Review Article

Bacteria and the Human Heart: The Occurrence, Etiopathogenesis, Treatment, and Challenges

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Abstract

Humans have a complicated relationship with microbes especially bacteria. Although each of us appears to be one single individual, our bodies are laced with various microscopic organisms that sit on the surface of our body and live within our organs. The majority of bacteria are good and humans depend on them for survival as they act as part of the immune system and digest foods such as dairy products, providing us with nutrients and minerals. Since the bacteria and humans live in a commensal relationship, the famous microbiologist Anne Maczulak has rightly said "As long as humans can't live without carbon, nitrogen, protection from disease and the ability to fully digest their food, they can't live without bacteria".

However, the same bacteria can turn into pathogens and develop a parasitic relationship when they invade the damaged epithelial lining, develop colonies and ultimately cause disease by secreting toxins or by inducing sensitivity to their antigenic properties.

The human heart is one such organ in which such a pathogenic relationship develops in form of Infective endocarditis when bacteria infect the damaged epithelial cells especially the heart valves. The average incidence is 15,000 cases per year in the United States with an in-hospital mortality rate of 15-20% and a 1-year mortality rate of 40%, despite the best of treatment. The issues like delay in diagnosis, antibiotic resistance, infection with atypical bacteria and increased virulence are also the challenges that result in increased mortality. We try to discuss an occurrence, etiopathogenesis, treatment and challenges of this pathogenic relationship in the form of infective endocarditis in this article.

Background

Bacteria are single-celled prokaryotes that have survived on Earth for millions of years. Lacking membrane-bound organelles, these microorganisms are made up of complex macromolecules that form their cell walls, cell membranes, ribosomes, and DNA. However, even though they are simple microorganisms, bacteria are very good at surviving in their environments and invading new ones. Much of the credit for this can be given to the two large events that caused the Domain Bacteria to evolve differently than the other two Domains. Bacteria have strong cell walls, among other barriers and methods, that protect them from their ambient environments. They are also well-equipped to deal with the pressures of many different environments because of the diversity in their DNA, a result of the adaptive radiation that ancestral lineages experienced, as well as the exchange of genes that subsequent generations of bacteria have done through processes like transduction, transformation, and conjugation. However, while bacteria can survive in many environments, they are still limited in what they can do because of their size and their simple structures. But, they have been able to overcome their limitations by working together.

Often, bacteria see the most success when they congregate in areas. For example, in host organisms, antagonistic bacteria are more successful at taking advantage of their host when they are in relatively large numbers or concentrations since multiple bacteria are more likely to overcome the host's defenses together than one bacterium is alone. This is also true in other environments. When bacteria are together, they are better able to obtain nutrients from their environment and fight off what would

normally destroy them. Because of this, high concentrations of planktonic bacteria can exist floating in liquids, such as the water in freshwater lakes. However, some bacteria do better when they congregate on solid surfaces.

On such surfaces, some species of bacteria can form biofilms composed of extracellular polymeric substances (EPS). Bacterial cells release macromolecules such as polysaccharides and proteins to form the EPS which surrounds them, encasing them in a community with a protective barrier to the ambient environment **(**1**)**. Since the process of creating biofilms requires a lot of energy and materials, bacteria only do it if they are in high enough concentrations for the process to work. A bacterium recognizes whether or not other bacterial cells are near it through the process of quorum sensing. Bacterial cells release chemicals to communicate with other cells to carry out certain processes **(**2**)**. They have receptors on their surfaces that recognize specific released chemicals and start the process of expressing certain genes when necessary. All bacteria recognize the molecule autoinducer-2 (AI-2). They use this molecule to determine the concentration of bacteria in certain areas. Once the concentration of AI-2 reaches the preferred or necessary level, bacterial cells will then release other molecules to signal that they are ready to start making a biofilm, repeating the process of quorum sensing. While the production of a biofilm can be an energy-intensive process, biofilms are very beneficial for bacteria for several reasons.

