 doi:10.20944/preprints202207.0126.v1

Review

Pathophysiology of Infective Endocarditis in High-Income Countries

Francesco Nappi[1], Giorgia Martuscelli[2], Francesca Bellomo, MD[3] , Sanjeet Singh Avtaar Singh[4] and Marc R Moon[5]

[1] Department of Cardiac Surgery, Centre Cardiologique du Nord 93200 Saint-Denis, France;francesconappi2@gmail.com; (F.N.)
[2] Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania Luigi Vanvitelli, 81100 Naples, Italy; martuscelligiorgia@gmail.com (G.M.)
[3] Department of Clinical and Experimental Medicine; University of Messina. 98122 Messina, Italy bellomofrancesca92@gmail.com (F.B)
[4] Department of Cardiothoracic Surgery, Aberdeen Royal Infirmary, Aberdeen, AB25 2ZN, United Kingdom sanjeetsinghtoor@gmail.com (S.S.A.S.)
[5] Department of Cardiac Thoracic Surgery, Washington University School of Medicine, St Louis, Missouri. moonm@wustl.edu (M.R.M)
* Correspondence: **author:** Email: francesconappi2@gmail.com

Abstract

Infective endocarditis remains an illness that carries a significant burden to healthcare resources. In recent times, there has been a shift from Streptococcus sp to Staphylococcus sp as the primary organism of interest. This has significant consequences given the virulence of Staphylococcus and its propensity to form a biofilm, rendering non-surgical therapy ineffective.

In addition, antibiotic resistance has affected treatment of this organism. The cohorts at most risk for Staphylococcal endocarditis are the elderly patients with multiple comorbidities. The innovation of transcatheter technologies alongside other cardiac interventions such as implantable devices have contributed to the increased risk attributable to this cohort.

We examine the role of the heart team for diagnosis and treatment of this condition. In addition, we examine the determinants of virulence of Staphylococcus aureus, the interaction with hosts immunity and the discovery and emergence of a potential vaccine. We also examine the potential role of prophylactic antibiotics during dental procedures.

With increasing rates of transcatheter device implantations, there is a projected increment of endocarditis especially in this high-risk group. A high index of suspicion is needed alongside early initiation of therapy and referral to the heart time to improve outcomes.

Keywords: Infective Endocarditis; Staphylococcus Aureus; Biofilm; Immune response; Fibronectin

 doi:10.20944/preprints202207.0126.v1

1. Introduction.

Infective endocarditis poses a significant challenge to the health professionals which is currently greater than in the past. The reasons are manifold. The elderly, often with many comorbidities, are the most affected patient population, have poorer reserves, and therefore more unwell than previous cohorts [1-3]. Virulent staphylococci downgraded the role of streptococci and penicillin sensitivity (a hallmark of streptococcal infection), becoming the most common cause of IE in many high-income countries [4-6] The population at risk of contracting IE has increased substantially abreast with the risk of staphylococcal bacteremia during healthcare. This today represents the most important challenge in the world because it is the primary mover for the development of IE. [7-9] Increased resistance to many antibiotics is an alerting concern in the modern-day healthcare because it constitutes a very serious threat. [10-12]

There are some key points to consider. The first relates to a substantial discrepancy in the presentation of symptoms and in the course of the disease which does not avoid arousing concern for healthcare professionals. [5,13] One of the biggest challenges has been to create dedicated teams that work on the collaboration of many specialists including immunopathologists, microbiologists, cardiologists, cardiothoracic surgeons, and radiologists. The multispecialty team had to tackle the lack of evidence in international guidelines which are mainly based on observational cohort studies rather than on randomized studies regarding this subject. [14-16] Before the creation of multispecialty teams, people affected by IE were seldom assisted with high-level coordinated care, which persists as a problem in low-income countries where the assistance offered is often not at the level of the current challenge.

The diagnosis of infective endocarditis is mostly reached by clinical, microbiological, and echocardiographic findings. The reliability of Duke criteria is critical with sensitivity and specificity of more than 80% and remains the reference criteria for diagnosis. [14-16] It should be noted that during the diagnosis of IE, clinical judgment remains the priority choice for each individual patient, especially in the first phase of treatment and it cannot be replaced by the Duke criteria.

Figure 1

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

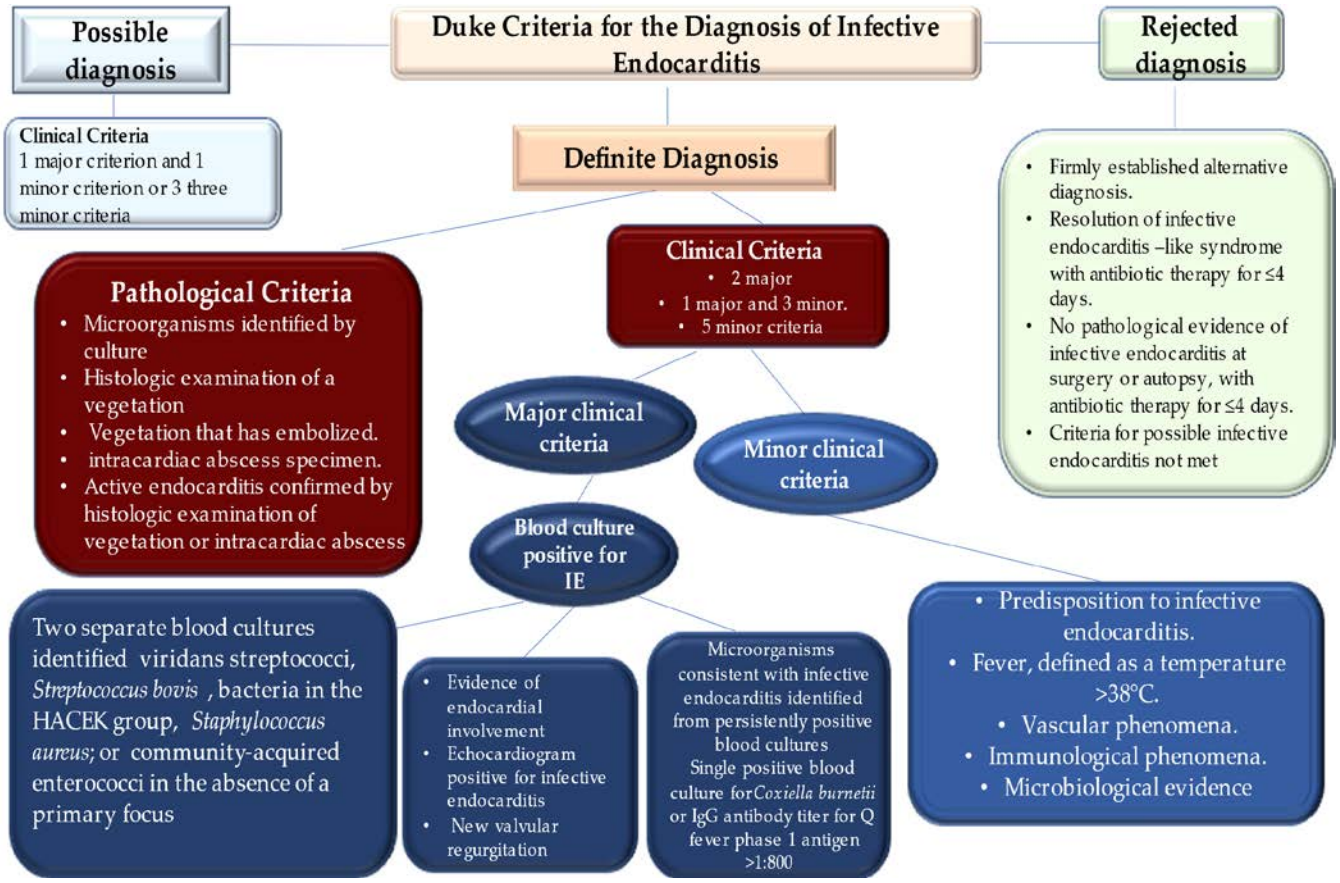


Figure 1 Depict Duke Criteria for the Diagnosis of Infective Endocarditis and it is based on data provided from Li JS et al (ref15). HACEK indicates haemophilus species, Aggregatibacter (formerly Actinobacillus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae. Patients who have prosthetic valves and possible infective endocarditis according to clinical criteria or infective transoesophageal echocardiography is recommended. For patients with native valve endocarditis transthoracic echocardiography is recommended. From Li JS et al. Clin Infect Dis 2000 ;30 :633-8.

As for clinical presentation, one of the main signs is fever noted in up to 80% of patients with IE [1-4,5]. Individuals frequently experience, as reported in vast current case series, a new cardiac murmur or worsening of a known murmur in 48% and 20% of cases, respectively. Clinical investigations to recognize other minor signs such as hematuria in 25% of cases, splenomegaly in 11%, splinter hemorrhages in 8%, Janeway's lesions in 5%, Roth's spots in 5%, and conjunctival hemorrhage in 5%. In such cases clinical manifestations can be more severe and characterized by sepsis, meningitis, unexplained heart failure, septic pulmonary emboli, stroke, acute peripheral arterial occlusion, and renal failure may also be presenting manifestations. [18-20] Blood chemistry tests generally report the following changes in patients with IE: elevated inflammatory markers reveal a high erythrocyte sedimentation rate and C-reactive protein level in two-thirds of cases while leukocytosis and anemia are found in about half of cases. [1,21,22]

 doi:10.20944/preprints202207.0126.v1

15 to 20% of patients disclose severe extracardiac complications of infective endocarditis leading to cerebral damage. [23,24] The latter may include ischemic and hemorrhagic stroke that crucially preceeds the diagnosis of infective endocarditis in 60% of cases [25,27]. Again, other typical cerebral complications are silent cerebral embolism, transient ischemic attack, brain abscess, mycotic aneurysm, and meningitis.

A substantial concern is related to the specific characteristics of vegetations. These may be large, mobile, located on the mitral valve [26], and dependent on the infectious foci of S. aureus infection [26,28-31] that have been linked with a notable augmentation of risk of symptomatic embolic events. A reliable diagnosis is offered by systematic magnetic resonance imaging (MRI) of the brain that may highlight cerebral abnormalities in up to 80% of patients, including embolic events that occur asymptomatically in 50% of cases. [32-34] As for the events related to mycotic aneurysms, their development result from a septic arterial embolism which affects the intraluminal space or vasa vasorum. The second step is the spread of infection through the vessel wall. Mycotic aneurysms were recorded in 5% of IE older patients', [35,36] with detection is more frequently registered recently because of the wider use of advanced imaging methods. Magnetic resonance angiography offers the best confirmation for depicting this lesion. [37,38]

2. Special Populations of Infectious Endocarditis in the 21st Century

The major concern due to the infective endocarditis is the discrepancy between the trends toward earlier diagnosis and surgical intervention with respect to the 1-year mortality that has not improved in over 2 decades. This indicates that IE persists as a primary concern despite its change in presentation from the pre-antibiotic era through the first generations of targeted antibiotic treatment and finally to the present patient population who have all have undergone variations in the microbiology profile [13,39]. In the past, IE occurred in young or middle-aged adults with underlying rheumatic heart disease or congenital heart disease (CHD). These patient populations have risk factors represented by prosthetic valve replacement, hemodialysis, venous catheters, immunosuppression, and intravenous (IV) drug use [40]. In the current era, the patient profiles include increasing age, frailty, and comorbidities which occur more frequently. At the same time, staphylococcus became the most widely found causative pathogen replacing oral streptococci. [1,2,4,5] Evidence has suggested that in the 21st century, the IE trend has seen an evolution that has led to the need for acquired health care in over 25% of cases [4]. Advances in cardiology have led to substantial changes in patient demographics and disease manifestation. Infective endocarditis greatly affects cardiac implantable electronic devices (CIED). [41,42]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

The use of percutaneous catheter procedures for the treatment of structural heart disease may herald higher rates of infective endocarditis than those detected after prosthetic valve implantation performed with the standard surgical approach. [42-45]

In this circumstance, it is of substantial importance to outline the epidemiology, pathophysiology, and pathological anatomy, to face the challenges posed by contemporary IE in developed countries. The analysis will clarify the reasons why diagnostics and therapeutic advances have failed to affirm a crucial impact on the disease.

3. Epidemiology

Infective endocarditis seldom occurs and its yearly incidence range between 3–10 per 100 000 individuals. [1-6,46,47]

Figure **2**

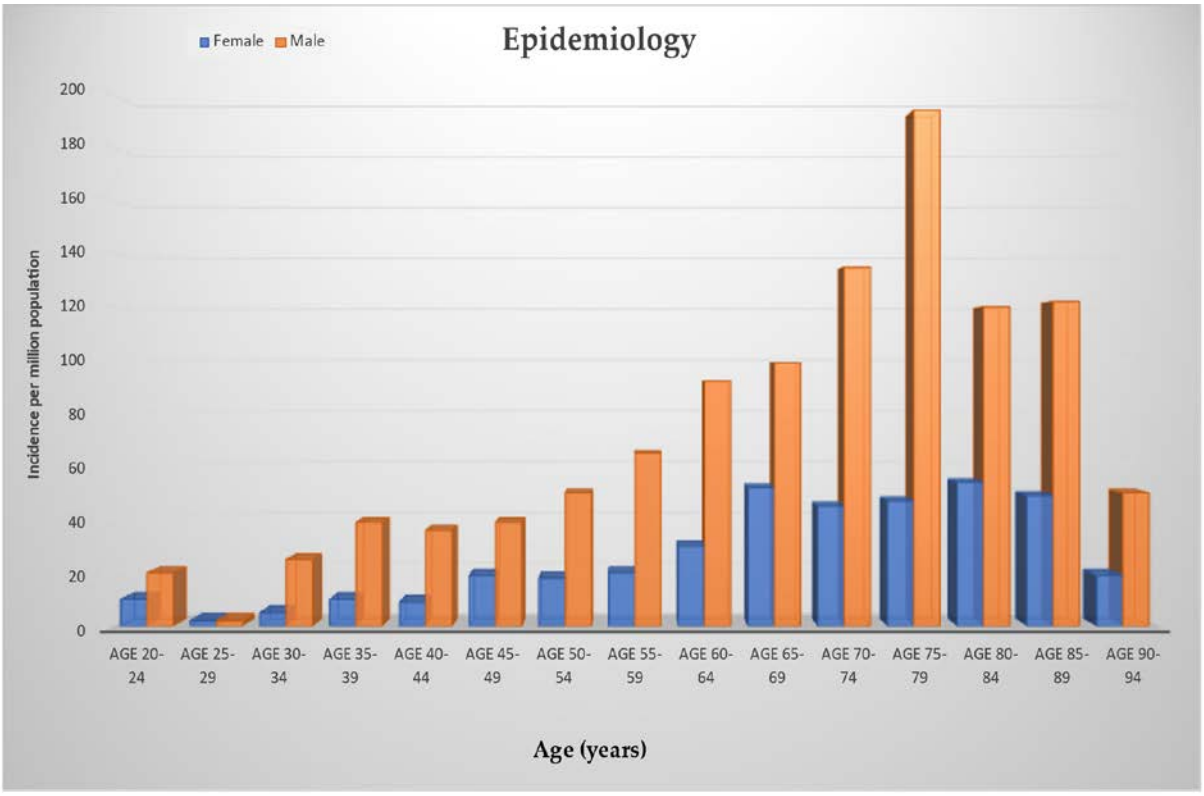


Figure 2. Depict the incidence of infective endocarditis according to age and sex in a French population study reporting data from 497 adults. The incidence peaks were reported at 194 cases per million in a population of men with IE aged 75–79 years. **Blue box**, female; **dark yellow box**, male

Variation in the pattern of IE has emerged worldwide with respect to the manifestation of disease during the early antibiotic era whereas epidemiology in low-income countries were similar to that of high-income countries. [4-6,48] In

 doi:10.20944/preprints202207.0126.v1

low-income countries the characteristic profile of rheumatic heart disease is revealed for two-thirds of cases as the principal key risk factor for infective endocarditis. [49-51] The disease occurs in young adult patients who develop the infection starting from oropharyngeal foci of penicillin-sensitive streptococci. Evidence of IE in high-income countries suggests a reduction in cases of rheumatic heart disease due to improved living standards and prophylactic administration of antibiotics to counter the spread of streptococcal pharyngitis. [52,53]. A detailed evaluation of IE trend suggested that the main risk factors are represented by the increase in degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease that replaced rheumatic heart disease. Furthermore, in analyzing the 2001-2006 epidemiological trend, infective endocarditis occurs at a higher rate in older individuals between 65 and 70 years of age, compared to the average age in the early 1980s which was reportedly around 40 years (figure 1). [54,55] The phenomenon of mutating epidemiology of infective endocarditis in high-income countries is related to substantial progress in the medical and surgical fields. [56-66] Therefore, an increase of 25-30% of contemporary cases of IE are acquired in the health sector, either due to the progressive increase in medical care offered during hospitalization or nosocomial admission or linked to the possibility of contracting the infection on an outpatient basis [1-7] In this context, there has been increasing use of long-term intravenous lines and invasive procedures which constitute an ideal gateway for pathogens leading to increased rates of staphylococcal bacteremia which today represents the first precursor of infective endocarditis. [67-70]

