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Infection of the periprosthetic joint: Current views and forecasts

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Abstract
Infections of the periprosthetic joint are catastrophic complications that can arise following arthroplasty. They are also associated with a significant increase in patient morbidity. More than twenty-five percent of all changes can be traced back to these illnesses, and it is anticipated that this number will continue to rise. This rise can be attributed, in part, to the rising rates of obesity and diabetes, as well as to an increased incidence of other comorbidities. Recognition of the difficulty of surgical site infections in general, and periprosthetic joint infections, has prompted implementation of enhanced prevention measures preoperatively, intra operatively (Ultraclean operative environment, blood conservation, etc.), and postoperatively. These enhanced prevention measures can be divided into three categories: preoperative, intraoperative, and postoperative (Refined anticoagulation and improved wound dressings). Indications for surgical management have also been refined, which is another positive development. In this Review, we investigate the risk factors, preventative measures, diagnostic procedures, clinical characteristics, and treatment choices associated with prosthetic joint infection. The most effective treatments and areas in which more investigation is required were determined during a meeting of experts worldwide to discuss these infections. Improvements in preventive, diagnostic, and treatment procedures could benefit the field of orthopedics.

Keywords: Periprosthetic joint infection, arthroplasty, biofilm, diagnosis, treatment

1. Introduction
Infection of the periprosthetic joint (PJI) affects 1% to 2% of primary and 4% of revision arthroplasties. The number of prosthetic joints that have been implanted is steadily increasing because of longer life expectancies, changing lifestyles among an aging population, and increased demands for mobility as people age [1]. The number of PJI patients likewise climbs rapidly along with the number of implantations. Over the implant's lifetime, longer prosthesis indwelling duration is linked to a higher overall risk for hematogenous infections. Even persistent illnesses that would have gone unnoticed in the past are now found thanks to the advancement of sophisticated detection techniques for microbial biofilms [2, 3].
The management of PJI necessitates sophisticated therapeutic approaches, such as numerous surgical revisions and protracted antimicrobial therapy. The best treatment plan to get rid of the infection must start with a precise diagnosis that includes the identification of the infecting microorganism(s) and its antibiotic susceptibility. When PJI is ignored or undertreated, the illness persists, requiring numerous surgical revisions that significantly reduce the quality of life. The treatment of PJI involves a variety of specialists with various methodologies, including orthopedic and plastic surgeons, infectious disease doctors, and microbiologists. For the best results, this interdisciplinary approach is essential. Regarding the pathophysiology, diagnosis, classification, and therapeutic strategy for PJI, we offer a perspective on current management methods in this review article [4-6].
Arthroplasties on the hip and knee are effective elective surgical procedures, with a 10-year survival rate of more than 95%. According to estimates, 1% of hip and 1% to 2% of knee arthroplasties each year result in periprosthetic infection. However, an analysis of patients who had primary arthroplasty from 2006 to 2009 suggested that infection rates (more than 2%) may be higher than previously thought.

Additionally, infections were the most frequent reason for revisions (25%) following knee arthroplasty and accounted for 14.8% of revisions following hip arthroplasty. Most early infections are thought to happen during implantation and are caused by external sources from the operating room or endogenous skin bacteria [7]. Patients with periprosthetic joint infections frequently need prolonged antibiotic regimens in addition to further operations. The emergence of antibiotic resistance is a worry, though. The creation of new antimicrobials has slowed over the past few decades, which has limited the alternatives available to fight resistant pathogens.

According to one study, *Staphylococcus* aureus and *Staphylococcus* epidermidis which are both methicillin-resistant and methicillin-sensitive, are the most often isolated microorganisms. Gram-negative and coagulase-negative staphylococci infections were less common, according to researchers from other studies. Up to 23% of Enterococci species and up to 46.7% of S aureus strains in the USA are vancomycin-resistant [8]. Nearly 9% of Enterococci spp. are vancomycin-resistant, 15% of S aureus strains are methicillin-resistant, and 12% of Streptococcus pneumoniae strains have decreased penicillin resistance. A subset of methicillin-resistant S. aureus (MRSA), which first surfaced in 2001, has demonstrated decreased vancomycin susceptibility. The advent of these resistant organisms is concerning, necessitating the development of new medications with innovative modes of action. The morbidity and mortality of the patient may increase as a result of these infections. These problems highlight the significance of the issue and the growing burden it is posing on healthcare systems [9-11].