Biofilms provide stability for the bacterial cells, keeping them attached to one place, rather than floating around in their environment. They also make it easier for bacterial cells to obtain nutrients by trapping nutrients and substances that cells would otherwise have to find by traveling through their environments for long periods. Beyond this, biofilms also provide more protection for cells. Not only are they a barrier to the outside world, but they also reduce the speed at which harmful substances travel to bacterial cells if they enter the biofilms. The proximity of bacterial cells also allows for the exchange of genes among cells, some of which allow for the development of resistance to certain antibiotics in the entire population, making it harder to eradicate the bacteria **(**3**)**. Thus, harmful bacteria (some armed with extra support from biofilms) can invade the human body and cause debilitating infections.

One of the places that such events can happen is the human heart, the muscle that pumps blood to the rest of the human body, providing oxygen to cells. However, before this can be addressed, it is important to understand the anatomy and physiology of the organ.

The heart is made up of three layers: the epicardium, the myocardium, and the endocardium **(**4**)**. The epicardium is the outer layer of the heart. It is a part of the pericardium. The epicardium is the visceral pericardium. Around this layer exists the parietal pericardium **(**5**)**. They make up the serous pericardium which is enveloped by the fibrous pericardium, the sac that envelops the entire heart.

The endocardium is the innermost layer. Both the epicardium and the endocardium are relatively thin. Between those two layers lies the myocardium, which is a thick layer of cardiac muscle.

The heart has four chambers: the right atrium, the right ventricle, the left atrium, and the left ventricle **(**6**)**. It pumps blood through two circulatory systems: the pulmonary circulatory system and the systemic circulatory system **(**7**)**. Deoxygenated blood from the systemic veins enters the right atrium and is deposited into the right ventricle. It is then pumped into the pulmonary artery to be taken to the lungs **(**7**)**. This is the start of the pulmonary circulatory system. The blood travels into smaller arteries and then into capillaries, where carbon dioxide is released and oxygen is picked up by red blood cells. Oxygenated blood then travels back to the heart through the pulmonary veins and enters the left atrium. It is emptied into the left ventricle. The left ventricle pumps blood through the aorta, sending it to all parts of the body (systemic circulatory system). The flow of blood from the atria to the ventricles happens when the heart relaxes during diastole, between heartbeats. It is pumped into either pulmonary circulation or systemic circulation during systole.

This blood flow is due to the pressures in the chambers of the heart, as well as both the systemic and pulmonary veins and arteries. The pressures in the atria are much lower than the pressures in the ventricles they are connected to because the atria have thinner walls **(**7**)**. Pressures in veins are less than those in the arteries. These are the natural pressure differences in the chambers of the heart, veins, and arteries, and they are the drivers of the hemodynamics of the heart. They contribute to the path of blood flow described above.

Because of the pressure difference among the chambers, veins, and arteries, as well as the contraction of ventricles during systole, barriers are required to prevent the backflow of blood from areas of higher pressure (such as the ventricles) to areas of lower pressure (such as the atria) when the heart is pumping blood. There are two types of valves in the heart that prevent such backflow **(**7**)**. The semilunar valves can be found between the ventricles and the major artery into which each ventricle pumps blood. The pulmonic valve exists between the right ventricle and the pulmonary artery, preventing blood from flowing back into the ventricle after it has been pumped into the artery. The aortic valve exists between the left ventricle and the aorta, preventing blood from flowing back into the ventricle after it has been pumped into the aorta. The second type of valves is the atrioventricular valves, which are found between the atria and ventricles. On the right side of the heart, the tricuspid valve separates the right atrium from the right ventricle. On the left side of the heart, the mitral valve (also known as the bicuspid valve) separates the left atrium from the left ventricle. These four valves open when blood travels from one cavity to the other and then immediately snap shut when the process is completed so that there is no

backflow. The semilunar valves open during systole and close during diastole, while the atrioventricular valves open during diastole and close during systole.

As stated before, the heart is not immune to bacteria. Infective endocarditis is a bacterial infection that affects the heart. It was first described in 1964 by Lazare Rivière, a professor who had a patient that died of the disease. It was also reported in 1706 by Giovanni Maria Lancisi after multiple people in Rome died of the disease. Many more people afterward wrote about the illness, including Giovanni Battista Morgagni in 1761, Edward Sandifort in 1777, Corvisart in 1806, and still more thereafter. They all reported similar findings, among which were thickened and inflamed heart valves **(**8**)**.