Advances in cardiological disciplines have allowed wider use of prosthetic heart valves and cardiac devices such as permanent pacemakers. The latter being in common use offers a higher risk of developing the infection inside the heart because it acts as a nidus for pathogens (figure 1). Indications for implantation of complex devices such as cardiac resynchronization therapy and implantable cardioverter defibrillators have increased, consequently leading to an expansion of infection rates related to cardiac device implants. [71-74]

The opposite spectrum is represented by the low incidence of infective endocarditis in the infant population. It is important to underline that despite the evidence reporting a substantial improvement in survival in the population with congenital heart disease, which is the most important risk factor, an increase in the incidence of IE in recent decades has been recorded. [75-77]. This increase mainly affects children with cyanotic congenital heart disease, high-velocity jets such as cases of ventricular septal defect or endocardial cushion defects. [78-80] There is a difference in the potential

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

risk of contracting infective endocarditis which is due to specific conditions. A reduced incidence of IE is reported after performing a repair procedure without the appearance of a residual shunt or using autologous material compared to the prosthetic one. Conversely, the cumulative risk may be higher in patients who require more elaborate procedures to repair complex congenital heart diseases, valve diseases, residual shunts, or when prosthetic substitutes are used. For example, the incidence reaches up to 21% in 30 years after surgery for the surgical correction of aortic valve stenosis. [81-83] In pediatric patients without congenital heart disease, the cause of infective endocarditis is attributable to a complication arising from indwelling vascular catheters, as occurs in premature infants. [84-86] **Figure 3**

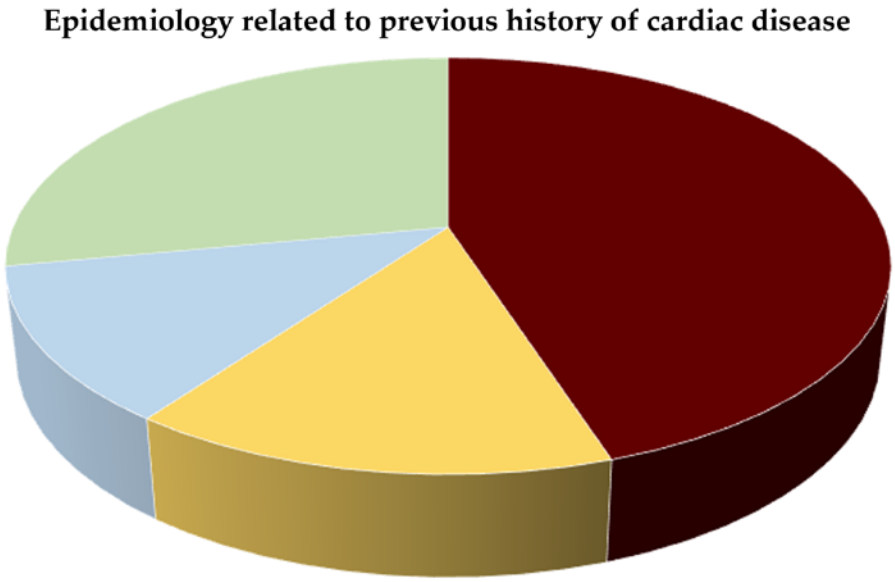


Figure 3. Depict the incidence of infective endocarditis according to the previous cardiac history in a French population study reporting data from 497 adults. **Red dark box**, no known cardiac disease; **yellow box**, prosthetic valve with or without intracardiac device; **blue box**, intracardiac device; **green box**, other cardiac device

4. Microbiology

80–90% of infective endocarditis is sustained by the gram-positive cocci of the staphylococcus, streptococcus, and enterococcus species. Among these pathogens, S aureus is the most frequently isolated causative bacteria associated with IE in high-income countries reaching up to 30% of cases of infection [1-9] IE determined by Staphylococcal foci affects several population of individuals, those who are traditionally included at-risk cohorts such as patients with hemodialysis treatment and intravenous drug users and others who

 doi:10.20944/preprints202207.0126.v1

can get the infection from native, prosthetic valves and cardiac implantable electronic devices (CIEDs). [41,72-74,87,88] In addition, Cocci of the staphylococcus manifests a deep-rooted propensity to acquire antibiotic resistance, thereby meticillin-resistant strains have emerged constituting a grave concern worldwide. [5,89,90]

The family of coagulase-negative staphylococci, including *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, and *Staphylococcus capitis*, stand out as far-reaching skin commensals. Coagulase-negative staphylococci have specific characteristics. They frequently colonize indwelling lines, CIEDs, and are the most common causative pathogens found in patients suffering from early prosthetic valvular endocarditis. [91-95] They are often responsible to cause hospital-acquired native valvular endocarditis. [96-98] Furthermore, these commensals express the worrying function of producing biofilms, which can lead to high rates of abscess formation and promote multi-antibiotic resistance [97]

In low-income countries causative bacteria leading to infective endocarditis are streptococci, of which the oral viridans group persists as the most common causative germ. [48,51] Its name is linked to the Latin term viridis, intended as green because this color characterizes the discoloration of the blood agar medium. Gram-positive Cocci of Streptococcus include Streptococcus mutans, Streptococcus salivarius, Streptococcus anginosus, Streptococcus mitis, and Streptococcus sanguinis which are distinguished as commensals of the oral, gastrointestinal, and urogenital tract. Cases of infective endocarditis associated with an underlying colon cancer have been found that were supported by group D streptococci (eg, Streptococcus gallolyticus, Streptococcus bovis), whose gateway was offered by the portal bloodstream. Infections linked to the development of enterococcal foci occur in 10% of individuals. [1-7] The type of germ isolated is mainly Enterococcus faecalis which is the cause of both native and prosthetic valve endocarditis occurring in elderly or critically ill patients. Cases of IE sustained by Enterococcus faecium leading to increased resistance to vancomycin, aminoglycosides, and ampicillin have been reported. [99]

From the conventional etiological model, it has emerged that a number of infectious endocarditis are mainly related to intracellular microorganisms, such as in cases of IE supported by causative pathogens including C. burnetii, Bartonella species or T. whippelii, in which host exposure and immune response may play a

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

prominent role. [100] Therefore about 10% of IE are represented by a mixture of fastidious bacteria, zoonotic bacteria, and fungi. Of particular interest the HACEK bacteria colonizing the oropharynx (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella corrodens, Kingella) and involving about 3% of individuals with IE. These pathogens are mainly characterized by slow growth. [101] Again, zoonotic endocarditis occurs after contact with pathogens such as Coxiella burnetii and Brucella (from cattle), Bartonella henselae (from cats), and Chlamydia psittaci (from parrots, pigeons). Lastly, rare pathogens include Gram-negative bacteria (eg, Acinetobacter spp, Pseudomonas aeruginosa), Legionella spp, Mycoplasma spp and Tropheryma whippelii. [100,102] Fungal infective endocarditis, usually caused by Candida or Aspergillus, are rare but often fatal causative germs. These occur in patients who are immunosuppressed or who have had heart surgery, mostly with colonization affecting prosthetic valves. [103,104] **Figure 4**

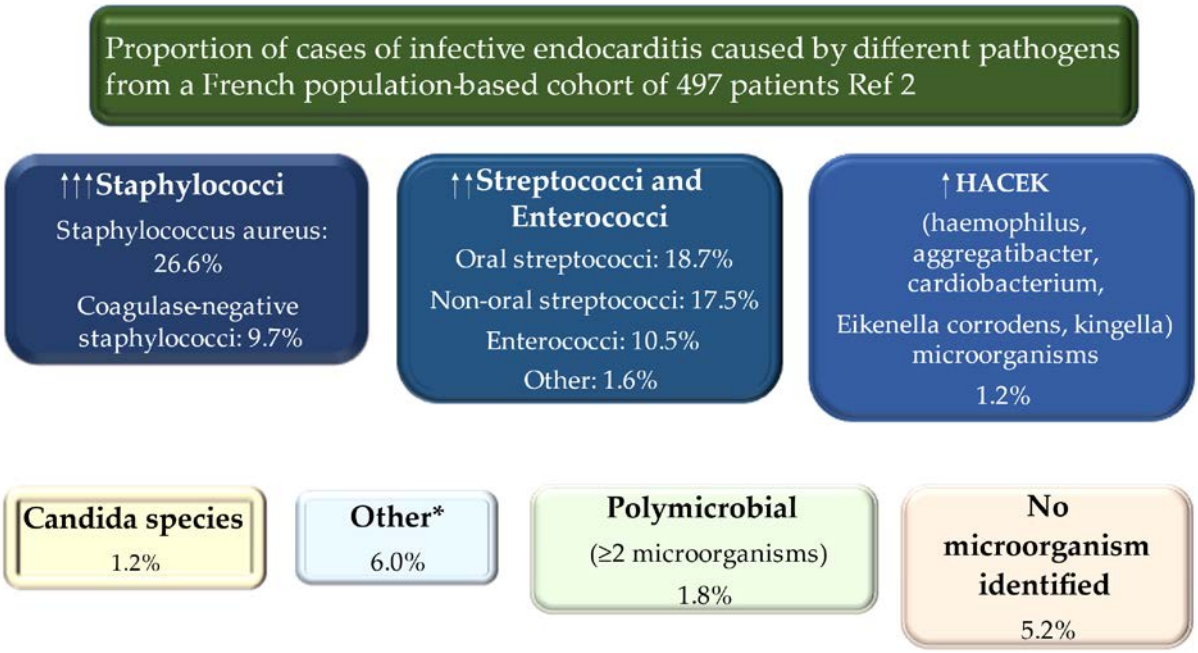


Figure 4 Major incidence of IE is revealed in elderly history of CIEDs, in younger with history of IDVU. Minor incidence in patients with central venous catheters HIV, CHD and immunosuppression. 26,6% of cases of IE are due to Staphylococcus aureus and CoNS are involved in 9,7% of cases *Collect low numbers of Coxiella burnetii, Bartonella quintana, Pseudomonas aeruginosa, Tropheryma whipplei, Enterobacteriaceae, Acinetobacter ursingii, Listeria monocytogenes, Propionibacterium acnes, Lactobacillus spp, Corynebacterium spp, Francisella tularensis, Erysipelothrix rhusiopathiae, Gordonia bronchialis, Bacillus spp, Catabacter hongkongensi, Moraxella catarrhalis, Campylobacter fetus, Neisseria elongata and Veillonella spp. Abbreviations; CIED, cardiac implantable electronic devices ; CHD, congenital heart disease; CoNS, coagulase negative; HIV; immunodeficiency virus; IDVU, intravenous drug user; IE, infective endocarditis. From Selton-Suty C et al Clin Infect Dis 2012; 54: 1230–39

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

4.1 Biofilm formation

In biofilms, microorganisms can live by adapting function and metabolism to a self-produced matrix which is made up of hydrated extracellular polymeric substances (EPS). This biofilm acts as an immediate functional environment formed directly by the bacteria. The main constituents that form EPS are molecules of polysaccharides, proteins, nucleic acids, and lipids. **Figure 5**

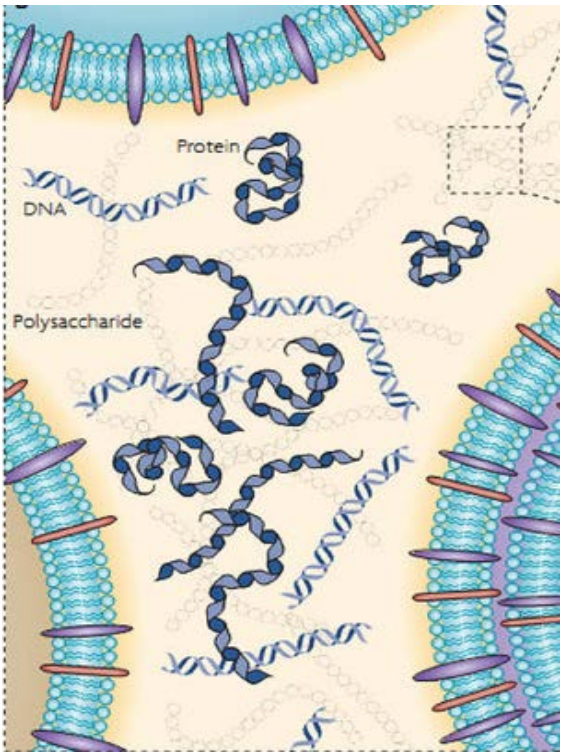


Figure 5. The main constituents that form EPS are molecules of polysaccharides, proteins, nucleic acids and lipids. Abbreviation EPS; extracellular polymeric substances

EPS perform multiple functions such as providing the mechanical stability of biofilms, mediating their adhesion to surfaces, and forming a cohesive, three-dimensional polymeric network that interconnects and transiently immobilizes the cells of the biofilm. It is important to underline the function of the external digestive system offered by the biofilm matrix. This step allows preservation of the extracellular enzymes close to the cells which can metabolize the dissolved, colloidal and solid biopolymers. [105-107]

During infective endocarditis, the formation of bacterial biofilms is a crucial moment for the nefarious evolution of the disease. IE begins as a minor injury of the heart structure and the damage generated is followed by a

 doi:10.20944/preprints202207.0126.v1

healing reaction, leading to the recruitment of fibrin and immune cells. In the first curative phase, the vegetations are sterile but potentially at risk of colonization during temporary bacteremia, thus leading to IE. Experimental in vitro models using simulated IE vegetation models produced from whole venous blood is of great use for the study of biofilms during infective endocarditis. In fact, these models made it possible to obtain stable bacterial colonization after 24 hours. Once structured in biofilm aggregates, the pathogens showed greater tolerance to antibiotics. [106,107]

Swartz et al recently evaluated the time to biofilm formation and how this impacts the development of antibiotic tolerance. Evidence suggested that reference strains of Staphylococcus aureus, as well as three clinical isolates of IE, formed biofilms on the IE vegetation model after 6 h. Furthermore, the earlier the antibiotic was administered, the more marked was its activity in containing the maturation of the biofilm, suggesting that early treatment was more effective in containing the development of the disease. The authors were able to follow the development of the biofilm under the microscope by viewing bacterial aggregates growing on the IE vegetation model and the interaction with the antibiotic. The formation of mature and antibiotic-tolerant biofilms was recorded after 6 hours, thus accelerating screening for optimal treatment strategies for IE. [108]

4.2 Staphylococcus aureus protective shield and host protection mechanisms. New evidence from infectious deployment.

Several animal models of invasive Staphylococcus aureus (S. aureus) infections indicated the two coagulases, von Willebrand factor binding protein (vWbp) and Coagulase (Coa), as factors leading to its virulence. These proteins constitute a functionally intricate structure that S. aureus forms to create a protective shield formed of fibrinogen/fibrin surrounding it. The creation of this shield gives the microorganism the ability to evade the defense mechanisms exerted by the host's phagocytic cells. One of the key functions of coagulases leads to the non-proteolytic activation of the zymogen prothrombin to convert fibrinogen into fibrin, thus promoting the formation of the fibrinogen/fibrin protective shield.

