteria (*Enterobacteriaceae* and non -fermentatives bacilli). Many years the leading cause of bacterial endocarditis was represented by streptococci, (over 75%, the viridans group). *Viridans streptococci* are a heterogeneous group of bacteria located in the oropharynx, generally sensitive to penicillin. Species included in this group are: *S. sanguis, S. mitis, S. salivarius, S. mutans* and *Gemella morbillorum.* Members of the species *S. milleri* (also called S. *anginosus*): *S. intermedius, S. constellatus* and *S. anginosus* must be treated differently than other viridans streptococci, as they have the ability to disseminate with metastatic marrow infections, rarely seen in other streptococci - visceral abscesses, septic arthritis, osteomyelitis. *Gemella morbillorum* and nutritional deffective streptococci, recently classified in other species (*Abiotrophia defectiva, Granulicatella spp.*), need longer antimicrobial therapy due to a property known as "tolerance to penicillin" - minimum bactericidal concentration (MBC) being more than 32 times the minimum inhibitory concentration (MIC). They grow heavily on the usual culture media, requiring special media. Group D streptococci, grouped as *Streptococcus bovis* group / *Str. equines* are commensal bacteria of the gastrointestinal tract. They generally occur in IE in the elderly, over 30% of cases highlighting malignant or premalignant gastrointestinal lesions. Thus in the case of *S. bovis / equines* screening with colonoscopy is recommended. *Streptococcus pneumoniae* is rarely involved in IE occurrence (1-3%). In this case endocarditis can be a part of the "Austrian triad" (pneumococcal pneumonia, endocarditis, meningitis), typically occurring with a high mortality (30-50%) in patients addicted to alcohol. IE with streptococcal species regimen use beta-lactams, in varying doses depending on MIC. *Staphylococcus* species frequency in IE exceeds the streptococci (34% native valve IE in Euro Heart Survey vs 33%) (7). Clasified in coagulase-positive species *(S. aureus*) and coagulase-negative *(S. epidermidis,* other spp). *S. aureus* is responsible for native valve endocarditis without pre-existing injuries, while *S. epidermidis* frequently causes prosthetic valves endocarditis . There is a high overlap between the two situations, there are frequent cases of *S. aureus* on prosthesis and vice versa (1, 3). First place in the etiology of native valve IE is occupied by *S. aureus,* due to the increasing number of prosthetic devices, intravascular catheters, and other surgery devices in the developed countries. Vegetation is typically occurring in left heart, and overall mortality is high, between 25-40%. In recent years oxacillin resistance in staphylococci (MRSA strains) is increasing and the problem is the apperance of vancomycin resistant strains. A particular type of staphylococcal IE is that occurred in intravenous drug users, responsible for 10% of cases of native valve. In this case vegetation occurs most frequently on the tricuspid valve (60-70%), followed by mitral valve (30-40% of cases) and the aortic one (5-10%). In 20% of cases the damage is total, 60% of these cases being caused by *S. aureus* endocarditis, located both on free valves and predisposing lesions, despite the virulence of the microorganism, in the right heart endocarditis, evolution is generally less severe (2-6% overall mortality) than the left heart IE with favorable response to treatment in more than 85% of cases. In these cases