Since these older recounts, we have been better able to study and understand the disease, including its occurrence and prognosis. Currently, in the United States, nearly 15,000 new patients are diagnosed with infective endocarditis each year **(**9**)**. The in-hospital mortality rate is about 15-20% **(**10**)**. The mortality rate for patients within the first year after their diagnosis is about 40% **(**9**)**. However, these numbers can vary depending on the nature and severity of the disease.

While many different factors go into classifying the specific type of infective endocarditis that a patient may have, we can divide up cases as those of acute endocarditis and subacute endocarditis based on the progression of the disease, as well as the damage it has done to the heart, at the time of diagnosis. Patients with acute endocarditis present with severe damage and die within weeks, while those with subacute endocarditis may not have as much structural damage and do not die until another deadly event (such as a mycotic aneurysm, which can occur as a result of infective endocarditis) occurs **(**11**)**. Those with the latter form of the disease are likely to live longer than those with the former.

Nevertheless, infective endocarditis is a deadly disease. It lowers a person's quality of life dramatically because of the complications it causes, and it quite often ends with heart failure and death **(**12**).** It is both a community-acquired disease and a nosocomial disease **(**11**)**. Thus, with our aging population and increased use of invasive cardiac devices, more people are at risk now than ever before **(**9**)**. This makes it extremely important that we understand the etiopathogenesis of the disease and look for ways to control and cure it.

Etiopathogenesis of Endocarditis

Infective endocarditis occurs when the endothelium of the heart comes into contact with a large number of microorganisms **(**11**)**. The endothelium is a thin layer of cells found in the endocardium **(**13**)**. Thus,

infective endocarditis, essentially, is seen developed on parts of the innermost layer of the heart. It has been noted by doctors for centuries that infective endocarditis does not affect the other layers of the heart or even associated arteries and veins; rather it only affects the endocardium and its endothelial layer **(**8**)**.

Infective endocarditis presents in patients on their heart valves, the low-pressure side of the ventricular septum if there is a defect, and the damaged parts of the mural endocardium **(**11**)**. In regards to heart valves, infective endocarditis has been observed on both native valves (native valve endocarditis) and prosthetic valves (prosthetic valve endocarditis). It can also happen on intracardiac devices implanted during surgeries.

The disease is caused by a plethora of different microorganisms. In many community-acquired cases, bacteria from the oral cavity, skin, and upper respiratory tract reach and infect the native valves, including viridans streptococci and staphylococci **(**11**)**. One specific example of a bacterium originating at one of the aforementioned locations and causing infective endocarditis is *Streptococcus sanguinis*, one of the top causes of infective endocarditis **(**14**)**. This bacterium often forms biofilms in the oral cavity. Biofilms of this bacterium can detach and enter the bloodstream, leading to bacteremia. The bacteria make their way to the heart where they attach to the endothelium by forming biofilms which provide stability for the bacterial communities. They can attach to intracardiac devices, as well. Often, this process happens as a result of invasive dental procedures that destabilize the biofilms of *S. sangunis* colonies in the mouth.

Cases of community-acquired infective endocarditis have also been traced to *Streptococcus Bovis* and Enterococcus species from the gastrointestinal tract and the genitourinary tract, respectively **(**11**)**. Some of these bacteria can also reach the heart through the use of intravenous drugs, as *S. sanguinis* has been documented to do **(**14**)**.

The occurrence of nosocomial native valve endocarditis is similar. Bacteremia occurs during procedures, such as intravascular catheters, causing infection in the heart **(**11**)**. The bacterium *Staphylococcus aureus* is usually observed in such cases. This bacterium is known to build biofilms when it causes infections in the human body, likely on the endothelium, as well as on intracardiac devices, in cases of infective endocarditis **(**15**)**.