Another characteristic offered by coagulases is their direct link with fibrinogen, whose interactions substantially support infection. The mechanism or mechanisms by which vWbp and Coa bind to fibrinogen involve distinct interactions of the two proteins with the molecule, despite their similar structure. The binding of Coa to soluble

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

fibrinogen has a significantly greater affinity than fibrinogen coated on a plastic surface. On the other hand, the vWbp did not reveal any preference between the two forms of fibrinogen. [109-113] **Figure 6**

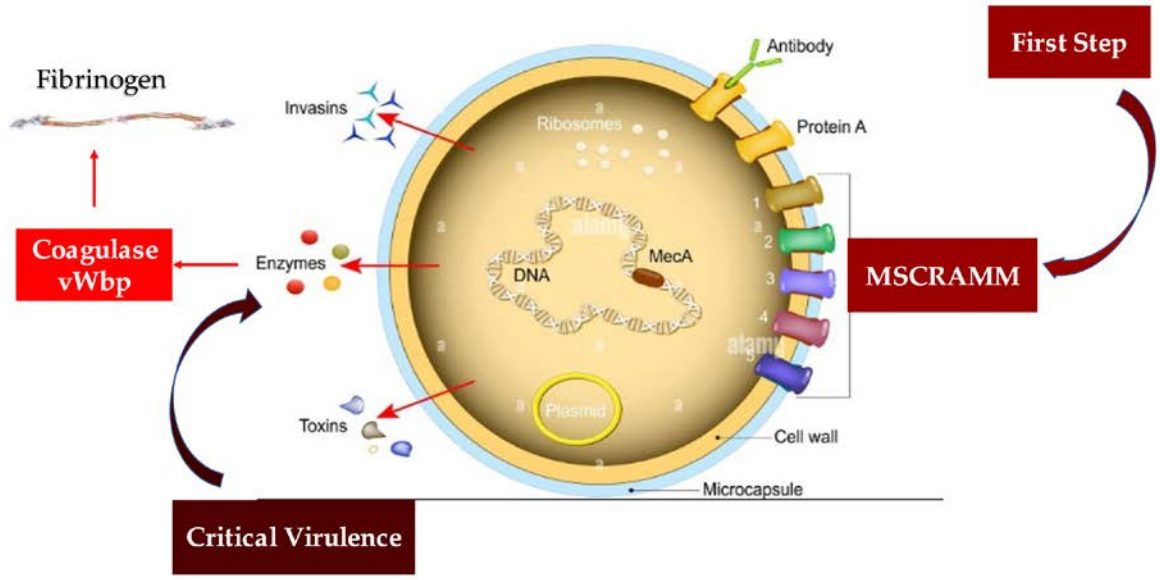


Figure 6. Depict Virulent factors of S. aureus. MSCRAMMs drive with a substantial key role the initiation of endovascular, bone and joint and prosthetic-device infections. These structures can bind to molecules such as collagen (mostly via Cna), fibronectin (via FnbAB), and fibrinogen (with ClfAB and Fib) and thus evade immune system. The development of infection is induced by Coa and von Willebrand factor binding protein that led to critical virulence. Coa binds preferentially soluble fibrinogen while vWbp did not disclose any preference between the two forms of fibrinogen. Abbreviations; Coa, coagulase; MSCRAMM, microbial surface components recognizing adhesive matrix molecules; vWbp, von Willebrand factor binding protein.

The recent study by Thomas et al provides crucial insights into the complex interactions between fibrinogen and S. aureus coagulase. Investigators suggested that vWbp and Coa target different sites on the fibrinogen, so there was no competition between the two molecules in fibrinogen binding. Both Coa and vWbp have N- and C-terminal halves that drive fibrinogen binding activity. [112,113]

Regarding the vWbp coagulase, the higher binding affinity for fibrinogen was identified in the vWbp-N region, contrary to Coa in which the greatest inclination toward the bind fibrinogen site was expressed in the C-terminal region. Interestingly, it has been reported that the peptides constituting the previously identified Fibrinogen Coa / Efb1 binding motif fail to inhibit the vWbp-C component from binding to fibrinogen, suggesting for vWbp-C the absence of a functional homolog to this motif. Again, although the N-terminal prothrombin-

 doi:10.20944/preprints202207.0126.v1

binding domains of both coagulases recognized the fibrinogen β-chain, they appear to interact with different sequence motifs in the host protein. The interaction of the two coagulases seems to be expressed with different sequence motifs in the host protein. Collectively, our data provide insight into the complex interactions between Fg and the S. aureus coagulases. [113]

Multidrug-resistant Staphylococcus aureus strains cause life-threatening diseases and pose a worldwide public health problem. The limitations of dealing with staph infection depend on both the treatment and the lack of an effective vaccine. S. aureus develops complex and precise mechanisms that allow it to coat itself with a protective shield of fibrinogen/fibrin. This coating has two substantial effects: 1) it allows the pathogen to survive in the blood making it invisible to the host's immune protection and 2) it offers the possibility of spreading and causing invasive diseases. Modifying this process represents a promising goal for new antistaphylococcal treatment strategies, however, the mechanisms that characterize it are not yet fully elucidated. S. aureus expresses a number of proteins that bind to fibrinogen. A redundant action exerted by some of these proteins with vWbp can limit its function. In fact, in the case in which proteins express similar functions, a sharing between them in the structural or functional motif has often been suggested. Thomas et al demonstrated the existence of a protein homologous (vhp) to the C-terminus of the von Willebrand factor binding protein (vWbp). This discovery makes a key contribution to both shield assembly and fibrinogen binding. Investigators identified a common Fg binding motif between vhp and vWbp. [113]

Recently Schwartz et al offered a very precise evaluation of the potential pathomechanisms involved in inducing infective endocarditis. The analysis was performed by studying 34 isolates of Staphylococcus aureus, collected from patients with S. aureus endocarditis and from healthy individuals in both in vitro and in vivo models. [114]

The strains of S. aureus isolated were tested in vitro to evaluate cytotoxicity, and the function of invading and interacting with platelets typically expressed by these pathogens. In order to correlate the ability of S. aureus to induce the development of vegetations on the aortic valves in vivo, the virulence factor expression profiles and cellular response were also studied and tested using an animal model. With the use of this method the presence of IE involving valves was assessed by in vivo magnetic resonance imaging at 9.4 T,

 doi:10.20944/preprints202207.0126.v1

with histological evaluation and with enrichment gene expression analysis. S. aureus isolates were tested in vitro for their cytotoxicity, the potential for invasion, and interaction with platelets. Although all strains of S. aureus isolated and tested in vivo revealed the ability to cause IE and the inflammatory response associated with the aortic valve's injuries; however, investigators were unable to differentiate and classify IE and inflammation based on the measurement of in vitro virulence profiles and cytotoxicity. [114]

Of relevance, Schwartz et al suggested that the in vitro test findings were unrelated to the severity of IE. However, a crucial finding highlighted that the isolated Staphylococcus strains differed substantially in the degree of activation and inhibition of pathoanatomic processes related to the extracellular matrix and in the characteristic of the inflammatory response. Investigators, therefore, suggest that the pathogenic capacity of bacteria does not confer a uniform response, and comprehensive approaches to host-pathogen interactions are required for its evaluation. Furthermore, this approach offers the possibility to study the corresponding immune pathways in order to highlight the differences in the host/pathogen interaction. [114]

Considering the etiology of Staphylococcus aureus-induced infective endocarditis, Schwarz et al opened a window to reach a better understanding of the interaction between virulence factors and immune response in S. aureus-borne infective endocarditis, to offer new possibilities for the development of therapeutic strategies and specific diagnostic imaging markers. [114]

5. Pathophysiology.

In the absence of cardiac pathology, the cardiac endothelium is not subject to the frequent bacteremia that can be induced by common daily activities, the most frequently represented by chewing and brushing the teeth. [115] Bacterial adhesion constitutes one of the fundamental stages in the pathophysiological process of infective endocarditis. Once the endothelial lesion is established, bacterial adhesion is favored, initially by the release of inflammatory cytokines associated with tissue factors and a second time by the expression of fibronectin which leads to the formation of a thrombus composed of platelets and fibrin. [116-118] We learned that the common

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

pathogens responsible for endocarditis colonize the valves with pre-existing sterile vegetations or valves in which minimal endothelial lesions occur. The inflammatory response established in the endothelium is orchestrated by the production of cytokines, integrins, and tissue factors, which in turn attract monocytes and platelets with associated production of fibronectin, due to the effect induced by chemokines. These structures allow the bacteria to attack and the latter further activate the inflammatory cascade which offers, through their incorporation, protection by the host's defenses. [117,118] **Figure 7**

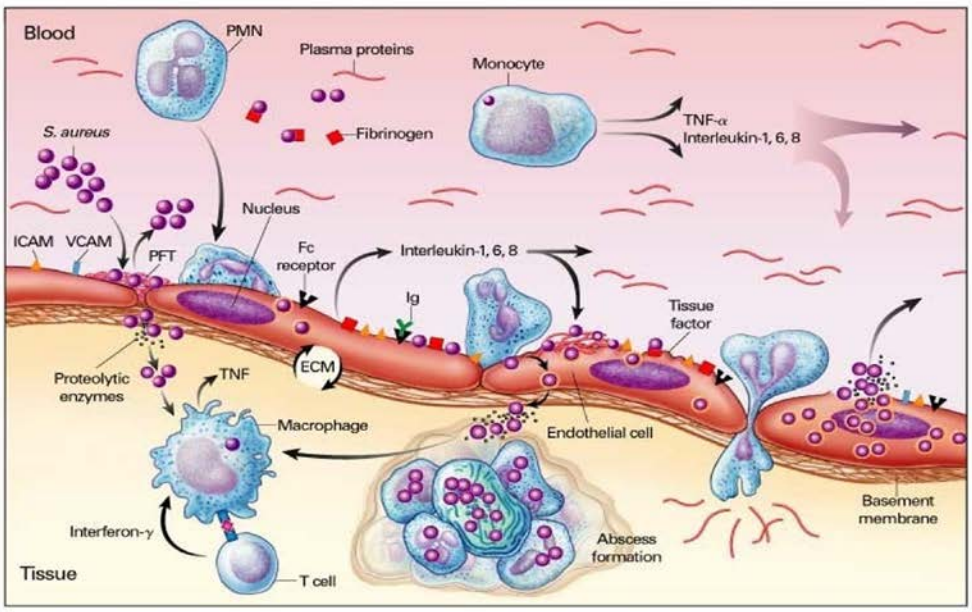


Figure 7 Bacterial adhesion induces the pathophysiological process of infective endocarditis. The first step led to inflammatory response with the involvement of inflammatory cells (PMN, monocyte and macrophage). The inflammation is mediated by the production of cytokines (TNF, α, interleukine 1,6 and 8), integrins, tissue factor, adhesion molecules (ICAM, VCAM), which in turn attract monocytes and platelets with associated production of fibronectin, due to the effect induced by chemokines. S. Aureus release Cytoxins that trigger the immunity response both innate and mediate (T-cell and B- cell). Abbreviations; ICAM, Inter Cellular Adhesion Molecule; S. Aureus, staphylococcus aureus; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule

There are 3 main insults inflicted on the endothelium by an IE: valvular sclerosis, rheumatic valvulitis, or the direct activity of the bacterial pathogen. The latter is particularly induced by the intervention of Staphylococcus aureus in the infectious field. [119] The pathophysiological analysis of infective endocarditis (IE) starting from heterogeneous groups of individuals has ranges from those successfully treated without adverse events to subjects who suffered serious complications and high mortality. A change in the temporal trends of the IE model

 doi:10.20944/preprints202207.0126.v1

in high-income countries over the past 5 decades has resulted in changing pathophysiological mechanisms involving increasingly unwell individuals who contract IE with increasing staphylococcal incidence and associated with health care. Consequently, based on pathophysiological knowledge, the prevention strategies have adapted to the change in trend, with less use of prophylaxis against streptococcal bacteremia during dental procedures and instead encouraging a more general approach to reduce the incidence of IE associated with health care. Therefore, the practitioners acquire greater learning of the mechanisms of vegetation formation, growth, and embolization on damaged or inflamed heart valves and cardiac devices. A better understanding of these mechanisms has also led to increased knowledge of how to combat the growing problem of antimicrobial resistance. From a pathophysiological point of view, two mechanisms of IE have proved to be a crucial key in the treatment of IE: the role of the immune response in elderly patients with IE and in particular after transcatheter implantation of the aortic valve as well as the mechanisms that trigger septic shock. This latter condition leads to a substantial increase in the risk of death in patients with IE. [120-124]

5.1 Staphylococcus aureus immunity

5.1.1 Staphylococcus aureus interact with host innate immunity

S. aureus can have many virulence factors both surface and secretery, which once activated offer a high capacity to oppose the host's immune defense mechanisms. [125,126] The main virulence factor of S. aureus is the Accessory Gene Regulatory System (Agr) which works for pathogen quorum detection. Although we know that Agr works on controlling the expression of phenol-soluble modulins (PSM) active against immune cells such as keratinocytes (KCs), how this mechanism was executed at the right time has not yet been demonstrated. [127] The innate immune response induces the response of dead KCs that produce a physical barrier due to the release of antimicrobial peptides such as human β-defensin 2 and 3, cathelicidins and RNase 7, which support a bacteriostatic action against infection by S. aureus. It has been reported that the antibacterial function of KCs is also induced by pattern recognition receptors (PRRs) such as TLRs and nucleotide-binding oligomerization domain (NOD) proteins. These two surveillance systems detect molecular patterns associated with invading pathogens (PAMPs), thus promoting timely defense against S. aureus. [128,129] The innate immune response

 doi:10.20944/preprints202207.0126.v1

is also supported by the action of other cells such as dendritic, B and T, macrophages, mast cells, natural killers (NK), plasma cells, and fibroblasts in the dermis. (Fig.1A) [130,131]

S. aureus infection has been proven to be supported by several mechanisms by which violation of innate immune system triggers is established. Furthermore, the other two stages fuel the infection of the pathogen, through entry into the bloodstream and dissemination into the host tissue once it has left the bloodstream. These two phases are supported by the specific function of molecules expressed by S. Aureus which interact with the endothelium, the blood, and the extracellular matrix. First, FnBPA and FnBPB bind fibronectin and interact with integrin $\alpha 5\beta 1$ on the surface of the vascular endothelium, thus triggering cell invasion and transmigration. The wallethic acid (WTA) and lipoteichoic acid (LTA) of S. aureus, polymers that form the bacterial envelope, intervene at this moment to promote the staphylococcal invasion of the host cells. In the second phase, staphylococci induce the formation of fibrin thrombi through the activation of the agglutination process mediated by Coa / vWbp and ClfA and bind to von Willebrand factor (vWF) on the endothelial surfaces, generating the formation of polymers such as Ultra Large vWF (ULVWF). The third phase leads to the secretion of Hla by the S. Aureus. Hla is a toxin that interacts with the ADAM10 receptor favoring the cessation of the physiological barrier functions of the endothelium vascular system. Finally, the trojan horse model is activated, whereby neutrophils containing intracellular S. aureus embedded by phagocytosis peel off to inject bacteria in host tissues.

5.1.2 Staphylo cytotoxins are a Trojan horse for excellent immune-modulation.

Since S. Aureus targets a wide variety of immune cells during infection, the pathogen's release of cytotoxins is crucial. It releases leukocidins, hemolysins, and PSM. Leukocidins include leukotoxins such as LukED and LukAB, gamma hemolysin which includes HlgAB and HlgCB, and PVL. Malachova revealed that LukAB is effective only on human polymorphonuclear leukocytes (PMNs) [132] and can kill dendritic cells, monocytes, and macrophages. [133,134] Recently Alonzo reported that LukED recognizes C-C chemokine receptor 5 of cellular receptor and induced the killing of dendritic cells, macrophages and lymphocytes. [133,134] On the other hand, at the micromolar level, a substantial role is played by PSM and Hla. The former acts with a noticeable ability to kill neutrophils after phagocytosis. [135] Furthermore, it can interact with disintegrin A and

 doi:10.20944/preprints202207.0126.v1

metalloprotease 1 (ADAM1) favoring the killing process of monocytes, macrophages, neutrophils, and T cells. [136] A fundamental key point concerns the role of cytotoxins as a Trojan horse to promote the spread of S. aureus which is distinct from the role offered by S. aureus in evading the host's immune response. Cytotoxins govern by significantly dampening both the innate and adaptive immune responses, allowing protection of S. aureus during travel in the host. (Fig. 2) [137]

5.1.3 Loss of B-cell vs T-cell cooperation due to cumulative effects of B-cell deletion and lack of T-cell help

The way in which S. aureus evades host immune surveillance is mediated by SpA proteins, which are integrated into the architecture of the S. aureus wall. They are released during the growth of the pathogen. Silverman et al and Goodyer et al demonstrated the presence of five domains in the SpA which were involved in the binding of immunoglobulins. The five immunoglobulin-binding domains bind to the IgG Fcγ domain and the Fab domain of the VH3 IgG and IgM clan. [138] This activity is driven by the cross-links of the B cell receptors which lead to the polyclonal proliferation of the B cells thus favoring the activity of the superantigen SpA.

By studying the phases of the infection, different growth response was observed evoking a variable expression of SpA. This event leads to the secretion of Hla toxin which activates specific B lymphocytes in positions further away from S. aureus. This is the immunological reason that humans generally produce antibodies against Hla despite most of the expressed SpA strains. It is important to consider that the Hla release function also is mediated from the cell wall of the pathogen.