isolated staphylococcal strains are usually methicllin-susceptible (3). Coagulase-negative staphylococci (NCS) are one of the most common cause of IE in patients with prosthetic and native valves but generally with predisposing lesions represented mainly by mitral valve prolapse, the clinical course being typically insidious. An exception is represented by highly virulent *S. lugdunensis*,a communitary species that tends to cause perivalvular endocarditis, and metastatic infections. This is difficult to distinguish from the rest of CNS staphylococci, most laboratories having no required capacity. Frequency of cases of IE caused by enterococci is increasing - 14% of cases of native valve and 15% of prosthetic valves in the Euro Heart Survey (7). They belong to D Lancefield group, differring from group D streptococci by different biochemical tests. The most common species involved in the occurrence of IE are *E. faecalis* and E. *faecium*. Cases occur more frequently in men over 60 years, in most cases being identified in the recent gastrointestinal or genitourinary maneuvers. Enterococci are characterized by a higher resistance to penicillin and vancomycin than the streptococci, these antibiotics having only a bacteriostatic effect on them, unless associated with aminoglycosides (streptomycin or gentamicin). Optimal bactericidal concentration of aminoglycosides to the ribosome level is obtained at high doses, with potentially toxic effects. Concomitant administration of aminoglycosides with beta-lactams for enterococci is a model of synergistic antibiotic action, beta-lactam augmenting the aminoglycoside cellular concentration by increasing cell wall permeability. 5-10% of cases of native valve IE are produced by slow-growing Gram-negative bacilli belonging to HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella* and *Kingella).* These bacteria belong to the normal flora of the oropharynx, grow slowly on media commonly used for culture (often only positivity of blood cultures is obtained) and are susceptible to IIIrd or IVth generation cephalosporins (ex. ceftriaxone). Gram negative non-HACEK bacilli are involved in ~ 2% of native valves IE, but commonly evolving to congestive heart failure with increased mortality, of 60-80%. Endocarditis with *Enterobacteriaceae* (*Salmonella sp., E. coli, Enterobacter sp., Serrtia marcescens, Shigella sp., Citrobacter sp., Yersinia sp.)* usually affects left heart, frequently occurring on normal valves, forming large vegetation with high embolic potential and valvular perforations. Infection due to *Pseudomonas* species occurs more often in IV drug users and poor prognosis is associated with embolic phenomena, involving major neurologic complications, local destruction, metastatic abscesses and low response to antimicrobial therapy, reasons for which the early surgery is often recommended. Other pathogens less frequently involved in occurrence of IE are species of *Neisseria sp., Moraxella sp., Streptobacillus* sp. etc, in total being identified ~ 275 species of bacteria responsible for its occurrence. Prophylaxis targets primarily on viridans streptococci and HACEK organisms before dental, oral, respiratory, and oesophageal procedures, and on enterococci and *Streptococcus bovis* before gastrointestinal and genitourinary procedures. A special cases group is represented by the infective endocarditis with negative blood cultures, data from different sources mentioning a frequency between 2.5 and 31% (6, 12). The main cause is antibiotic treatment before diagnosis, other causes being represented by atypical germs: spirochetae, rickettsiae (*Coxiella burneti* - etiologic agent of Q fever), chlamydia (*Chlamydia psittaci, C. pneumoniae*), fungi (*Candida sp., Aspergillus sp.*), anaerobic or slow-growing bacteria or abacterian endocarditis (Libman-Sachs) (5). In some situations, such microorganisms can be determined by serological tests, highlighting the specific antibody titers anti-*Legionella, Coxiella, Bartonella* etc.

Valvular prosthetic IE

Valvular prosthetic EI incidence is between 7 and 25%, the highest risk of endocarditis being recorded in the first 6 months postoperatory (13,14,15). There are two entities with different prognosis and mechanism - early and late EI. Arbitrary time limits between the two is 60 days (two months) postoperatory. Early endocarditis onset in the first two months, is often determined either by intraoperatory contamination or nosocomial infections and has the main etiology SCN infection (30% of cases) and *S. aureus* (20%). Intraoperatory contamination may be responsible for late-onset IE, usually between 2 months and 1 year after surgery. There is a combination of two types. Microbiology of late-onset IE is similar to the community IE, and is represented by streptococci, enterococci, *Staphylococcus aureus*, with a lower incidence of coagulase- negative staphylococci. 10-15% of fungal infections have late onset, usually with high vegetation that interferes with the prosthesis functionality (4,5). Pacemaker and ICD's IE has an incidence between 0.2-7%. The infection can be localized in the pocket device, electrodes, valvular or mural endocarditis. In the first months after implantation, *S. aureus* infections predominate and later *S. aureus* and SCN have equal contributions. Other pathogens (fungi, Gram-negative bacilli) are rarely involved in this type of IE (8). In evaluating laboratory IE bacteraemia or fungemia, the key element is isolating the pathogens in blood cultures. Bacteraemia in IE is continuous, so that blood cultures can be harvested at any time, without having to harvest in feverish spurt mentioned in older books. Blood cultures are obtained at least three bridges in three different veins, at an optimal interval of at least one hour. In case of IE with acute evolution, antibiotic therapy must not delay more than 2-3 hours. If the patient has taken antibiotics before hospital presentation, following European clinical guides, effective antibiotic timing is recommend for 3 days, followed by blood culture collection. Blood should be cultured in aerobic and anaerobic conditions, and clinical suspicion of infection with bacteria with slow growth should be communicated. They require incubation up to 21 days. Besides blood cultures, the involved germs can be isolated from fragments of vegetation or emboli obtained after surgery and for *Coxiella*, *Chlamydia psittaci* and *Legionella* using serological tests.