Infective endocarditis can also occur on prosthetic valves. If it occurs within two months after surgery was done to put in the prosthetic valve, it is classified as a nosocomial disease, and it is usually because of the contamination of the valve during surgery or some episode of bacteremia shortly after surgery **(**11**)**. Such events are caused by microorganisms such as *S. aureus* and coagulase-negative

staphylococci, among others. In some cases, coagulase-negative staphylococci have been observed to cause nosocomial infections on the prosthetic valves well after the two-month timeframe under which most nosocomial infections are classified. This is because such infections have a delayed onset. Furthermore, many cases involving coagulase-negative staphylococci within the first year after surgery are methicillin-resistant. The causes of cases of prosthetic valve endocarditis that occur more than twelve months after surgery are analogous to those that cause community-acquired native valve endocarditis.

The bacterium *Mycobacterium fortuitum* has also been shown to cause prosthetic valve endocarditis on an aortic porcine valve months after surgery **(**16**)**. This particular bacterium was interesting because it did not present with all of the structural damage that other bacteria cause, such as vegetation (which will be discussed later). However, it did produce biofilms on the heart valves, leading to inflammation, which is seen in all cases of infective endocarditis.

S. aureus and coagulase-negative staphylococci also lead to infections on implanted intracardiac devices, such as pacemaker leads and defibrillators **(**11**)**. These infections are classified as nosocomial infections, as well, because they occur during invasive procedures in the hospital. Infective endocarditis, both on native valves and prosthetic valves which develops within a few weeks of the procedures. Now that the etiology of infective endocarditis has been reviewed, the pathogenesis of the disease can be discussed.

First, it is important to understand that none of the aforementioned microorganisms (with the exception of *S. aureus* in certain cases) can infect the heart unless the endothelium of the endocardium is injured **(**11**)**. Bacteria are not able to infect a healthy endothelium. Usually, the endothelium can be damaged over time by numerous diseases and conditions such as hypertension, hypercholesterolemia, ventricular septal defects, and rheumatic heart disease, among others, as well as other risk factors and activities such as aging and smoking **(**11 & 17**)**. This can result in two things: the formation of lesions and the formation of thrombi in the heart **(**11**)**. The former can happen when injuries cause small tears in the endothelial layer. The formation of thrombi, however, is more complex. The endothelium naturally has high levels of antithrombotic factors, which decrease clot formation that promote the regular flow of blood in the heart and blood vessels **(**18**)**. When the endothelium is damaged, the levels of those antithrombotic factors fall while the levels of prothrombotic factors, which increase clot formation rise, resulting in some cases in the formation of uninfected platelet-fibrin thrombi, which leads to nonbacterial thrombotic endocarditis **(**11 & 17**)**. Regular thrombi can also develop because of injury to the endothelium. Both lesions and thrombi can contribute to the development of infective endocarditis.

Some bacteria can directly infect open lesions and surrounding endothelial cells. Examples of such bacteria include *S. aureus* and *M. fortuitum*, both of which create biofilms to attach directly to the endothelial lining of the heart **(**11 & 16**)**. However, most other species of bacteria attach to thrombi **(**11**)**. Often, many bacteria die soon after coming into contact with a thrombus. The body has two ways to fight bacteria after they attach but before they start to multiply. The first way involves blood serum and its bactericidal activity. The second way involves platelets. While platelets are known for their role in forming clots to prevent blood loss and to encourage tissue regeneration, they also play a vital role in defending the body from pathogenic microorganisms **(**19**)**. Platelets fight such microorganisms in many different ways, but their main response to bacteria especially in the heart is the release of antimicrobial peptides: proteins that kill bacteria **(**11 & 19**)**. It has previously been shown in rabbits that infective endocarditis only developed if the bacteria causing it in this case, various strains of viridans streptococci are resistant to the effects of platelets **(**20**)**. In other words, they must survive after adhering to a surface to colonize the area. Since then, some of the specific antimicrobial peptides that cause certain bacteria to die have been better understood. Examples include platelet factor 4 and thymosin β-4 both of which have been shown to affect *S. aureus* and other species of bacteria, reducing their concentrations in lab tests **(**21**)**.