Therefore, the superantigen activity exerted by SpA proteins can have an effect remotely from the infection, providing a crucial point for the development of the vaccine. A specific effect has been reported of SpA proteins which escape recognition by B cells resulting in a state called "lethargy" - a normal initial response to the antigen. In this case, the B cells may not collect a secondary signal to support their activation leading to a state of shock called "anergy". Anergy is a process that occurs in the colonization of S. aureus, in the persistence of its infection, and in the weakening of T cell help related to the fact that the effect of superantigens against T cell and cytotoxins leads to low affinity to the antibodies. [139,140] **Figure 8**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

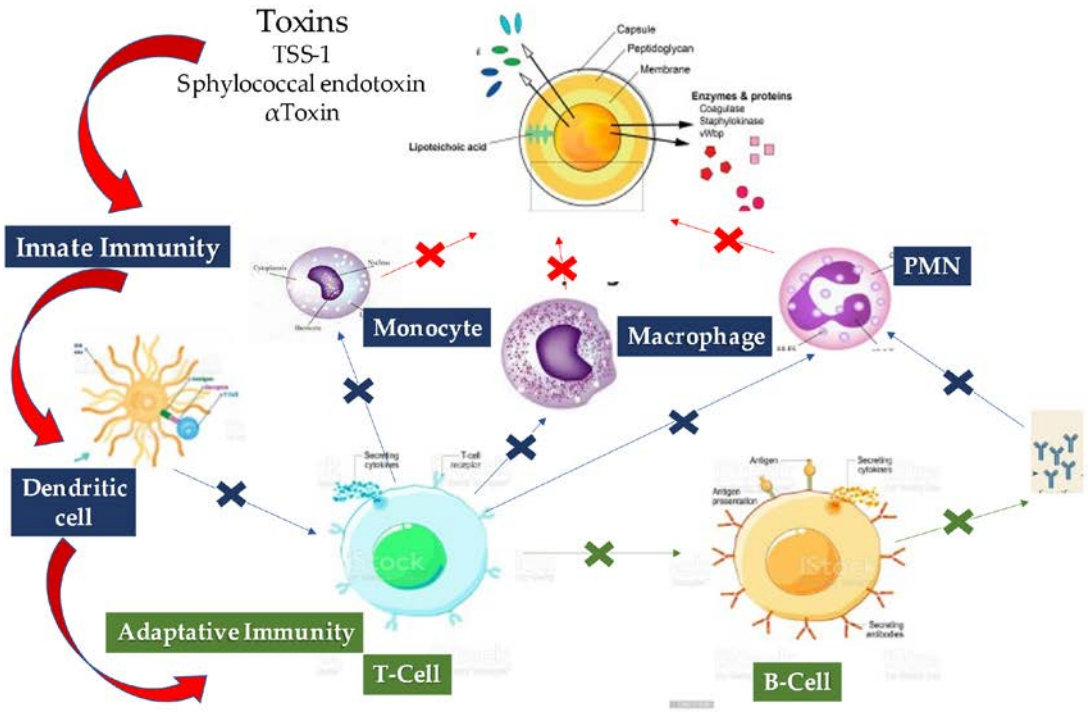


Figure 8. Staphylocytotoxins interfere (great blue arrow) with the cells of the innate **(blue box)** and adaptive **(green box)** immune response. Cytoxins (TSS-1, Staphylococcal endotoxin and alpha toxin) are capable of lysing immune cells including PMN, monocytes and macrophages involved in the clearance of S. aureus (red arrow). Cytotoxins can also impair the function of adaptive immune cells (green arrows) represented by T and B lymphocytes. Finally, cytotoxins can impair the interaction between innate and adaptive immune cells (blue arrows). Abbreviation ; TSS-1, Toxic Shock Syndrome-1

5.1.4 Immuno Response and Vaccine

The development of a vaccine against the Staphylococcus aureus is an important goal related to the emergence of drug-resistant strains. The latter has resulted in driving investigations for alternative treatments, such as immunotherapeutic approaches. However, understanding the immune response to S aureus infection and the production of an active vaccine go hand in hand. Whether the capacity of a S. aureus vaccine antigen can be extended to protect multiple mouse models infected with different strains of the pathogen has been reported in several published reports. This procedure allowed the evaluation of immune cross-protection between different models in presence of unlike strain of S Aureus.

Concerns related to the development of effective humoral response may be mitigated by converging immune-evasion mechanisms of S. aureus. Unquestionably the requirement for obtaining a promising vaccine in terms of efficacy and safety against S. aureus depends on a clear understanding of the immune, innate and adaptive response. The immune response to S. aureus is articulate and comprises of the humoral response,

 doi:10.20944/preprints202207.0126.v1

T cell help, blocking complement factors, and killing immune players by its toxins. All of these are the important determinants that require attention. The main contrasting mechanism exerted by S. aureus lies in hindering the immune action; this feature can lead to the failure of the development of targeted vaccines. Therefore, the crux of the matter may be the development of immunological interventions that can effectively obstruct the mechanisms by which S. aureus counteracts immunity. This process could ensure future success in vaccine development. [141-144]

ESAT-6-like proteins secreted by S. aureus, S. aureus EsxA (SaEsxA), and SaEsxB, as possible targets for a vaccine were investigated. Although mice that were vaccinated with the administration of purified proteins elicited high titers of anti-SaEsxA and anti-SaEsxB antibodies, the immune response mediated by antibodies could not avoid S. aureus infection. On the other hand, mice treated with the use of recombinant SaEsxA (rSaEsxA) and rSaEsxB disclosed Th1- and Th17-biased immunity. In addition, they reported substantially improved survival rates when challenged with S. aureus compared with the controls. These results suggested that SaEsxA and SaEsxB functioned as two promising Th1 and Th17 candidate antigens with potential expansion towards developing multivalent and serotype-independent vaccines against S. aureus infection. [142]

Brady et al worked on genetically inactivated alpha-toxin mutant HlaH35L and studies the protection afforded by this antigen in three models of infection using the same vaccine dose, regimen, route of immunization, adjuvant, and challenge strain. Using a systemic infection model challenged by mice immunized with HlaH35L, a limited but statistically significant decrease in bacterial colonization was recorded compared to that observed with control mice. Instead, using a prosthetic implant model of chronic biofilm infection, the investigators disclosed no significant differences in bacterial levels compared to controls. These findings suggest that although vaccines may lead to protection against one form of S. aureus disease, they are nonetheless not active in offering protection against several disease manifestations and thus underline a significant challenge in S. aureus vaccine development. [143]

The potential for S. aureus colonization reaches from 20 to 80% of humans leading to a variety of illnesses constituting a real nightmare for the healthcare- and community-associated bacterial infections. [141,144]

 doi:10.20944/preprints202207.0126.v1

In this context vaccine development against S. aureus has failed, proving unsuccessful each time its application has been attempted to date. The reason is likely due to an insufficient comprehension of the mechanisms sustaining the immune defense against this pathogen. In humans, S. aureus provokes bacteremia, meningitis, endocarditis, pneumonia, osteomyelitis, sepsis, and skin and soft tissue infections. Individuals' carriers are at increased risk for infection and transmission to others. The spread of multidrug-resistant strains of S. aureus limits the optimal medical treatment with the use of antibiotic administration options. [141,144]

Recently the awareness of opening a window on the future vaccine development against S. aureus strains provided notable insights. Zhang et al illustrated the importance to generate multipronged B-cell, Th1-, and Th17-mediated that are effective to trigger a response against S. aureus antigens. Likewise, this precise immune response confers enhanced and broad protection against S. aureus and counteracts invasive infection, mucosal colonization as well as skin and soft tissue infection. [144]

Today the impact of an immunotherapy approach is increasingly encouraged and supported, which in particular can be conferred by the administration of the vaccine against S. aureus infection. A crucial key role is played by S. aureus manganese transport protein C (MntC). This protein is a highly-conserved cell surface molecule that may arouse protective immunity against S. aureus and Staphylococcus epidermidis. Wei et al studied the humoral immune response and CD4+ T cell-mediated immune responses revealing essential protection for mice to reduce invasion of S. aureus evoked by MntC-specific antibodies. The evidence strongly reinforced the specific function of MntC-induced immunity response revealing that Th17 played a remarkable part in preventing S. aureus infection. MntC-specific antibodies and MntC-specific Th17 cells act synergistically in preventing S. aureus infection. MntC-induced protective immunity decreased after neutralization of IL-17 by the antibody in vivo and adoptive Th17 transferred from mice may not be fully resistant to S. aureus challenge. [145]

5.2 Pathogen-Host Interaction in Determining Inflammation

Particular attention is paid to the substantial pathogenic action of Staphylococcus aureus, which is mediated by adhesion proteins such as the fibronectin-binding protein and staphylococcal aggregation factors A and B,

 doi:10.20944/preprints202207.0126.v1

which play the role of bacterial mediators of adhesion and are the key determinants of pathogenicity.[146-149] Findings in an animal model with induced experimental endocarditis proved that the expression of Staphylococcus aureus adhesins in Lactococcus lactis suggested a crucial role of clumping factor A (ClfA) and fibronectin-binding protein A (FnBPA) for valve colonization. [146]

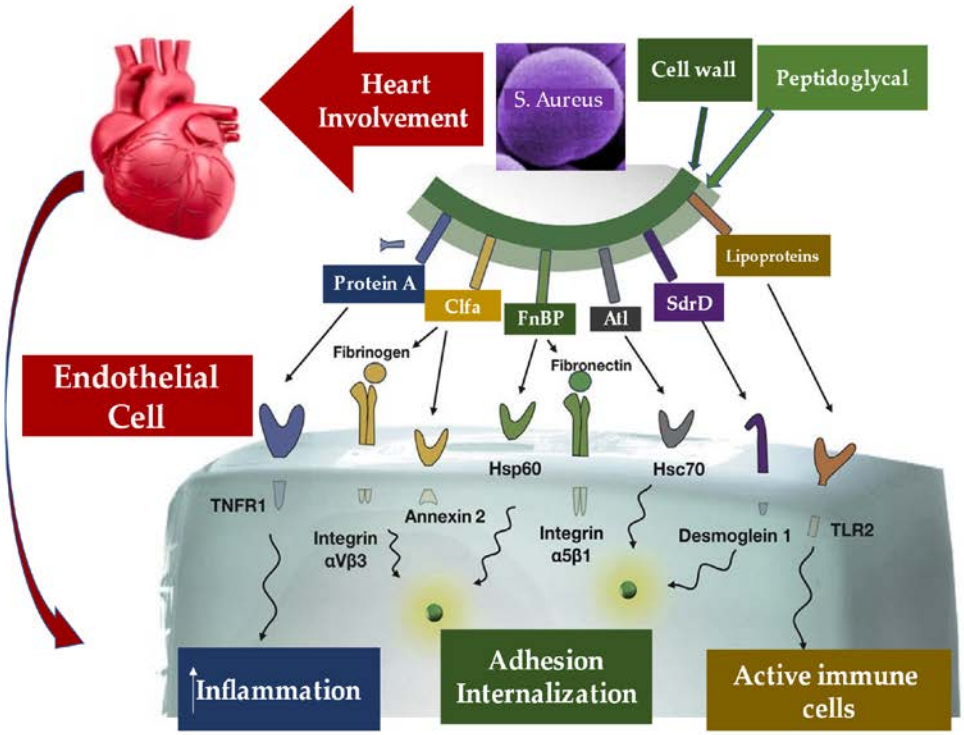
Que et al [146] evaluated the role of progression of infective endocarditis in animals that were followed for three days. Investigators noted that ClfA-positive lactococci successfully colonized damaged valves, nevertheless, the eradication of infection was spontaneously observed over 48 h. As for FnBPA-positive lactococci, pathogens titers progressively increased both in vegetations and in spleens. Imaging findings revealed that while ClfA-positive lactococci were limited to the vegetations, FnBPA-positive lactococci also overran to the adjacent endothelium. This process explained the ability of FnBPA to trigger cell internalization in vitro. FnBPA carries both fibrinogen and fibronectin-binding domains, so the role of these two selective functionalities in causing infection was assessed by depriving FnBPA of the fibrinogen binding domain and integrating it with the fibrinogen binding domain of ClfA in cis. or in trans. Although the abrogation of the fibrinogen binding domain of FnBPA did not change fibronectin binding and cellular internalization in vitro; however, it completely led to the elimination of valve infectivity in vivo. The ability to induce infection was restored in cis with the insertion of the fibrinogen binding domain of ClfA into truncated FnBPA while in trans was obtained by co-expressing full-length ClfA and truncated FnBPA, by using two separate plasmids. Therefore, it can be inferred that in S. aureus infection the binding of fibrinogen and fibronectin could cooperate for valve colonization and endothelial invasion in vivo. [146]

Staphylococcus aureus infection is supported by bacteremia which not only leads to complications such as infective endocarditis and osteomyelitis but promotes the pathogen's exit from the bloodstream to cause metastatic abscesses. The bacterium's interaction process with endothelial cells plays a substantial role in causing these complications. At this stage of the infection, several bacterial proteins have been shown to be involved. A fundamental role is offered by the extracellular adhesion protein of S. aureus (Eap) which has many functions including that binding various host glycoproteins. [150-154]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

It has also been shown to have both pro and anti-inflammatory activity. Difficulties have emerged in robustly testing the role of Eap in vivo, due to the difficulties expressed in defining its activity in mutant strains. Substantial evidence has been reported on the pro-inflammatory role of Eap and on the activity that purified native adhesion protein of S. aureus has in triggering the release of TNFα in human whole blood in a dose-dependent manner. TNFα production promotes S. aureus adhesion to endothelial cells with a 4-fold increase through a mechanism involving protein A on the bacterial surface and gC1qR / p33 on the surface of endothelial cells. This finding suggested that Eap's contribution to disease severity during S. aureus bacteremia is crucial. It was genetically engineered for an isogenic set of strains, in which the Eap gene was inactivated and integrated after inserting an intact copy of the gene elsewhere on the bacterial chromosome. Using a mouse bacteremia model, it was shown that Eap-expressing strains cause a more severe infection, suggesting the major role of Eap in invasive disease. [151,153,154]

Bacterial colonization offers the trigger for additional cycles of endothelial damage and thrombus deposition resulting in the implantation of infected vegetation. In this phase, the production of a biofilm which is formed by a multilayer with a bacterial aggregate containing a polysaccharide associated with a protein matrix assists bacterial persistence and contributes to antibiotic tolerance. [105] **Figure 9**



 doi:10.20944/preprints202207.0126.v1

Figure 9 The substantial pathogenic action of Staphylococcus Aureus is depicted during infection of the heart and endothelial cells. The process involves three crucial stages: an increase in the inflammatory response **(blue box),** adhesion and internalization of the pathogen **(green box)** and the development of an active immune response **(brown box).** The external envelope of S. Aureus, consisting of the cell wall and peptidoglycans, expresses the different molecules involved in the three physopathological processes. Abbreviations; Atl, autolysin; Clfa, clumping factor A: FnBP, fibronectin binding protein; Hsc70, Heat shock cognate; Hsp60, Heat shock protein; SdrD, Serine Aspartate repeat containing protein D; TLR2, Toll-like receptor 2; TNFR1, tumor necrosis factor receptor 1