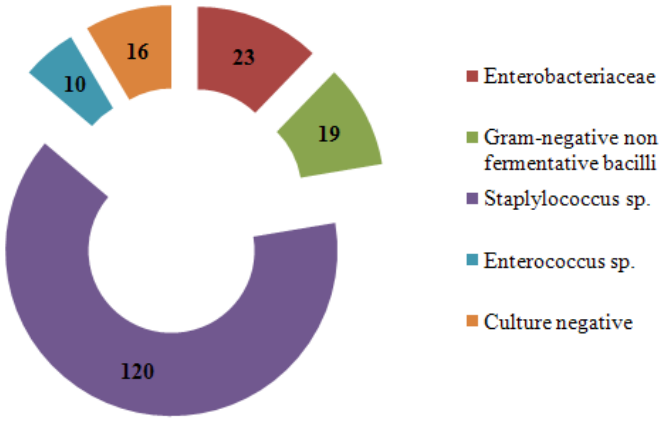

Figure 1: *The taxonomic affiliation of microbial strains isolated from blood cultures in patients with underlying cardiovascular diseases*

The same picture was maintained in case of microbial strains isolated from prosthetic devices associated infections in the same category of patients (Fig. 2).

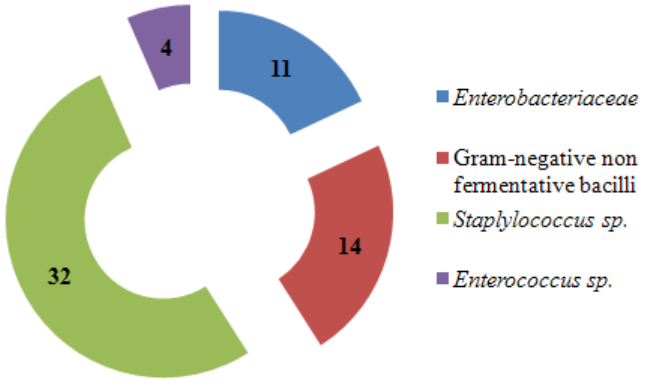

Figure 2: *The taxonomic affiliation of microbial strains isolated from prosthetic devices pieces in patients with underlying cardiovascular diseases*

In a survey performed in the National Institute for Cardiovascular Emergencies, concerning the microbial strains isolated from blood cultures in patients with underlying cardiovascular diseases during 2010-2011, the top etiology was still dominated by Gram-positive cocci, especially *S. aureus* and CNS (Fig. 1). After collecting blood cultures empirical antibiotic treatment is initiated, differentiated by the presence or not of

valvular prostheses. In case of IE caused by streptococci, there are used generally penicillin G, ceftriaxone, vancomycin or teicoplanin. Daily dose of penicillin G is12-20 million U generally administered in 4-6 divided doses, the half-time ~ 20-30min. Doses of more than 5 million U is not encouraged, due to increased risk of side effects (1). Continuous administration of penicillin is reserved for special cases (18). Ceftriaxone, is effective in the treatment of streptococcal IE, being administered once daily, 2 g intravenously. Vancomycin is an alternative to patients allergic to penicillins or cephalosporins, 15mg/kg being administered intravenously every 12 hours, maximum 2g/day. It requires slow infusion (30-45 min) and plasma level monitoring, optimal value being of 10-15mg/l. Teicoplanin, administered 10mg/kg /iv/2 times /day/9 doses, then 10mg/kg/day, is another solution of streptococcal IE treatment. Due to bactericidal synergistic effect, aminoglycosides are frequently associated. Staphylococci (coagulase positive or negative) resistant to penicillins play an important role in choosing therapy. While the pathogens involved in community endocarditis are usually methicillin sensitive, those responsible for nosocomial endocarditis are most commonly resistant to this class of antibiotics. In terms of allergy to penicillin for MRSA strains, there is administered vancomycin. The activity of vancomycin against *S. aureus* is lower than that of penicillin resistant strains. Rifampicin treatment coud be added for IE methicillin-resistant staphylococci on native valves or prosthetic valves in complicated cases. IE produced by *Enterobacteriaceae* is generally treated with beta-lactam antibiotics in high doses and aminoglycoside for 4-6 weeks. HACEK group strains are sensitive to the third generation cephalosporins, treatment consisting of ceftriaxone 2g/zi, 3-4 weeks and 6 weeks for IE on native valve prosthesis. Treatment option in *Coxiella burnetii* IE is represented by doxycycline, 100 mg IV every 12 hours, in combination with rifampin. In case of prosthetic valve surgery IE continuous treatment is recommended for at least a year, sometimes for the entire lifetime. Drug treatment of fungal endocarditis requires the use of amphotericin B, or flucytosine 1mg/kg/day iv.Concerning the resistance markers of Gram-positive strains isolated in our survey from blood cultures and prosthetic devices in patients with underlying cardiovascular diseases, the rate of methicillin resistance and of macrolides lincosamides streptogramines resistance was exceedint 50%, both in *S. aureus*,ias well as in CNS strains. The mupirocin, fluoroquinolones and rifampicin resistance rates were much lower, not exceding 15%. Concerning the enterococcal strains, the resistance rates were below 15% for ampicillin, ciprofloxacin, levofloxacin, tetracycline and erithormycin, and higher (~30%) for aminoglycosides (high level resistance) in *E. faecium* strains. The Gram-negative bacterial strains isolated from blood cultures exhibited generally lower resistance rates, not eceeding 20%, excepting amikacin in *Enterobacteriaceae* strains (Fig. 3).