If the attached bacteria can survive both the serum and the platelets, they start to multiply and cause the development of a procoagulant state by using the tissue factor of the monocytes (white blood cells**)** that are near or on the endothelial lining **(**11**)**. This causes large amounts of fibrin to collect in the area. They combine with clusters of platelets that are already near the injured area (because of the tissue factor and bacteria**)**. This leads to the development of infected vegetation in the injured area. The term vegetation is used to refer to lesions where platelets, fibrin, microorganisms, and inflammatory cells have accumulated **(**11**)**. They are very common in cases of infective endocarditis most often on valves in the left side of the heart, including the mitral valve and the aortic valve **(**22**)**.

When the bacteria in such vegetations initially tried to adhere to the epithelium, it did so by using surface proteins **(**11**)**. Gram-positive bacteria and streptococci use fibronectin-binding proteins and glucans, respectively, whereas other bacteria such as *S. aureus* use various clumping factors, proteins that bind to both fibrinogen and fibrin to attach to the epithelium **(**11 & 23**)**. These same surface proteins are used to attach more fibrin to the vegetation, causing it to grow bigger.

Ordinarily, the coagulation that leads to such vegetation would not occur in the heart. The endothelium's antithrombotic factors would limit clot formation, thereby preventing both thrombi and procoagulant structures in the heart **(**18**)**. However, because of the damage to the endothelium, the levels of these factors in the endothelial layer of the endocardium decrease **(**17**)**. Therefore, the size of vegetation can

keep increasing without anything stopping it. Even when bacteria on the outer areas of the vegetation are destabilized by blood rushing through the heart, other bacteria take their place, along with more fibrin and platelets (11). With the body's defenses already weakened before even the infection of the microorganisms occurs, bacteria can thrive during the development of infective endocarditis, leading to more complications and diseases.

Relevance to Human Health and Microbiology

The pathogenesis of infective endocarditis shows us how bacteria can invade the body and take advantage of damaged areas. However, it does not stop there. Many different diseases and conditions can arise as a result of infective endocarditis. It is important to understand both the etiopathogenesis of infective endocarditis and the development of diseases and problems related to the illness to better understand how harmful bacteria affect human health, as well as how to stop them from doing so. A few of the major complications that may occur as a result of infective endocarditis are discussed below.

Vegetation present most often on the mitral and aortic valves (22). In the mitral valve (an atrioventricular valve), leaflet dysfunction is the major cause of valvular destruction (24). In other words, vegetation on the mitral valve occurs on the leaflets, the cusps that open and close on the atrial side of the valve, specifically on the line of closure thus preventing the valve from closing properly (24 & 25). This is because the vegetation interferes with the leaflets, and they are not able to seal the passageway between the left atrium and the left ventricle properly, resulting in holes. Thus, when the left ventricle contracts to push blood out of the heart and into the aorta to be taken to the rest of the body, some blood goes back through the holes between the leaflets and back into the left atrium, which experiences increasing pressures (26).

This leads to reduced cardiac output (27). The left ventricle does not push enough blood out of the heart and into the body. When the ejection fraction (the proportion of blood in the ventricle that is pushed out of the ventricle) falls under 50%, congestive heart failure has officially developed. To incorporate the lower amounts of blood being ejected, heart rate often increases, as well. Congestive heart failure is the most common complication of infective endocarditis, and it can lead to other problems.

One of the diseases that can develop because of congestive heart failure in the left side of the heart and the increase in atrial pressure is pulmonary hypertension, occurring when the mean pulmonary artery pressure reaches at least 25 mmHg (27 & 28 & 29). When atrial pressure rises, pressures in the pulmonary veins rise, as well (29). This can cause damage to the veins, as well as the alveoli in the lungs

resulting in alveolar-capillary stress failure. The capillaries start to leak, leading to alveolar edema. While this damage can be fixed if the patient is treated on time and effectively, high pulmonary venous pressure for long periods can cause the permanent remodeling of the alveolar-capillary membrane. Pressures continue rising and damaging the lungs even more. They also rise in the pulmonary arteries, which can raise the pressures in the right ventricle leading to right ventricle dilation. When this occurs, the ventricle grows bigger and thinner to handle the higher pressures and hold greater amounts of blood. However, because the heart muscles have thinned, it is harder for the right ventricle to pump blood. A negative correlation between right ventricular ejection and the pressure in pulmonary arteries has been documented **(**30**)**. This means that severe or prolonged pulmonary hypertension lowers the ability of the right ventricle to properly pump enough blood into the pulmonary circulatory system. The right ventricle, thus, starts to fail **(**29**)**. This event also brings about the dilation of the tricuspid annulus, leading to higher levels of tricuspid regurgitation and right ventricular dysfunction **(**29**)**. Thus, mitral regurgitation caused by the development of vegetation in cases of infective endocarditis can impact all parts of the pulmonary circulatory system, the chambers of the heart, the lungs, and the pulmonary arteries, veins, and capillaries. Combined with the congestive heart failure occurring as a result of the left ventricle, this can have dire consequences.