5.3 Interaction between infective endocarditis pathogens, vascular endothelium, and blood constituents

Surface molecules of Staphylococcus aureus play a crucial role in the colonization of vascular endothelium which is a fundamental primary event in the pathogenesis of infective endocarditis. The ability of these molecules to also launch endothelial procoagulant and proinflammatory responses, which lead to the development of IE, was extensively investigated. [146, 155-158] Heying et al [155] studied the individual abilities of three important molecules expressed on S. aureus surface. Fibronectin-binding protein A (FnBPA) and B (FnBPA) and clumping factor A (ClfA) work to contribute to the bacterial adherence process that distinguishes the cultured human endothelial cells (ECs) when interacting with Staphylococcus aureus. Likewise, these molecules promote the phenotypic and functional changes in ECs. The method used included a non-invasive surrogate bacterium Lactococcus lactis, which, by gene transfer, expressed staphylococcal FnBPA, FnBPA or ClfA molecules. FnBPA- or FnBPB-positive recombinant lactococci lead to an increase of infection of ECs that reached 50- to 100-fold. Other important findings revealed EC activation, production of interleukin-8 associated with concomitant monocyte adhesion as well as an augmentation of surface expression of ICAM-1 and VCAM-1. On the contrary, infections that were induced by ClfA-positive lactococci did not activate EC. The prominent action of FnBPA-positive L. lactis favored a significant response mediated by tissue factor-dependent endothelial coagulation that was enhanced by cell-bound monocytes. Evidence suggested that S. aureus FnBPs, but not ClfA worked to invasiveness and pathogenicity to non-pathogenic L. lactis microorganisms indicating that bacterium-EC interactions mediated by these adhesins were strongly prone to favor both inflammation and procoagulant activity at infected endovascular sites. [155]

 doi:10.20944/preprints202207.0126.v1

Experimental endocarditis induced by Staphylococcus aureus experimental endocarditis anticipated the function of sequential fibrinogen binding responsible for valve colonization and the paramount action of fibronectin-binding that leads to endothelial invasion. These processes are sustained by peptidoglycan-attached adhesins. The function exerted by fibronectin-binding protein A (FnBPA) favored a synthesis between these two specific properties, combined with the binding of elastin, in promoting experimental endocarditis. Piroth et al [156] revealed as the minimal subdomain of FnBPA responsible for fibrinogen and fibronectin-binding may promote cell invasion in vivo endocarditis. FnBPA was expressed in Lactococcus lactis and tested in vitro and in animals. The subdomain needed in determining infective endocarditis consisted of 127 amino acids which represented the fulcrum of the FnBPA fibrinogen-binding and fibronectin-binding regions and were sufficient to confer the charge of these properties. Although in animals evidence supported the substantial role of fibrinogen binding to lead endocarditis induction; however, the work of fibronectin-binding was not significantly associated with endocarditis induction. On the contrary, as for disease severity, both fibrinogen binding and fibronectin-binding were crucial. In addition, the synergic combination of fibrinogen binding and fibronectin-binding suggested a remarkable increase in the infectious invasion of cultured cell lines, underlining a critical characteristic to be correlated with endocarditis severity. As a consequence, the idea of a sequential action of fibrinogen binding and fibronectin binding in promoting colonization and invasion fell in support of the unexpectedly intertwined role offered in endocarditis by fibrinogen binding and fibronectin binding in terms of both functional anatomy and pathogenetic mechanism. This refined and unexpected feature of FnBPA paves the way for the development of anti-adhesin strategies. [156] **Figure 10**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0126.v1

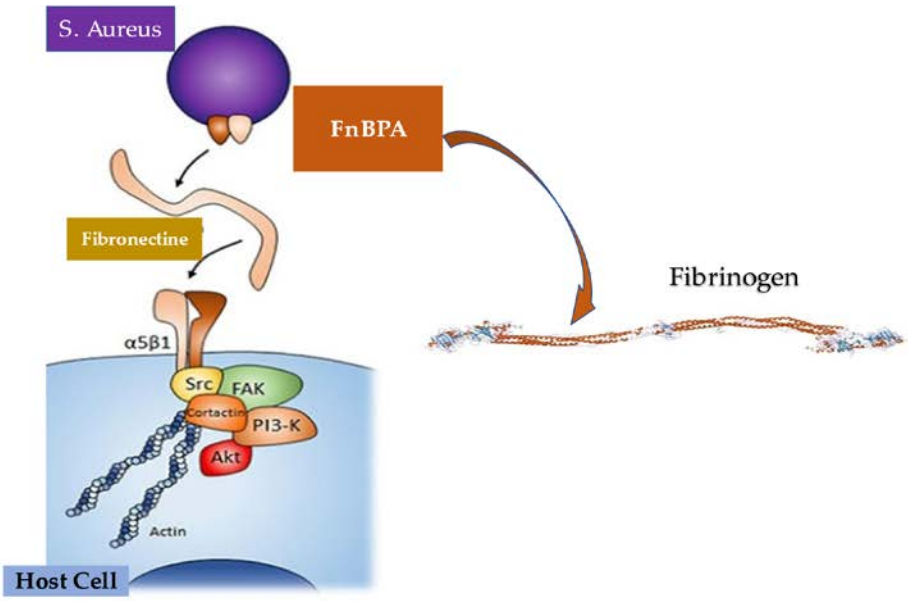


Figure 10 Experimental endocarditis induced by Staphylococcus aureus marked the crucial function of sequential fibrinogen binding responsible for valve colonization and the paramount action of fibronectin binding leading to endothelial invasion. FnBPA responsible for fibrinogen and fibronectin binding may promote cell invasion in vivo endocarditis

Microbiologists learned that bacterial proteins such ClfA and FnBPA intervene to mediate adhesion to EC surface molecules. This function is associated with the role of subendothelial matrix proteins including fibrinogen, fibrin, fibronectin, and von Willebrand factor (vWF). [157] Again, Pappelbaum et al, reported that ultra large von Willebrand factor (ULVWF) substantially contributed to the initial pathogenic step of S aureus-induced endocarditis in patients who disclosed an intact endothelium. The use of heparin and ADAMTS13 to reduce ULVWF production may suggest the use of novel therapeutic options to prevent infective endocarditis. [158]

Three reports recently investigated the synergistic role of ClfA, FnBPA and von Willebrand factor (vWF) in determining the adhesion of Staphylococcus aureus to endothelial cells (ECs) and markedly confirm the fundamental importance of these molecules in IE. [159-161]

In a first recently published report Claes et al explained by demonstrating that vWbp interacts with a staphylococcal surface protein, mediating S. aureus adhesion to VWF and vascular endothelium under shear stress. The method used included various Sortase A (SrtA) deficient mutants and SrtA-dependent surface proteins, as well as Lactococcus lactis expressing single staphylococcal surface proteins. The authors suggested

 doi:10.20944/preprints202207.0126.v1

that S. aureus first bound to the endothelium via VWF, subsequently secreted VWF-binding protein (vWbp) mediated the adhesion of S. aureus to VWF under shear stress, and finally, vWbp interacted with VWF and the Sortase A ClfA dependent surface protein. Therefore VWF-vWbp-ClfA anchored S. aureus to the vascular endothelium under shear stress. [159]

In another publication, Claes et al examined the influence of shear flow and plasma on the binding of ClfA and FnBPA, including its sub-domains A, A16+, ABC, CD, vWF, fibrinogen /fibrin, fibronectin or confluent ECs. The method used a genetically engineered Lactococcus lactis that expressed these adhesins heterologously. The investigators revealed that global adherence profiles were similar in static and flow conditions. Notably, in the absence of plasma, L. lactis- ClfA binding to fibrinogen increased with shear forces, whereas binding to fibrin did not produce the same effect. [160]

The degree of adhesion of L. lactis- FnBPA to EC-bound fibronectin and of L. lactis- ClfA to EC-bound fibrinogen was similar to that of L. lactis- ClfA to coated vWF domain A1, in the presence of vWF-binding protein (vWbp). Interestingly, in plasma, the adhesion of L. lactis-ClfA to activated EC-vWF / vWbp was decreased by 80% in 10 minutes and was related to disintegrin-mediated and metalloproteinase-mediated vWF hydrolysis with thrombospondin motif type 1, member 13. Likewise, in absence of plasma, the adhesion of L. lactis- FnBPA was reduced by > 70% compared. In contrast, plasma fibrinogen supported high L. lactis- ClfA binding to resting and activated ECs. The investigators offered the explanation that in plasma S. aureus adhesion to active endothelium occurs mainly via two complementary pathways: a rapid but short-lived vWF/vWbp pathway and a stable integrin-coupled - fibrinogen pathway. In consequence, these results supported the pharmacological inhibition of ClfA-fibrinogen interactions which may constitute a valuable additional treatment in infective endocarditis. [160]

The detrimental action caused by Staphylococcus aureus, which actively invades the endothelium, induces apoptosis and endothelial damage. We know that the role of Staphylococcus aureus is crucial in causing IE because it promotes infection through the key role offered by protein clotting factor A (ClfA), which is associated with the cell wall of S. aureus. On the other hand, as regards the role played by secreted plasma coagulation factors staphylo-coagulase (Coa) and by the protein binding von Willebrand factor (vWbp), has

 doi:10.20944/preprints202207.0126.v1

recently been clarified. Mancini et al [161] described, in rats with catheter-induced aortic vegetations, the role of staphylococcal secreted coagulase (Coa-positive staphylococci) and Staphylococcus aureus encodes a von Willebrand factor binding protein (vWbp) in the initiation of infective endocarditis. They used Lactococcus lactis mutants expressing coa, vWbp, ClfA or vWbp / clfA and S. aureus Newman Δcoa, ΔvWbp, ΔclfA or Δcoa / ΔvWbp / ΔclfA. Researchers noted that vWbp expression statistically increased L. lactis-induced valve infection as compared with parental and coa-expressing strains. Similarly, the expression of ClfA revealed increased infectivity of L. lactis, which was not further affected by the co-expression of vWbp. Importantly, deletion of the Coa or vWbp genes in S. aureus did not reduce infectivity while deletion of ClfA dramatically reduced valve infection. Importantly, the activity of clfA was not affected by the triple deletion of Δcoa / ΔvWbp / ΔclfA. Evidence has suggested that Coa does not support initial IE colonization by using L. lactis as the pathogen without other key virulence factors. Unquestionably, the presence of vWbp contributes to the onset of IE induced by L. lactis but its role is marginal in the presence of ClfA. [161]

We learned that Staphylococcus aureus has generally been contemplated as an extracellular pathogen, however, these microorganisms have also the ability to be integrated by host cells, including certain phagocytes. Hence, they may work inside endothelial cells, epithelial cells, or osteoblasts. The intracellular S. aureus position concurs with the establishment of infection. The entry gate of pathogens is mediated by the binding of integrin $\alpha 5\beta 1$ expressed on the membrane of the host cell which recognizes fibronectin. This bridge facilitates the recognition between pathogen and host cell leading to subsequent cell integration. [162-165] Although the osteoblasts evidenced high expression of $\alpha 5\beta 1$-integrin and fibronectin and the bacteria disclosed a high affinity to adhere to osteoblasts, Niemann et al demonstrated, through internalization tests and immunofluorescence microscopy, that S. aureus was less swallowed. in osteoblasts compared to epithelial cells. [166]

During cell infection with S. aureus, the authors added exogenous fibronectin, which resulted in increased uptake in epithelial cells that was not recorded in osteoblasts. This finding supports a clear contrast to previous claims regarding the pathogen uptake mechanism, which gave integrin and fibronectin expression a key role in promoting bacterial uptake in host cells. The organization of extracellular fibronectin surrounding osteoblasts and epithelial cells is different. In the former, it is organized in a fibrillar network. Investigators reported a

 doi:10.20944/preprints202207.0126.v1

significant increase in osteoblast uptake of S. aureus, resulting in inhibition of fibril formation, brief reduction in RNA-mediated fibronectin expression, and disruption of the fibronectin-fibril network. From the work of Nieman et al it emerges that the fibronectin fibril network appears to strongly reduce the absorption of *S. aureus* in a given host cell, indicating that the supramolecular structure of the fibronectin can direct the different ability of particular host cells to internalize the pathogen. [166]

The recent study by Niemann et al suggests the non-determining role played by the crude quantity of fibronectin but rather the substantial role established by the supramolecular structure of the fibronectin molecules. Once deposited on the eukaryotic cell surface, they play an essential role in bacterial uptake by host cells. These results can explain the great variability expressed in the efficacy of S. aureus absorption considering different types of host cells. Again, the differences found in vivo between the courses of bacterial infections and the localization of bacteria in different clinical settings. [166]

The molecular basis of the pathogenicity of S. aureus is related to the expression of a variety of virulence factors, including proteins that mediate adherence to the host plasma and extracellular matrix proteins. Between these, evidence proved that IsdB-expressing bacteria bound to both soluble and immobilized vWF. [167] More recently Alfeo et al discovered that the iron-regulated surface determinant B (IsdB) protein, besides being involved in iron transport and vitronectin binding, interacts with von Willebrand Factor (vWF). [168]

The researchers found that the bond established between IsdB and the recombinant vWF was stopped by heparin and was reduced due to high ionic strength. Furthermore, using the administration of ristocetin, an allosteric agent that promotes exposure to the A1 domain of vWF, the substantial effect of enhancing the binding between IsdB and vWF was obtained. An important finding supported that IsdB binding and S. aureus adhesion were significantly inhibited by a monoclonal antibody against the A1 domain as well as IsdB reactive IgG isolated from patients experiencing staphylococcal endocarditis. Therefore, the reported evidence suggests both the importance of IsdB in favoring the adhesion of S. aureus, and its role in the colonization of the endothelium by S. aureus. IsdB can serve as a potential therapeutic target. [168]

5.4 Infective Endocarditis and Platelets

 doi:10.20944/preprints202207.0126.v1

Although the use of antibiotic prophylaxis is presently recommended in patients with high-risk infective endocarditis, however infective endocarditis persists with the features of a challenging disease and statistically confirms its higher mortality. Furthermore, the concerns related to the administration of antibiotics are confronted with their low efficacy, further contributing to the emerging infection rate for the selection of antibiotic-resistant strains. Given this scenario, the need to find new therapeutic strategies remains a firm point against IE. Platelets are essential in the initial phase of infective endocarditis, acting as first-line immune responders. [148,149,169]

Evidence based on in-vitro mechanistic studies has shown that the work undertaken by platelets is of crucial importance in the initial phase of infective endocarditis, constituting the first front of the immune response. The first phase of the disease is supported by the interaction of pathogens with platelets for which counteracting platelet antimicrobial activity is a priority. Experimental in vitro and animal models have suggested that the effect of aspirin can limit bacterial-platelet interactions leading to the prevention of vegetation development and showing promising results. However, the data evoked in clinical studies on the outcome of patients with infective endocarditis who undergo medical therapy with aspirin administration remain controversial. Conflicting results cast a veil of uncertainty about the benefit of antiplatelet agents in the prevention of infective endocarditis. In the same way, in addition to aspirin, a therapeutic effect has been attributed to the antagonist of the platelet receptor P2Y12, ticagrelor, which would combine its powerful and well-known antiplatelet activity with strong antibacterial properties. Furthermore, a recent study based on a mouse animal model reported a marked ability of ticagrelor to eradicate Staphylococcus aureus bacteremia. [169-171]

6. Evidence from deploying maneuvers as a risk factor for bacteremia related to infective endocarditis

Although Staphylococcus aureus remains the undisputed leading causative pathogen in infectious endocarditis, attention must be paid to those microorganisms such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Streptococcus mutans that mainly occur as aetiologic agents of dental caries and aggressive periodontitis. These bacteria can pose concerns for populations at risk of infective endocarditis. [172-178]

 doi:10.20944/preprints202207.0126.v1

6.1 Special Population Required Attention

7.1.1 Tooth extraction and Toothbrushing

Lockart et al compared the incidence, duration, nature, and magnitude of endocarditis-related bacteremia in patients who had single-tooth extraction and toothbrushing. [115, 176] Authors determined the impact of amoxicillin prophylaxis on single-tooth extraction. 290 individuals were enrolled for randomization in a double-blind, placebo-controlled study as a follow: (1) toothbrushing, (2) single-tooth extraction with amoxicillin prophylaxis, or (3) single-tooth extraction with an identical placebo. Blood was drawn for bacterial culturing and identification at 6-time points before, during, and after these interventions. Investigators focused their analysis on the role of bacterial species that was reported to lead to infective endocarditis. 98 bacterial species were identified and 32 of these were revealed to be the cause of endocarditis. Results suggested that cumulative incidence of endocarditis-related bacteria from all 6 blood draws was detected in 23%, 33%, and 60% of the toothbrushing, extraction-amoxicillin, and extraction-placebo groups, respectively ($P<0.0001$). Interestingly the prophylaxis administration of amoxicillin resulted in a significant decrease in positive cultures ($P<0.0001$). The findings of Lockhart's study suggest that although amoxicillin has a significant impact on bacteraemia resulting from single tooth extraction, however, as the increased frequency of oral hygiene is exerted by tooth brushing, the latter may represent a greater threat to people at risk of infective endocarditis. [115]

Landmark RCT of Lockhart et al substantially supported that oral hygiene and gingival disease indexes were associated significantly with the development of infective endocarditis-related bacteremia after toothbrushing. Individuals enrolled with a mean plaque and calculus scores of 2 or greater revealed an increased risk of developing bacteremia between 3.78- and 4.43-fold. Investigators found that the occurrence of generalized bleeding after toothbrushing was associated with an almost eightfold increase in risk of developing bacteremia. However, no remarkable link has been reported between any of the estimates of periodontal disease and the incidence of bacteremia after tooth brushing. Interestingly Lockart et al found that the oral hygiene or disease status of a tooth was not crucially related to the manifestation of bacteremia after dental extraction. [176]