Diagnosis. History, symptoms, signs and laboratory tests. The diagnosis of IE is established (definite IE) if during asystemic infection involvement of the endocardium is demonstrated (16,17). If, in addition, bacteraemia (positive blood cultures) or bacterial DNA are found, IE is defined and microbiologically positive, otherwise IE is defined but culture/microbiologically negative. Duke or modified Duke criteria may be used to make the diagnosis in otherwise unclear cases (11).

Standard blood culture techniques. Three or more blood cultures (BC) should be taken irrespective of body temperature at least 1 h apart. If the patient has been on short-term antibiotics, one should wait, if possible, at least for three days after discontinuing antibiotic treatment before new BCs are taken. Blood cultures after long-term antibiotic treatment may not become positive after treatment it has been discontinued for 6–7 days. One BC consists of one aerobic and one anaerobic bottle, each containing approx. 50 ml of medium (less in pediatric BC bottles). Venous blood, minimally 5 ml and better 10 ml in adults and 1–5 ml in children should be added to each bottle. Minimum inhibitory concentrations should be determined for the drugs of choice.

Culture-negative endocarditis (CNE). The most frequent cause of CNE is previous antimicrobial treatment. If traditional (non-automatic) BC systems

are used, longer incubation periods (>6 days) are required when organisms of the HACEK group, *Propionibacterium* spp., *Neisseria* spp., *Brucella sp.*, *Abiotrophia* spp., or *Campylobacter* spp. are suspected. Especially in CNE all material excised during cardiac surgery for active IE should also be cultured and examined. The value of serology has been proven for IE do to *Bartonella sp.*, *Legionella sp.*, *Chlamydia* (immunofluorescence) and *Coxiella burnetii*. The use of broad-spectrum polymerase chain reaction (PCR) provides a significant improvement in the capability to detect difficult-to-culture organisms and even dead bacteria.

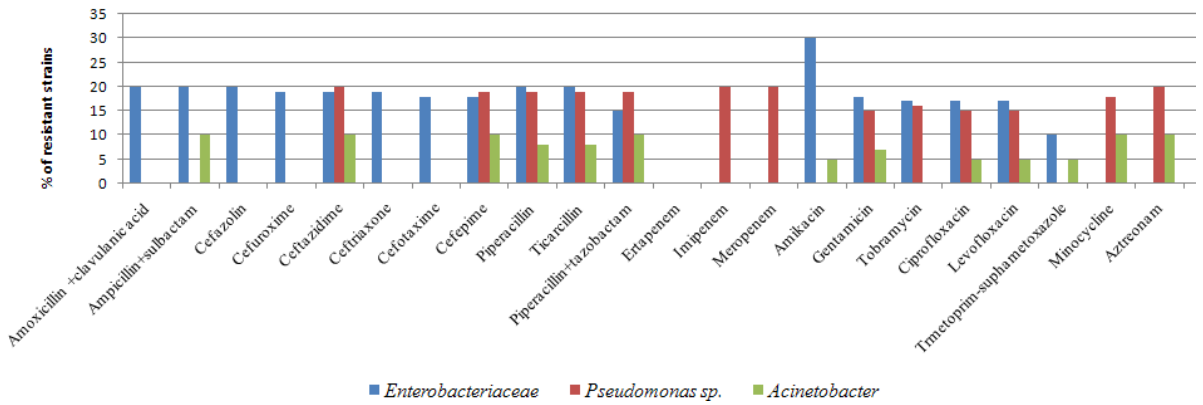

Figure 3: *The Gram-negative bacterial strains isolated from blood cultures exhibited generally lower resistance rates, not eceeding 20%, excepting amikacin in Enterobacteriaceae strains*

Conclusions

In our hospital, the etiology of positive blood cultures and prosthetic devices associated infections occurred in patients with cardiovascular diseases is dominated by Gram-positive cocci, especially *S. aureus* and coagulase-negative staphylococci (CNS), followed by Gram-negative fermentative and non-fermentative bacilli. The major concerns regarding the resistance markers of the isolated strains are the methicillin and macrolides lincosamides streptogramines resistance exceeding 50%, both in *S. aureus* and CNS and the aminoglycosides high level resistance (30%) in *E. faecium* strains.

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