Pulmonary hypertension and congestive heart failure and other associated diseases can also occur as a result of aortic regurgitation, which has similar pathophysiology to mitral regurgitation, caused by infective endocarditis **(**25 & 27 & 31**)**. Therefore, infections on aortic valves are also very important. Congestive heart failure in infective endocarditis cases occurs more often as a result of complications with the aortic valve than the mitral or tricuspid valves which are the second and third-most-common reasons for heart failure in infective endocarditis **(**9**)**.

Another problem that can occur in cases of infective endocarditis once again relates to vegetation. Sometimes, parts of it can break off or embolize. This is most likely to happen with large vegetations on the mitral valve **(**32**)**. They are pumped out of the heart with oxygenated blood and can travel to different parts of the body, including the brain which is affected in about 25% of infective endocarditis cases **(**33**)**. The most common neurological problem that occurs is an acute ischemic stroke which happens in 20-40% of patients **(**32**)**. It occurs when the vegetation blocks blood flow to the brain in the cerebral artery, causing damage. Other times, however, the piece of vegetation may not be big enough to block a blood vessel. It may be that only a few bacterial cells broke off from the site of the infection in the heart. This can also lead to devastating complications. Infectious intracranial aneurysms can occur in 2-4% of patients **(** 32**)**. Bacteria infect the vasa vasorum of cerebral vessels such as the cerebral artery, destroying the vessel wall. This leads to the development of aneurysms. In some cases of infective endocarditis (about 1-20%**)**, meningitis can also occur from bacteria traveling to the brain **(**32**)**. It most often occurs

as a result of *S. aureus* or enterococci. It develops when bacteria infect the meninges, and it can be very fatal **(** 34**)**. All of these neurological conditions along with others such as hemorrhage and cerebral abscesses can lead to encephalopathy, or permanent brain damage **(**32**)**.

From a public health and healthcare perspective, infective endocarditis is a relevant disease that is rightfully being studied. It infects and kills many people each year. It causes numerous other painful complications that often either result in permanent damage to various organs or death. Therefore, it is important that we not only find effective treatments for it, but we look for possible cures, as well. The illness is also relevant from a microbiology perspective. Contemporary treatments for infective endocarditis require the use of numerous antibiotics for extended periods. This can lead to other problems, such as antibiotic resistance. Thus, microbiologists must find better ways to deal with bacterial infections.

Treatment modalites For Infective Endocarditis

Since infective endocarditis is caused by bacteria, a treatment that is similar for both native valves and prosthetic valves (besides the duration of doses**)** is centered around antibiotics **(**11**)**. However, it can be difficult for a few reasons **(**11**)**. Host defenses cannot reach much of the bacteria on vegetation. Beyond that, the bacteria have stopped growing and are no longer metabolically active. To eradicate the infection, though, all the bacteria must be killed. Thus, antibiotics are given for longer periods and are given intravenously to ensure that their concentrations in the blood serum reach and maintain high levels. Such levels are required for the antibiotics to kill bacteria in all parts of the vegetation.

The antibiotic given to a patient depends on the microorganism causing the disease **(**11**)**. Until the specific species of bacteria can be detected, however, doctors must proceed with empirical therapy — which usually includes either vancomycin or ampicillin (with sulbactam, a β-lactamase inhibitor**)**, along with an aminoglycoside such as gentamicin **(**11& 35 & 36**)**. This combination of different antibiotics is given to account for all of the different bacteria that could potentially have caused the disease since, at this point, it is not certain which one did. Sometimes, this is all that is given and people can recover (although it may take longer than organism-specific therapies**)**. Other times, however, it is important to specify the causative microorganism. Once the specific bacteria behind a case of infective endocarditis is determined, organism-specific antibiotic therapy can begin. Some treatments for the most common causative microorganisms are described below.