The manifestation of IE in the young population of patients requiring cardiac surgery has aroused great interest. A double-blind, randomized, placebo-controlled study evaluated the impact of amoxicillin prophylaxis on the

 doi:10.20944/preprints202207.0126.v1

incidence, nature, and duration of bacteremia from nasotracheal intubation and dental procedures in children. As for the impact of antibiotic prophylaxis on the incidence, nature, and duration of bacteremia in individuals after intubation and dental procedures. Lockart et al reported that at 1.5 minutes after the initiation of dental extractions, bacteremia occurred in 76% of the children enrolled in a placebo cohort as compared to 15% of the amoxicillin group (P<0.001). Evidence suggested that bacteremia occurrence rates were higher in the placebo group of children who received specific treatment as intubation, after dental restorations and cleaning as compared to those who were managed with the amoxicillin (18% and 20 vs 4% and 6%; P=0.05 and P=0.07, respectively). It is important to note that in the majority of the 152 positive cultures and of the 29 different bacteria the causative pathogens responsible for IE were Gram-positive cocci. Individuals included in the placebo group disclosed bacteremia that persisted longer over time. [177]

7.1.2 Causative Pathogens of Interest and Related Mechanism Leading to Disease

Porphyromonas gingivalis is considered a major periodonto-pathogen and is responsible for the pathogenesis of periodontitis. This process is mediated by increased production of Interleukin-1β (IL-1β) which work at regulating innate immune responses with a crucial function excreted in the host's defense against bacterial infection. However, evidence proved that an excessive IL-1β was related to periodontal demolition. Again, toll-like receptor (TLR) signaling and inflammasome activation substantially influenced IL-1β synthesis, maturation, and secretion with higher levels of inflammasome components in the gingival tissues of patients with chronic periodontitis than in those from healthy controls. Park et al investigated the molecular mechanisms by which P. gingivalis infection causes IL-1β secretion focusing the findings on the characteristics of P. gingivalis-induced signaling in differentiated THP-1 cells. Importantly, the activation of TLR2 and TLR4 anticipated P. gingivalis-induced IL-1β release. P. gingivalis infection evoked a higher secretion of IL-1β secretion associated with inflammatory cell death via caspase-1 activation. Both increased IL-1β secretion and pyroptotic cell death were sustained by NLRP3 and AIM2 inflammasome activation. The activation of the NLRP3 inflammasome was mediated by ATP release, the P2X7 receptor, and lysosomal damage. The innate immune response against P. gingivalis infection which could potentially be used for the prevention and therapy of periodontitis reach a remarkable significance in patient at risk of developing infective endocarditis. [179]

 doi:10.20944/preprints202207.0126.v1

Evidence suggested that Streptococcus mutans (S. mutans), cover a role as a major aetiologic agent of dental caries and it is involved in systemic diseases, such as bacterial endocarditis, if it enters the bloodstream through temporary bacteraemia. The infection sustained by S. mutans is chacterized by a high-level synthesis of Interleukin (IL)-1β, a proinflammatory cytokine, that is engaged by the host's defences against pathogens. This process of synthesis, maturation, and secretion were closely adjusted by the activation of the inflammasome, an inflammatory signaling complex. Song et al examined the signaling mechanism of the S. mutans-induced inflammasome pathway at IL-1β secretion, thus securing the basis of the mechanism that can support systemic oral streptococcal infection. Investigators provided novel insight with regards to the innate immune response against S. mutans infection. After infection of THP-1 cells with S. mutans there was an increase in the inflammasome expression associated with IL-1β secretion through activation of caspase-1, NLR family pyrin domain-containing 3 (NLRP3), and NLR family CARD domain-containing 4 (NLRC4). Of note is that the S. mutans-induced NLRP3 inflammasome activity was mediated by adenosine triphosphate (ATP) release, potassium depletion and lysosomal damage. [180]

Aggregatibacter actinomycetemcomitans lead to aggressive periodontitis which denotes the peculiar characteristic of early-onset and rapid progression of periodontal destruction. Lee et al suggested that A. actinomycetemcomitans upgraded bacterial internalization by phagocytosis in infected macrophages, by the increase in LC3-II, autophagy-related gene 5/12, and Beclin-1 expression through the Toll-like receptors and extracellular signal-regulated kinase signaling pathways. This process restricted the disproportionate inflammatory response by downregulation of IL-1β and ROS production. Bacterial internalization through phagocytosis in macrophages could be suppressed through the inhibition of autophagy induced by A. actinomycetemcomitans thereby increasing the production of interleukin (IL) -1β. A. actinomycetemcomitans-induced autophagy. [181]

7.3 Cardiac Device Infection

Infection that occurs in CIEDs is increased and favored by coagulase-negative staphylococci. The trend of infection rate of CDIs, including permanent pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy devices, reaches the incidence of 1 to 10 per 1,000 device years (approximately 1 per

 doi:10.20944/preprints202207.0126.v1

1,000 device years for pacemakers and 8 to 9 per 1,000 device-years for complex devices). [182-184] In addition, in the United States, the trend of infection rate of CDIs has augmented out of proportion to the increase in implantation rates (128) leading to noticeable higher short- and long-term morbidity and mortality associated with the incremental cost of management. [185,186] The IE is due to the onset of risk factors for CDIs that may be patient-, procedure-, or device-related determinants. [187] Patients presenting at great specific risk of infection include those who receive corticosteroid administration, heart failure, diabetes mellitus, endstage kidney disease, chronic obstructive pulmonary disease, malignancy, and previous device infection. Of note that procedural risk factors suggesting for increased development of IE are post-operative hematoma complications (OR: 8.46; 95% CI: 4.01 to 17.86), reintervention due to lead displacement, long procedure times, and implantation of ≥2 leads. In patients who required a revision procedure, the IE occurs with a 2- to 5-fold higher risk than the first implantation. The use of antibiotic prophylaxis administration has been disclosed to give substantial protection against CDI in both RCTs and observational studies. [188-194]

CDI may develop in various sites, involving the generator pocket, device leads, or endocardial (valvular or non-valvular) surfaces (or any combination of these locations). The main characteristic of the infection located at the level of pocket infections is cellulitis, erythema, wound discharge, and pain. Patients may experience an inchoate or overt erosion of the skin overlying the pocket. On the contrary, in patients who have an infection that involves CIED leads or the endocardial surface (CIED-IE), fevers and rigors occur; frequently CIED leads or CIED-IE coexists with pocket infections. IE may arise from an infection located at the level of the pocket or it occurs by spreading of infection to the leads via the bloodstream.

It has been suggested that Staphylococci with particularly CoNS strain are involved reaching 60% to 80% of cases with a critical key role sustained by Fibronectin (fn) and fibrinogen (fg). These molecules are major host proteins present in the extracellular matrix, blood, and coatings on indwelling medical devices. Infections localized on medical devices are strictly dependent on the high capacity of favorable interactions between Staphylococcus aureus with these host ligands. The survival and persistence of CoNS S. aureus on medical devices may depend on complementary roles offered by fibronectin-binding proteins A and B, as they interact

with different conformations of Fn or Fg. The latter may be compact in solution vs. extended on a surface and are present in different physiological and pathological conditions. [195,196]

The interactions are from bacterial adhesins, FnBPA and FnBPB, and host ligands explained the pathogenesis of clumping and adhesion during device infection sustained by CoNS strain of Staphylococcus aureus. Studies using the combination of seven different strains of S. aureus and Lactococcus lactis, a Gram-positive surrogate that naturally lacks adhesins to mammalian ligands, suggested that in the absence of soluble ligands (i.e fn or fg), both FnBPA and FnBPB were able to interact with adjacent FnBPs of neighboring bacteria to mediate aggregation. With the addition of soluble host ligands, in particular fn, and under shear stress, the aggregation was enhanced. However, FnBPB revealed a greater ability to aggregate than FnBPA suggesting a distinct role for the two closely related bacterial adhesins. FnBPB and FnBPA have different functional abilities to interact with host ligands in different contexts such as, for example, the "soluble" or "immobilized" condition. [196]

Conclusion

Infective endocarditis is only projected to increase with further implantation of devices and transcatheter valves. The need for a vaccine is therefore increasing given the high-risk nature of this cohort of patients with multiple comorbidities. Early index of suspicion is needed with prompt initiation of treatment and referral to a heart team to ensure good outcomes. Infective endocarditis remains a major burden on healthcare systems especially in the western world with the ageing population.

Author Contributions: Conceptualization, F.N.; methodology, F.N, G.M, F.B.; software, G.M.,F.B;SS.AS.; validation, F.N.,G.M.,F.B.,SS. AS.; M.R.M.; formal analysis, F.N. G.M, F. B.; investigation, F.N. G.M, F. B.; data curation, F.N., G.M., F. B., SS. AS.; M.R.M; writing—original draft preparation, F.N.; writing—review and editing F.N., G.M., F. B., SS. AS.; M.R.M,.; visualization, F.N., G.M., F. B., SS. AS.; M.R.M.; supervision, F.N., SS. AS.; M.R.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest

Reference

1. Murdoch DR, Corey GR, Hoen B, et al, and the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century : the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009 ; 169 : 463–73.
2. Liaqat W, Palaiodimos L, Li W, et al. Epidemiologic and clinical characteristics of infective endocarditis : a single-center retrospective study in the Bronx, New York. Infection. 2022 May 25.
3. Paul G, Ochs L, Hohmann C, et al. Surgical Procedure Time and Mortality in Patients with Infective Endocarditis Caused by Staphylococcus aureus or Streptococcus Species Clin Med. 2022 Apr 30 ;11(9):2538.
4. Selton-Suty C, Celard M, Le Moing V, et al, and the AEPEI Study Group. Preeminence of Staphylococcus aureus in infective endocarditis : a 1-year population-based survey. Clin Infect Dis 2012 ; 54 : 1230–39.
5. Chen H, Zhan Y, Zhang K, et al. The Global, Regional, and National Burden and Trends of Infective Endocarditis From 1990 to 2019 : Results From the Global Burden of Disease Study 2019.Front Med (Lausanne). 2022 Mar 9 ;9 :774224.
6. Resende P Jr, Fortes CQ, do Nascimento EM, et al. In-hospital Outcomes of Infective Endocarditis from 1978 to 2015 : Analysis Through Machine-Learning Techniques. CJC Open. 2021 Sep 11 ;4(2) :164-172.
7. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries : systematic review and meta-analysis. Lancet 2011 ; 377 : 228–41.
8. Bagheri Nejad S, Allegranzi B, Syed SB, Ellis B, Pittet D. Health-care-associated infection in Africa: a systematic review. Bull World Health Organ. 2011 Oct 1 ;89(10):757-65.
9. Joubert D, Cullati S, Briot P, et al. How to improve hospital admission screening for patients at risk of multidrug-resistant organism carriage : a before-and-after interventional study and cost-effectiveness analysis. BMJ Open Qual. 2022 Apr ;11(2): e001699.
10. Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol 2015 ; 13 : 42–51.
11. Martínez JL Antibiotics and antibiotic resistance genes in natural environments. Science. 2008 Jul 18 ;321(5887) :365-7.
12. Yang M, Zhang J, Wei Y, Zhang J, Tao C Recent advances in metal-organic framework-based materials for anti-staphylococcus aureus infection. Nano Res. 2022 May 11 :1-23.
13. Prendergast BD. The changing face of infective endocarditis. Heart 2006 ; 92 : 879–85.
14. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009 ; 30 : 2369–413.
15. van den Brink FS, Swaans MJ, Hoogendijk MG, et al. Increased incidence of infective endocarditis after the 2009 European Society of Cardiology guideline update : a nationwide study in the Netherlands. Eur Heart J Qual Care Clin Outcomes. 2017 Apr 1 ;3(2) :141-147.
16. Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease : Executive Summary : A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.J Am Coll Cardiol. 2021 Feb 2 ;77(4) :450-500.

17. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000 ;30 :633-8.
18. Richet H, Casalta JP, Thuny F, et al. Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. J Antimicrob Chemother 2008 ;62 :1434-40
19. Mahabadi AA, Mahmoud I, Dykun I, Totzeck M, Rath PM, Ruhparwar A, Buer J, Rassaf T. Diagnostic value of the modified Duke criteria in suspected infective endocarditis -The PRO-ENDOCARDITIS study. Int J Infect Dis. 2021 Mar ;104 :556-561.
20. Gouriet F, Tissot-Dupont H, Casalta JP, et al. Marseille scoring system for empiric treatment of infective endocarditis. Eur J Clin Microbiol Infect Dis. 2018 May ;37(5) :841-849.
21. Crawford MH, Durack DT. Clinical presentation of infective endocarditis. Cardiol Clin 2003 ;21 :159-66.
22. Dabbous M, Saba M, El Orra S, Najjar C Confusion as an Unusual Presentation of Infective Endocarditis. Cureus. 2021 Dec 29 ;13(12) : e20809.
23. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis : a prospective multicentre study. Eur Heart J 2007 ;28 :1155-61.
24. Sonneville R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients : the ENDOcardite en REAnimation prospective multicenter study. Crit Care Med 2011 ;39 :1474-81.
25. Dickerman SA, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis : an analysis from the ICE Prospective Cohort
Study (ICE-PCS). Am Heart J 2007 ;154 :1086-94.
26. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis : prognostic value of echocardiography : a prospective multicenter study. Circulation 2005 ;112 :69-75. [Erratum, Circulation 2005 ;112(9) : e125.
27. Nunes MC, Gelape CL, Ferrari TC. Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period : prognostic factors and in-hospital outcome. Int J Infect Dis. 2010 May ;14(5) : e394-8.
28. Di Salvo G, Habib G, Pergola V, et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol 2001 ;37 :1069-76.
29. Vilacosta I, Graupner C, San Román JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol. 2002 May 1 ;39(9) :1489-95.
30. Nappi F, Spadaccio C, Dreyfus J, Attias D, Acar C, Bando K. Mitral endocarditis : A new management framework. J Thorac Cardiovasc Surg. 2018 Oct ;156(4) :1486-1495.e4.
31. Avtaar Singh SS, Costantino MF, D'Addeo G, Cardinale D, Fiorilli R, Nappi F. A narrative review of diagnosis of infective endocarditis-imaging methods and comparison. Ann Transl Med. 2020 Dec ;8(23):1621.
32. Duval X, Iung B, Klein I, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis : a prospective study. Ann Intern Med 2010 ;152 :497-504.
33. Béraud G, Tubiana S, Erpelding ML, et al ; AEPEI study group ; COMBAT study group. Combined Bacterial Meningitis and Infective Endocarditis : When Should We Search for the Other When Either One is Diagnosed ? Infect Dis Ther. 2022 May 26.
34. Vitali P, Savoldi F, Segati F, Melazzini L, et al. MRI versus CT in the detection of brain lesions in patients with infective endocarditis before or after cardiac surgery. Neuroradiology. 2022 May ;64(5) :905-913.

35. Corr P, Wright M, Handler LC. Endocarditis- related cerebral aneurysms : radiologic changes with treatment. AJNR Am J Neuroradiol 1995 ;16 :745-8.
36. Champey J, Pavese P, Bouvaist H, Maillet M, Kastler A, Boussat B, Francois P ; and the investigator groups. Is brain angio-MRI useful in infective endocarditis management ? Eur J Clin Microbiol Infect Dis. 2016 Dec ;35(12) :2053-2058
37. Peters PJ, Harrison T, Lennox JL. A dangerous dilemma : management of infectious intracranial aneurysms complicating endocarditis. Lancet Infect Dis 2006 ;6 :742-8.
38. Serrano F, Guédon A, Saint-Maurice JP, et al. Endovascular treatment of infectious intracranial aneurysms complicating infective endocarditis : a series of 31 patients with 55 aneurysms. Neuroradiology. 2022 Feb ;64(2) :353-360.
39. Nappi F, Spadaccio C, Mihos C Infective endocarditis in the 21st century.
40. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades : a systematic review. PLoS One 2013 ;8 : e82665.
41. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States : 1996 through 2003. J Am Coll Cardiol 2006 ;48 :590–1.
42. Nappi F, Iervolino A, Singh SSA. The New Challenge for Heart Endocarditis : From Conventional Prosthesis to New Devices and Platforms for the Treatment of Structural Heart Disease. Biomed Res Int. 2021 Jun 14 ;2021 :7302165
43. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation : results from a large multicenter registry. Circulation 2015 ; 131 :1566–74.
44. Mangner N, Woitek F, Haussig S, et al. Incidence, predictors, and outcome of patients developing infective endocarditis following transfemoral transcatheter aortic valve replacement. J Am Coll Cardiol 2016 ;67 :2907–8.
45. Van Dijck I, Budts W, Cools B, et al. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart 2015 ; 101 :788–93.
46. Duval X, Delahaye F, Alla F, et al, and the AEPEI Study Group. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications : three successive population-based surveys. J Am Coll Cardiol 2012 ; 59 : 1968–76.
47. Hoen B, Alla F, Selton-Suty C, et al, and the Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study Group. Changing profile of infective endocarditis : results of a 1-year survey in France. JAMA 2002 ; 288 : 75–81.
48. Yew HS, Murdoch DR. Global trends in infective endocarditis epidemiology. Curr Infect Dis Rep 2012 ; 14 : 367–72.
49. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005 ; 5 : 685–94.
50. Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med 2007 ; 357 : 470–76.
51. Rwebembera J, Nascimento BR, Minja NW, et al. Recent Advances in the Rheumatic Fever and Rheumatic Heart Disease Continuum. Pathogens. 2022 Jan 28 ;11(2) :179.
52. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol 2011 ; 3 : 67–84
53. Belay W, Dessie A, Ahmed H, et al. Secondary prevention of rheumatic heart disease in Ethiopia : a multicenter study. BMC Cardiovasc Disord. 2022 Feb 2 ;22(1) :26.

54. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis : a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 2010; 85: 422–26.
55. Baddour LM, Shafiyi A, Lahr BD, Anavekar NS, Steckelberg JM, Wilson WR, Sohail MR, DeSimone DC. A Contemporary Population-Based Profile of Infective Endocarditis Using the Expanded Rochester Epidemiology Project. Mayo Clin Proc. 2021 Jun ;96(6):1438-1445
56. Fowler VG Jr, Miro JM, Hoen B, et al, and the ICE Investigators. Staphylococcus aureus endocarditis : a consequence of medical progress. JAMA 2005 ; 293 : 3012–21
57. Marks LR, Calix JJ, Wildenthal JA, Wallace MA, et al. Staphylococcus aureus injection drug use-associated bloodstream infections are propagated by community outbreaks of diverse lineages. Commun Med (Lond). 2021 Nov 30 ;1 :52.
58. Paul G, Ochs L, Hohmann C, Baldus S, Michels G, Meyer-Schwickerath C, Fätkenheuer G, Mader N, Wahlers T, Weber C, Jung N. Surgical Procedure Time and Mortality in Patients with Infective Endocarditis Caused by Staphylococcus aureus or Streptococcus Species. J Clin Med. 2022 Apr 30 ;11(9):2538.
59. Benedetto U, Avtaar Singh SS, Spadaccio C, Moon MR, Nappi F. A narrative review of the interpretation of guidelines for the treatment of infective endocarditis. Ann Transl Med. 2020 Dec ;8(23) :1623
60. Benedetto U, Spadaccio C, Gentile F, Moon MR, Nappi F. A narrative review of early surgery versus conventional treatment for infective endocarditis : do we have an answer ? Ann Transl Med. 2020 Dec ;8(23) :1626.
61. Nappi F, Spadaccio C, Moon MR A management framework for left sided endocarditis : a narrative review. Ann Transl Med. 2020 Dec ;8(23) :1627.
62. Pollari F, Ziegler R, Nappi F, Grossmann I, Steinmann J, Fischlein T. Redo aortic valve replacement for prosthesis endocarditis in patients previously classified as high or prohibitive risk : a narrative review.
63. Ann Transl Med. 2020 Dec;8(23):1629.
64. Nappi F, Singh SSA, Spadaccio C, Acar C. Revisiting the guidelines and choice the ideal substitute for aortic valve endocarditis. Ann Transl Med. 2020 Aug ;8(15) :952.
65. Nappi F, Nenna A, Petitti T, Spadaccio C, Gambardella I, Lusini M, Chello M, Acar C. Long-term outcome of cryopreserved allograft for aortic valve replacement. J Thorac Cardiovasc Surg. 2018 Oct ;156(4) :1357-1365.e6.
66. Nappi F, Spadaccio C, Acar C. Use of allogeneic tissue to treat infective valvular disease: Has everything been said? J Thorac Cardiovasc Surg. 2017 Apr ;153(4) :824-828.
67. Nappi F, Spadaccio C. keep fumbling around in the dark when it comes to infective endocarditis, or produce new, reliable data to redesign the guidelines? J Thorac Cardiovasc Surg. 2018 Jan ;155(1) :75-76.
68. Lyytikainen O, Ruotsalainen E, Jarvinen A, Valtonen V, Ruutu P. Trends and outcome of nosocomial and community-acquired bloodstream infections due to Staphylococcus aureus in Finland, 1995–2001. Eur J Clin Microbiol Infect Dis 2005 ; 24 : 399–404.
69. Ammerlaan HSM, Harbarth S, Buiting AGM, et al. Secular trends in nosocomial bloodstream infections : antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis 2013 ; 56 : 798–805.
70. Forsblom E, Kakriainen A, Ruotsalainen E, Järvinen A. Methicillin-sensitive Staphylococcus aureus bacteremia in aged patients : the importance of formal infectious specialist consultation. Eur Geriatr Med. 2018 ;9(3):355-363

71. Bonnet I, Millon B, Meugnier H, Vandenesch F, Maurin M, Pavese P, Boisset S. High prevalence of spa type t571 among methicillin-susceptible Staphylococcus aureus from bacteremic patients in a French University Hospital. PLoS One. 2018 Oct 9 ;13(10) : e0204977.
72. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillator in the United States 1993 to 2008. J Am Coll Cardiol 2011 ; 58 : 1001–06.
73. Traykov V, Blomström-Lundqvist C. Antibiotic-Eluting Envelopes for the Prevention of Cardiac Implantable Electronic Device Infections : Rationale, Efficacy, and Cost-Effectiveness. Front Cardiovasc Med. 2022 Mar 28 ;9 :855233.
74. Elad B, Perl L, Hamdan A, et al. The clinical value of the endocarditis team : insights from before and after guidelines implementation strategy. Infection. 2022 Feb ;50(1) :57-64.
75. Han HC, Hawkins NM, Pearman CM, Birnie DH, Krahn AD. Epidemiology of cardiac implantable electronic device infections : incidence and risk factors. Europace. 2021 Jun 23 ;23(23 Suppl 4) : iv3-iv10.
76. Day MD, Gauvreau K, Shulman S, Newburger JW. Characteristics of children hospitalized with infective endocarditis. Circulation 2009 ; 119 : 865–70.
77. Ware AL, Tani LY, Weng HY, Wilkes J, Menon SC Resource utilization and outcomes of infective endocarditis in children. J Pediatr. 2014 Oct ;165(4) :807-12. e1.
78. Simpkins J, Miller S, Shirley DA. Extended Interval Aminoglycoside Treatment for Klebsiella Pneumoniae Endocarditis in an Extremely Low Birth Weight Neonate. J Pediatr Pharmacol Ther. 2022 ;27(1) :85-89.
79. Rushani D, Kaufman JS, Ionescu-Ittu R, et al. Infective endocarditis in children with congenital heart disease : cumulative incidence and predictors. Circulation 2013 ; 128 : 1412–19.
80. Sun LC, Lai CC, Wang CY, et.al. Risk factors for infective endocarditis in children with congenital heart diseases - A nationwide population-based case control study. Int J Cardiol. 2017 Dec 1 ;248 :126-130
81. Snygg-Martin U, Giang KW, Dellborg M, Robertson J, Mandalenakis Z. Cumulative Incidence of Infective Endocarditis in Patients with Congenital Heart Disease : A Nationwide, Case-Control Study Over Nine Decades. Clin Infect Dis. 2021 Oct 20 ;73(8) :1469-1475
82. Morris CD, Reller MD, Menashe VD. Thirty-year incidence of infective endocarditis after surgery for congenital heart defect. JAMA 1998 ; 279 : 599–603.
83. Havers-Borgersen E, Butt JH, Smerup M, et al. Incidence of Infective Endocarditis Among Patients With Tetralogy of Fallot. J Am Heart Assoc. 2021 Nov 16 ;10(22) : e022445.
84. Nappi F, Spadaccio C, Mihos C, Shaikhrezai K, Acar C, Moon MR. The quest for the optimal surgical management of tricuspid valve endocarditis in the current era : a narrative review. Ann Transl Med. 2020 Dec ;8(23) :1628
85. Valente AM, Jain R, Scheurer M, et al. Frequency of infective endocarditis among infants and children with Staphylococcus aureus bacteremia. Pediatrics 2005 ; 115 : e15–19.
86. Bendig EA, Singh J, Butler TJ, Arrieta AC The impact of the central venous catheter on the diagnosis of infectious endocarditis using Duke criteria in children with Staphylococcus aureus bacteremia. Pediatr Infect Dis J. 2008 Jul ;27(7) :636-9.
87. Kumarachandran G, Johnson JK, Shirley DA, Graffunder E, Heil EL. Predictors of Adverse Outcomes in Children With Staphylococcus aureus Bacteremia Pediatr Pharmacol Ther. 2017 May-Jun ;22(3) :218-226.

88. Durante-Mangoni E, Bradley S, Selton-Suty C, et al, and the International Collaboration on Endocarditis Prospective Cohort Study Group. Current features of infective endocarditis in elderly patients : results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med 2008 ; 168 : 2095 – 103
89. Zampino R, Iossa D, Ursi MP, Bertolino L, Karruli A, Molaro R, Esposito G, Vitrone M, D'Amico F, Albisinni R, Durante-Mangoni E, On Behalf Of The Monaldi Hospital CardiovascularInfection Group.
Clinical Significance and Prognostic Value of Hemostasis Parameters in 337 Patients with Acute Infective Endocarditis. J Clin Med. 2021 Nov 18 ;10(22) :5386.
90. Molton JS, Tambyah PA, Ang BSP, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. Clin Infect Dis 2013 ; 56 : 1310 – 18.
91. Çağlayan Ç, Barnes SL, Pineles LL, Harris AD, Klein EY. A Data-Driven Framework for Identifying Intensive Care Unit Admissions Colonized With Multidrug-Resistant Organisms. Front Public Health. 2022 Mar 17;10:853757
92. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. Clin Microbiol Rev 2014; 27: 870–926.
93. López J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. Eur Heart J 2007 ; 28 : 760–65.
94. Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg 2010; 139: 887–93.
95. Xu Z, Chen L, Chen X, Tang A, Huang D, Pan Q, Fang Z. Prevalence and Molecular Characterization of Methicillin-Resistant Staphylococci Recovered from Public Shared Bicycles in China. Int J Environ Res Public Health. 2022 Apr 8 ;19(8) :4492.
96. Argemi X, Hansmann Y, Prola K, Prévost G. Coagulase-Negative Staphylococci Pathogenomics.
Int J Mol Sci. 2019 Mar 11;20(5):1215
97. Chu VH, Woods CW, Miro JM, et al, and the International Collaboration on Endocarditis-Prospective Cohort Study Group. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. Clin Infect Dis 2008 ; 46 : 232–42.
98. Chu VH, Miro JM, Hoen B, et al. International Collaboration on Endocarditis-Prospective Cohort Study Group. Coagulase-negative staphylococcal prosthetic valve endocarditis--a contemporary update based on the International Collaboration on Endocarditis : prospective cohort study. Heart. 2009 Apr ;95(7) :570-6.
99. Alawad MJ, Ali GA, Goravey W. Underrecognized pathogen ; Staphylococcus warneri-associated native mitral valve endocarditis in an immunocompetent host : A case report and literature review. Clin Case Rep. 2022 Apr 22 ;10(4) : e05591
100. Nigo M, Munita JM, Arias CA, Murray BE. What’ s new in the treatment of enterococcal endocarditis ? Curr Infect Dis Rep 2014 ; 16 : 431.
101. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001 ; 14 : 177–207.
102. Das M, Badley AD, Cockerill FR, Steckelberg JM, Wilson WR. Infective endocarditis caused by HACEK microorganisms. Annu Rev Med 1997 ; 48 : 25–33.
103. Oumarou Hama H, Aboudharam G, Barbieri R, Lepidi H, Drancourt M. Immunohistochemical diagnosis of human infectious diseases : a review. Diagn Pathol. 2022 Jan 30 ;17(1) :17.
104. Baddley JW, Benjamin DK Jr, Patel M, et al, and the International Collaboration on Endocarditis-Prospective Cohort Study Group (ICE-PCS). Candida infective endocarditis. Eur J Clin Microbiol Infect Dis 2008 ; 27 : 519–29.

105. Huggins JP, Hohmann S, David MZ. Candida Infective Endocarditis : A Retrospective Study of Patient Characteristics and Risk Factors for Death in 703 United States Cases, 2015-2019. Open Forum Infect Dis. 2020 Dec 18 ;8(2) : ofaa628.
106. Flemming H-C, Wingender J. The biofilm matrix. Nat Rev Microbiol 2010 ; 8 : 623–33.
107. Schwartz FA, Christophersen L, Laulund AS, et al. Novel human in vitro vegetation simulation model for infective endocarditis. APMIS. 2021 Nov ;129(11) :653-662.
108. Di Domenico EG, Rimoldi SG, Cavallo I et al. Microbial biofilm correlates with an increased antibiotic tolerance and poor therapeutic outcome in infective endocarditis. BMC Microbiol. 2019 Oct 21 ;19(1) :228.
109. Schwartz FA, Nielsen L, Struve Andersen J, et al. Dynamics of a Staphylococcus aureus infective endocarditis simulation model. APMIS. 2022 Apr 23.
110. McAdow M, Missiakas DM, Schneewind O. Staphylococcus aureus secretes coagulase and von Willebrand factor binding protein to modify the coagulation cascade and establish host infections.
J Innate Immun. 2012 ;4(2) :141-8.
111. Thomer L, Schneewind O, Missiakas D. Multiple ligands of von Willebrand factor-binding protein (vWbp) promote Staphylococcus aureus clot formation in human plasma. J Biol Chem. 2013 Sep 27 ;288(39) :28283-92.
112. Ko YP, Kang M, Ganesh VK, Ravirajan D, Li B, Höök M. Coagulase and Efb of Staphylococcus aureus Have a Common Fibrinogen Binding Motif. mBio. 2016 Jan 5 ;7(1) : e01885-15.
113. Thomas S, Liu W, Arora S, Ganesh V, Ko YP, Höök. The Complex Fibrinogen Interactions of the Staphylococcus aureus Coagulases. Front Cell Infect Microbiol. 2019 Apr 16 ;9 :106.
114. Thomas S, Arora S, Liu W, Churion K, Wu Y, Höök M. vhp Is a Fibrinogen-Binding Protein Related to vWbp in Staphylococcus aureus. mBio. 2021 Aug 31 ;12(4) : e0116721
115. Schwarz C, Töre Y, Hoesker V, et al. Host-pathogen interactions of clinical S. aureus isolates to induce infective endocarditis. Virulence. 2021 Dec ;12(1) :2073-2087
116. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation 2008 ; 117 : 3118–25.
117. Widmer E, Que YA, Entenza JM, Moreillon P. New concepts in the pathophysiology of infective endocarditis. Curr Infect Dis Rep 2006 ; 8 : 271–79.
118. Moreillon P, Que YA, Bayer AS. Pathogenesis of streptococcal and staphylococcal endocarditis. Infect Dis Clin North Am. 2002 Jun ;16(2) :297-318.
119. Mancini S, Oechslin F, Menzi C, et al.. Marginal role of von Willebrand factor-binding protein and coagulase in the initiation of endocarditis in rats with catheter-induced aortic vegetations. Virulence. 2018 ;9(1) :1615-1624.
120. Werdan K, Dietz S, Löffl B, et al. Mechanisms of infective Endocarditis : pathogen-host interaction and risk states. Nat Rev Cardiol 2014 ; 11 : 35–50.
121. Regueiro A, Linke A, Latib A, et al. Infective Endocarditis Following Transcatheter Aortic Valve Replacement : Comparison of Balloon- Versus Self-Expandable Valves. Circ Cardiovasc Interv. 2019 Nov ;12(11) : e007938
122. Rodríguez-Vidigal FF, Nogales-Asensio JM, Calvo-Cano A, et al. Infective endocarditis after transcatheter aortic valve implantation : Contributions of a single-centre experience on incidence and associated factors. Enferm Infecc Microbiol Clin (Engl Ed). 2019 Aug-Sep ;37(7):428-434.
123. Ciofu O, Moser C, Jensen PØ, Høiby N Tolerance and resistance of microbial biofilms. Nat Rev Microbiol. 2022 Feb 3