When infective endocarditis is caused by viridans streptococci or *S. bovis*, either penicillin G or ceftriaxone is usually given to patients, in some cases with gentamicin **(**11 & 36**)**. These regimens are given for two to four weeks, depending on the antibiotics given. Some strains of viridans streptococci or *S. bovis* may be penicillin-resistant. Depending on how resistant they are, the aforementioned regimens can still be given, albeit for longer periods. If the bacteria are fully resistant, ampicillin and gentamicin are given together for four to six weeks.

To treat infective endocarditis caused by enterococci, a cell wall-active antibiotic is used, along with an aminoglycoside **(**11**)**. Most enterococci are susceptible to penicillin and ampicillin, both of which are antibiotics that target the cell wall **(**11 & 36**)**. They are given with aminoglycosides such as gentamicin or streptomycin for four to six weeks. For strains that are resistant to penicillin, sulbactam is also given with ampicillin and gentamicin for six weeks to destroy β-lactamases and increase the efficacy of ampicillin **(**35 & 36**)**.

When infective endocarditis is caused by staphylococci, slightly different antibiotics are used. Most are resistant to penicillin because they produce penicillinase to destroy the antibiotic **(**11**)**. Therefore, antibiotics such as nafcillin, oxacillin, or cefazolin are given to patients for six weeks **(**36**)**. The use of gentamicin is optional and is only restricted to three to five days if used (in cases where the bacteria are susceptible to it) to prevent complications associated with it **(**11 & 36**)**. Treatment can differ depending on whether or not prosthetic valves or intracardiac devices are present and affected in the heart **(**11**)**. If bacteria are growing on the surfaces of the aforementioned objects, rifampin is often used in addition to the other antibiotics mentioned above. It is effective in killing those bacteria that are sticking to the surfaces.

Sometimes, however, surgery may be needed. In some cases, antibiotics are not able to bring the infection under control **(**11**)**. The infection can keep growing and spreading, leading to more invasive diseases such as perivalvular cellulitis and intracardiac fistulae **(**11 & 37**)**. In such cases, the areas where the infection has spread to (areas of cellulitis, fistula, etc.) are found and operated on first **(**37**)**. Any foreign material in these areas is removed to clear the infection and prevent future infections. Then, surgeons either repair the existing valves or replace them with grafts of human tissue or bovine tissue. Surgery can also be required for certain cases of prosthetic valve endocarditis, as well as cases with large emboli and vegetations **(**37**)**. The process is very similar. Surgery at the proper time greatly reduces the chances of heart failure or other advanced cardiac diseases, as well as the mortality rate of infective endocarditis, in most patients **(**11**)**.

Challenges

Even though infective endocarditis has been studied for centuries, there are still many challenges associated with both the disease and its treatments. Some include the difficulties encountered in trying to kill the bacteria. Others revolve around the diagnosis and treatment regimens of the disease, including the use of antibiotics and their interactions with bacteria.

There are a few challenges that make it hard to kill the bacteria causing infective endocarditis. Firstly, the vegetations that develop in patients house high numbers of bacteria, many of which are so deeply buried that antibiotics may not always be able to reach them **(**11**)**. Thus, if proper concentrations of antibiotics are not reached, some bacteria can still survive treatment. The second challenge is caused by persister cells which are dormant cells that are tolerant to the effects of antibiotics that are present in some colonies of bacteria **(**38**)**. *S. aureus* are known to contain persister cells in their colonies **(**39**)**. They form biofilms (which protect the microorganisms) on cardiac tissues, as well as on intracardiac devices. These biofilms house persister cells that can survive the antibiotic regimens given to patients. Thus, even if it seems that bacteria have been eradicated and the patient no longer has infective endocarditis, the disease can develop again when the persister cells start to multiply. This can make it very hard to kill all of the bacteria resulting in a person having chronic infective endocarditis (as well as much more serious complications) unless surgery is done.

The other challenges that are caused by infective endocarditis are associated with the diagnosis and treatment regimens of the disease. The first of these challenges involves the time it takes to diagnose the disease **(**40**)**. It can be tough to tell if a person has infective endocarditis by just their clinical presentation **(**40**)**. Further tests are often required. The entire process can take some time, which delays the start of antibiotic therapy. Such delays can lead to the development of major complications and diseases. In some cases, it can also lead to death. To avoid this, doctors must diagnose the disease quickly and start treatment.

The next challenge arises as a result of the treatment regimens. Antibiotics can have many adverse effects. Some take only a few days to develop, while others may take longer. One of the conditions that can develop shortly after taking antibiotics is nephrotoxicity **(**11**)**.

Gentamicin, which is sometimes used to treat infections caused by *S. aureus* (among other bacteria) can cause renal dysfunction, even when given in low doses for a few days **(**41**)**. That is why it is important to limit its use often to a low dose for only four to five days if possible **(**11 & 36 & 41**)**.

Infective endocarditis can be caused both by bacteria that are susceptible to antibiotics, as well as resistant to antibiotics. Since high amounts of antibiotics are given for many weeks to patients with the disease, the development of antibiotic resistance is common. When antibiotics are given, the bacteria that are susceptible to the antibiotics die, while the resistant bacteria survive **(**42**)**. The survivors then multiply. The new population, therefore, is resistant to the antibiotics, which makes it harder to treat diseases caused by those microorganisms. Bacteria are also able to share their genetic material through transformation, transduction, and conjugation. Bacterial cells with genes that code for resistance against a certain antibiotic pass those genes often using plasmids to bacterial cells that lack such genes. This also allows more of the population to become resistant to certain antibiotics once again making it harder to treat patients. The rate of horizontal gene transfer is even higher in communities of biofilms **(**43**)**. In other words, bacteria that form biofilms in the heart can share genes more easily among one another, and populations develop antibiotic resistance faster. This is because biofilms keep bacteria close to each other, making processes such as conjugation and transformation happen more often.

Antibiotic resistance has already been observed for multiple strains of bacteria that cause infective endocarditis, including enterococci strains and *S. aureus* strains **(**44**)**. Enterococci can develop resistance against most antibiotics, while *S. aureus* can be resistant to β-lactam antibiotics such as penicillin and methicillin because they produce β-lactamases. There are many cases each year caused by such bacteria. They start to develop resistance to a greater number of antibiotics (including vancomycin, which is used very often) because of long antibiotic therapies, making it harder to treat infective endocarditis.

Infective endocarditis is a serious disease that kills many people each year and infects many more. Because of the many challenges and problems associated with antibiotic use, it is important to find better ways to deliver treatment that will allow treating the disease without causing more problems. To achieve this, a more targeted approach is needed, one that will only allow antibiotics to be used in the heart.

In recent years, the use of nanomaterials to carry antibiotics to different parts of the body has been studied **(**45**)**. The effect of nanoparticles carrying penicillin G on methicillin-resistant *S. aureus* has shown promise in recent studies **(**46**)**. The antibiotics were able to kill the bacteria, even though they were resistant to the drugs because the nanoparticles prevented the antibiotics from being destroyed by β-lactamases. Therefore, the use of nanoparticles in cases of infective endocarditis caused by resistant forms of bacteria may also make treatments for such bacteria more effective.

However, what this research mainly demonstrates is that nanoparticles can carry antibiotics effectively. Right now, though, more research is needed to determine which nanoparticles are safe to use. Since the heart is such a delicate and complex organ, the use of most nanoparticles is too dangerous. However, in a recent study aimed at understanding the use of nanoparticles in heart theranostics, certain upconverting nanoparticles that do not adversely affect cardiac function have been identified **(**47**)**. While this research is new and does not directly pertain to antibiotics, it could be used to help create nanoparticles that can carry antibiotics directly to vegetation in the heart. These nanoparticles would be designed such that they only release the antibiotics once they reach the heart. This targeted therapy could decrease the amount of time antibiotic regimens need to be given, as well as the amount. Thus, treating infective endocarditis without causing other problems would be much easier.

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