124. Annappah D, Saling M, Prodafikas J, Badie AN. Device-associated aortic valve endocarditis due to a complicated Enterobacter cloacae urinary tract infection. ID Cases. 2021 Dec 16 ;27 : e01365
125. Di Carluccio C, Forgione RE, Bosso A, et al. . Molecular recognition of sialoglycans by streptococcal Siglec-like adhesins : toward the shape of specific inhibitors. RSC Chem Biol. 2021 Oct 18 ;2(6) :1618-1630.
126. Manukumar H.M., Umesha S. MALDI-TOF-MS based identification and molecular characterization of food associated methicillin-resistant Staphylococcus aureus. Sci Rep. 2017 Sep 12 ;7(1) :11414
127. Mempel M., Schnopp C., Hojka M, et al. Invasion of human keratinocytes by Staphylococcus aureus and intracellular bacterial persistence represent haemolysin-independent virulence mechanisms that are followed by features of necrotic and apoptotic keratinocyte cell death. Br J Dermatol. 2002 Jun ;146(6) :943-51.
128. Nakagawa S, Matsumoto M., Katayama, Y, et al. Staphylococcus aureus virulent PSMα peptides induce keratinocyte alarmin release to orchestrate IL-17-dependent skin inflammation. Cell Host Microbe 22, 667–677. 2017 Nov 8 ;22(5) :667-677.e5.
129. Fournier, B., Philpott, D.J. Recognition of Staphylococcus aureus by the innate immune system. Clin. Microbiol. Rev. 2005 Jul ;18(3) :521-40.
130. Kawa T, Akira S. The role of pattern-recognition receptors in innate immunity : update on toll-like receptors. Nat. Immunol. 2010 May ;11(5) :373-84.
131. Kupper T.S, Fuhlbrigge R.C. Immune surveillance in the skin : mechanisms and clinical consequences. Nat. Rev. Immunol. 2004 Mar ;4(3) :211-22.
132. Nestle F.O, Di M.P, Qin, J.Z., Nickoloff, B.J. Skin immune sentinels in health and disease. Nat. Rev. Immunol. 2009 Oct ;9(10) :679-91.
133. Malachowa N, Whitney A.R., Kobayashi S.D, et al. Global changes in Staphylococcus aureus gene expression in human blood. PLoS One 6, e18617. 2011 Apr 15 ;6(4) : e18617
134. Alonzo 3rd F, Kozhaya, L., Rawlings S.A, et al. CCR5 is a receptor for Staphylococcus aureus leukotoxin ED. Nature 2013 Jan 3 ;493(7430):51-5.
135. Alonzo 3rd F, Torres V.J. Bacterial survival amidst an immune onslaught : the contribution of the Staphylococcus aureus leukotoxins. PLoS Pathog. 2013 Feb ;9(2) : e1003143.
136. Cheung G.Y, Joo H.S, Chatterjee S.S. et al. Phenol-soluble modulins–critical determinants of staphylococcal virulence. FEMS Microbiol. Rev. 2014 Jul ;38(4) :698-719.
137. Berube BJ, Bubeck Wardenburg J. Staphylococcus aureus α-toxin : nearly a century of intrigue. Toxins (Basel). 2013 Jun ;5(6) :1140-66.
138. Foster TJ. Immune evasion by staphylococci. Nat Rev Microbiol. 2005 Dec ;3(12) :948-58.
139. Silverman GJ, Goodyear CS. Confounding B-cell defences : lessons from a staphylococcal superantigen. Nat Rev Immunol. 2006 Jun ;6(6) :465-75
140. Kim HK, Cheng AG, Kim HY, Missiakas DM, Schneewind O. Nontoxigenic protein A vaccine for methicillin-resistant Staphylococcus aureus infections in mice. J Exp Med. 2010 Aug 30 ;207(9) :1863-70
141. Becker S, Frankel MB, Schneewind O, Missiakas D. Release of protein A from the cell wall of Staphylococcus aureus. Proc Natl Acad Sci U S A. 2014 Jan 28 ;111(4) :1574-9.

142. Zhang X, Marichannegowda MH, Rakesh KP, Qin HL. Master mechanisms of Staphylococcus aureus : consider its excellent protective mechanisms hindering vaccine development ! Microbiol Res. 2018 Jul-Aug ;212-213 :59-66.
143. Zhang BZ, Hua YH, Yu B, et al. Recombinant ESAT-6-like proteins provoke protective immune responses against invasive Staphylococcus aureus disease in a murine model. Infect Immun. 2015 Jan ;83(1) :339-45.
144. Brady RA, Mocca CP, Prabhakara R, et al. Evaluation of genetically inactivated alpha toxin for protection in multiple mouse models of Staphylococcus aureus infection. PLoS One. 2013 Apr 29 ;8(4) : e63040.
145. Zhang F, Ledue O, Jun M, Goulart C, Malley R, Lu YJ. Protection against Staphylococcus aureus Colonization and Infection by B- and T-Cell-Mediated Mechanisms. mBio. 2018 Oct 16 ;9(5) : e01949-18.
146. Yu W, Yao D, Yu S, Wang X, Li X, Wang M, Liu S, et al. Protective humoral and CD4+ T cellular immune responses of Staphylococcus aureus vaccine MntC in a murine peritonitis model. Sci Rep. 2018 Feb 26 ;8(1) :3580.
147. Que Y-A, Haefliger J-A, Piroth L, et al. Fibrinogen and fibronectin binding cooperate for valve infection and invasion in Staphylococcus aureus experimental endocarditis. J Exp Med 2005 ; 201 : 1627 – 35.
148. Edwards AM, Bowden MG, Brown EL, Laabei M, Massey RC. Staphylococcus aureus extracellular adherence protein triggers TNFα release, promoting attachment to endothelial cells via protein A.
PLoS One 2012 ; 7 : e43046.
149. Fitzgerald JR, Foster TJ, Cox D. The interaction of bacterial pathogens with platelets. Nat Rev Microbiol 2006 ; 4 : 445 – 57.
150. Veloso TR, Chaouch A, Roger T, et al. Use of a human-like low-grade bacteremia model of experimental endocarditis to study the role of Staphylococcus aureus adhesins and platelet aggregation in early endocarditis. Infect Immun 2013 ; 81 : 697–703.
151. Sinha B, Herrmann M. Mechanism and consequences of invasion of endothelial cells by Staphylococcus aureus. Thromb Haemost. 2005 Aug ;94(2) :266-77.
152. Hussain M, Haggar A, Heilmann C, et al. Insertional inactivation of Eap in Staphylococcus aureus strain Newman confers reduced staphylococcal binding to fibroblasts. Infect Immun. 2002 Jun ;70(6) :2933-40
153. Palankar R, Binsker U, Haracska B, et al. Interaction between the Staphylococcus aureus extracellular adherence protein Eap and its subdomains with platelets. Int J Med Microbiol. 2018 Aug ;308(6):683-691.
154. Hussain M, Haggar A, Peters G, et al. More than one tandem repeat domain of the extracellular adherence protein of Staphylococcus aureus is required for aggregation, adherence, and host cell invasion but not for leukocyte activation. Infect Immun. 2008 Dec ;76(12) :5615-23.
155. Harraghy N, Hussain M, Haggar A, et al. The adhesive and immunomodulating properties of the multifunctional Staphylococcus aureus protein Eap. Microbiology (Reading). 2003 Oct ;149(Pt 10):2701-2707
156. Heying R, van de Gevel J, Que YA, Moreillon P, Beekhuizen H Fibronectin-binding proteins and clumping factor A in Staphylococcus aureus experimental endocarditis : FnBPA is sufficient to activate human endothelial cells. Thromb Haemost. 2007 Apr ;97(4) :617-26
157. Piroth L, Que YA, Widmer E, et al. The fibrinogen- and fibronectin-binding domains of Staphylococcus aureus fibronectin-binding protein A synergistically promote endothelial invasion and experimental endocarditis. Infect Immun. 2008 Aug ;76(8) :3824-31.
158. Claes J, Vanassche T, Peetermans M, et al. Adhesion of Staphylococcus aureus to the vessel wall under flow is mediated by von Willebrand factor-binding protein. Blood. 2014 Sep 4 ;124(10) :1669-76.

159. Pappelbaum KI, Gorzelanny C, Grässle S, et al. Ultralarge von Willebrand factor fibers mediate luminal Staphylococcus aureus adhesion to an intact endothelial cell layer under shear stress. Circulation. 2013 Jul 2 ;128(1):50-9

160. Claes J, Liesenborghs L, Peetermans M, et al. Clumping factor A, von Willebrand factor-binding protein and von Willebrand factor anchor Staphylococcus aureus to the vessel wall. J Thromb Haemost. 2017 May ;15(5) :1009-1019.

161. Claes J, Ditkowski B, Liesenborghs L, et al. Assessment of the Dual Role of Clumping Factor A in S. Aureus Adhesion to Endothelium in Absence and Presence of Plasma. Thromb Haemost. 2018 Jul ;118(7) :1230-1241

162. Mancini S, Oechslin F, Menzi C, et al. . Marginal role of von Willebrand factor-binding protein and coagulase in the initiation of endocarditis in rats with catheter-induced aortic vegetations. Virulence. 2018 ;9(1) :1615-1624

163. Foster TJ. The remarkably multifunctional fibronectin binding proteins of Staphylococcus aureus. Eur J Clin Microbiol Infect Dis. 2016 Dec ;35(12) :1923-1931

164. Ahmed S, Meghji S, Williams RJ, Henderson B, Brock JH, Nair SP. Staphylococcus aureus fibronectin binding proteins are essential for internalization by osteoblasts but do not account for differences in intracellular levels of bacteria. Infect Immun. 2001 May ;69(5) :2872-7.

165. Massey RC, Kantzanou MN, Fowler T, et al. Fibronectin-binding protein A of Staphylococcus aureus has multiple, substituting, binding regions that mediate adherence to fibronectin and invasion of endothelial cells. Cell Microbiol. 2001 Dec ;3(12) :839-51.

166. Ridley RA, Douglas I, Whawell SA. Differential adhesion and invasion by Staphylococcus aureus of epithelial cells derived from different anatomical sites. J Med Microbiol. 2012 Dec ;61(Pt 12) :1654-1661.

167. Niemann S, Nguyen MT, Eble JA, et al. More Is Not Always Better-the Double-Headed Role of Fibronectin in Staphylococcus aureus Host Cell Invasion. mBio. 2021 Oct 26 ;12(5) : e0106221

168. Pietrocola G, Pellegrini A, Alfeo MJ, et al. The iron-regulated surface determinant B (IsdB) protein from Staphylococcus aureus acts as a receptor for the host protein vitronectin. J Biol Chem. 2020 Jul 17 ;295(29) :10008-10022.

169. Alfeo MJ, Pagotto A, Barbieri G, et al. Staphylococcus aureus iron-regulated surface determinant B (IsdB) protein interacts with von Willebrand factor and promotes adherence to endothelial cells. Sci Rep. 2021 Nov 23 ;11(1) :22799

170. Leeten K, Jacques N, Lancellotti P, Oury C Aspirin or Ticagrelor in Staphylococcus aureus Infective Endocarditis : Where Do We Stand ? Front Cell Dev Biol. 2021 Oct 7 ;9 :716302

171. Ditkowski B, Bezulska-Ditkowska M, Jashari R, et al Antiplatelet therapy abrogates platelet-assisted Staphylococcus aureus infectivity of biological heart valve conduits. Congenital Cardiology and Cardiac Surgery Group. J Thorac Cardiovasc Surg. 2021 Jun ;161(6): e457-e472.

172. Hannachi N, Habib G, Camoin-Jau L Aspirin Effect on Staphylococcus aureus-Platelet Interactions During Infectious Endocarditis. Front Med (Lausanne). 2019 Oct 15 ;6 :217.

173. Park, E. et al. Activation of NLRP3 and AIM2 inflammasomes by Porphyromonas gingivalis infection. Infect. Immun. 82, 112–123 (2014)

174. Nagata, E. & Oho, T. Invasive Streptococcus mutans induces inflammatory cytokine production in human aortic endothelial cells via regulation of intracellular toll-like receptor 2 and nucleotide-binding oligomerization domain. Mol Oral Microbiol. 2017 Apr ;32(2) :131-141.

175. Kim JS, Kim KD, Na HS, Jeong SY, et al. Tumor necrosis factor-α and interleukin-1β expression pathway induced by Streptococcus mutans in macrophage cell line RAW 264.7. Mol. Oral. Microbiol 17, 149–159 (2012).

176. Tornos, P., Gonzalez-Alujas, T., Thuny, F. & Habib, G. Infective endocarditis : the European viewpoint. Curr Probl Cardiol. 2011 May ;36(5) :175-222.
177. Lockhart PB, Brennan MT, Thornhill M, Michalowicz BS, Noll J, Bahrani-Mougeot FK, Sasser HC. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. J Am Dent Assoc. 2009 Oct ;140(10) :1238-44.
178. Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteremia in children after intubation and dental procedures. Circulation. 2004 Jun 15 ;109(23) :2878-84
179. Karikoski E, Junttila K, Järvinen M, Sarkola T, Blomqvist M Parental perceptions and experiences of an oral health care promotion intervention for children with congenital heart defects. Int J Qual Stud Health Well-being. 2022 Dec ;17(1) :2070968.
180. Park E, Na HS, Song YR, Shin SY, Kim YM, Chung J. Activation of NLRP3 and AIM2 inflammasomes by Porphyromonas gingivalis infection. Infect Immun. 2014 Jan ;82(1) :112-23
181. Song Y, Na HS, Park E, Park MH, Lee HA, Chung J. Streptococcus mutans activates the AIM2, NLRP3 and NLRC4 inflammasomes in human THP-1 macrophages. Int J Oral Sci. 2018 Aug 6 ;10(3) :23
182. Lee HA, Park MH, Song Y, Na HS, Chung J. Role of Aggregatibacter actinomycetemcomitans-induced autophagy in inflammatory response. J Periodontol. 2020 Dec ;91(12) :1682-1693
183. Uslan DZ, Sohail MR, St. Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection : a population based study. Arch Intern Med 2007 ;167 :669–75.
184. Johansen JB, Jørgensen OD, Møller M, et al. Infection after pacemaker implantation : infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011 ;32 :991–8
185. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation : rate of surgical revisions and impact on survival : insights from the Italian Clinical Service Database. Circulation 2011 ;123 : 2526–35.
186. Rizwan Sohail M, Henrikson CA, Braid- Forbes M, et al. Increased long-term mortality in patients with cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol 2015 ;38 :231–9.
187. Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011 ;171 :1821–8.
188. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection : a systematic review and metaanalysis. Europace 2015 ;17 :767–77.
189. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation : a meta-analysis. Circulation 1998 ; 97 :1796–801.
190. Blomstrom-Lundqvist C, Ostrowska B. Prevention of cardiac implantable electronic device infections : guidelines and conventional prophylaxis. Europace. 2021 May 25 ;23(Suppl 4) : iv11-9
191. de Oliveira JC, Martinelli M, Nishioka SA, Varejão T, Uipe D, Pedrosa AA, Costa R, D'Avila A, Danik SB. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillator : results of a large, prospective, randomized, double-blinded, placebo-controlled trial. Circ Arrhythm Electrophysiol. 2009 Feb ;2(1) :29-34.
192. Satriano UM, Nenna A, Spadaccio C, Pollari F, Fischlein T, Chello M, Nappi F. Guidelines on prosthetic heart valve management in infective endocarditis : a narrative review comparing American Heart Association/American College of Cardiology and European Society of Cardiology guidelines. Ann Transl Med. 2020 Dec ;8(23):1625.

 doi:10.20944/preprints202207.0126.v1

193. Pollari F, Spadaccio C, Cuomo M, Chello M, Nenna A, Fischlein T, Nappi F. Sharing of decision-making for infective endocarditis surgery : a narrative review of clinical and ethical implications. Ann Transl Med. 2020 Dec ;8(23) :1624.

194. Mihos CG, Nappi F. A narrative review of echocardiography in infective endocarditis of the right heart. Ann Transl Med. 2020 Dec ;8(23):1622.

195. Scialla S, Martuscelli G, Nappi F, Singh SSA, Iervolino A, Larobina D, Ambrosio L, Raucci MG. Trends in Managing Cardiac and Orthopedic Device-Associated Infections by Using Therapeutic Biomaterials. Polymers (Basel). 2021 May 12 ;13(10) :1556.

196. Casillas-Ituarte NN, Staats AM, Lower BH, Stoodley P, Lower SK. Host blood proteins as bridging ligand in bacterial aggregation as well as anchor point for adhesion in the molecular pathogenesis of Staphylococcus aureus infections. Micron. 2021 Nov ;150 :103137