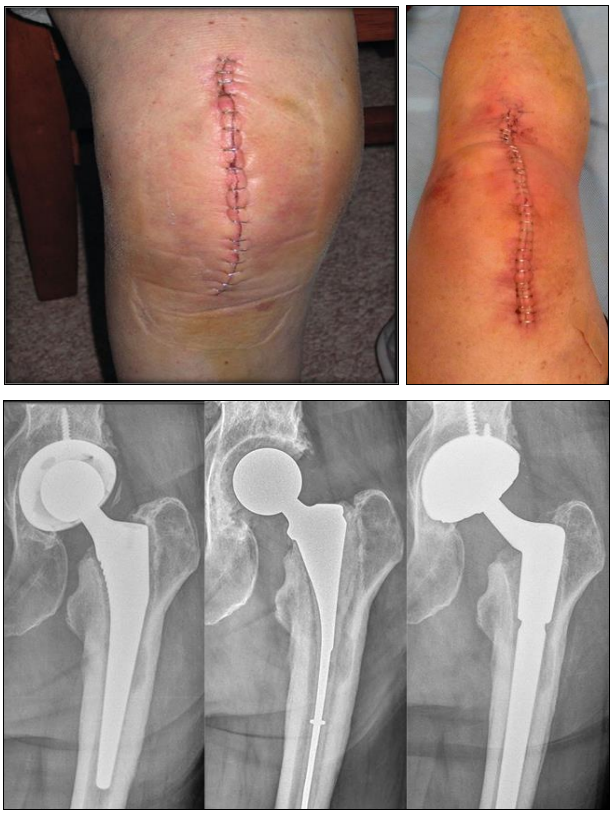

Fig 1: Periprosthetic joint infection

Pathogenesis

There are several ways that infections can spread, including recurrent infections, hematogenous spread from different body sites, and direct seeding from external pollutants or contiguous dissemination. In environments with foreign bodies, infection susceptibility is elevated and may lead to biofilm development, a bacterial adaptation in implant-associated illnesses. Microorganisms are inoculated intraoperatively in about two-thirds of PJI cases. Depending on the virulence of the microbes, PJI may show symptoms immediately or after some time. Early infections are typically brought on by pathogenic microorganisms and show clear local and systemic indications of inflammation. Low-virulent organisms induce delayed infections, which show softer signs, including joint soreness and early loosening [12-14]. Germs initially attach to the prosthesis, but research in animal models demonstrates that the number of bacteria required to cause infection is much lowered when a foreign body is present (by a factor of more than 100000).

Additionally, interacting with a foreign body might cause neutrophil defects, which increase an infection's susceptibility. Microcolonies of bacteria that are attached to the prosthesis grow and are enclosed in glycocalyx (biofilms). Deep within the biofilm, organisms are shielded from host defenses [15]. Patients and the operating environment are two causal factors that can cause periprosthetic joint infections. Although the patient, risk factors, and comorbidities influence the pathogen type, the properties of the organism and the timing of the infection are equally crucial for determining causality. For instance, S aureus small-colony variations have been found when routine antibiotic treatment for periprosthetic joint infection has failed. These strains are subpopulations with sluggish growth rates and distinctive characteristics. Additionally, some patients with infections have negative cultures and may require empirical antibiotic therapy; however, this therapy should be postponed until a microbiological diagnosis is confirmed, apart from severe sepsis cases [16].

Epidemiology

The epidemiology of periprosthetic joint infections differs by country regarding microbes and resistance. Methicillin-resistant and methicillin-sensitive S aureus and methicillin-resistant and methicillin-sensitive S epidermidis are the most prevalent microorganisms in the USA. Most coagulase-negative *Staphylococcus spp*., as well as S aureus, streptococcus, and enterococcus species, have been found in Europe. Reoperations, extended recuperation periods, and prolonged usage of antibiotics and analgesics have all been linked to these expenses. The anticipated increase in revision procedures represents a financial burden that could destabilize the global healthcare system. Up to 23% of infected patients report being satisfied with their surgery, while 18% are wholly unsatisfied. Individuals with periprosthetic joint infections have a lower health-related quality of life than patients with straightforward arthroplasty. Infected patients do not regain the functionality that equivalently matched groups do. High mortality is caused by infections; after two-stage hip revisions for infections, the all-cause mortality rate within two years might reach 25%. Recurrent infections have been reported to have a mortality rate as high as 45% at a mean age of 4 to 7 years [17-19].

Risk factors

Periprosthetic joint infection risk is influenced by a variety of patient-specific comorbidities and demographic factors. Important risk factors include joint infections of any kind, septicemia, active cutaneous or deep tissue infections, and blood transfusions. Uncontrolled diabetes, malnutrition,

morbid obesity, use of tobacco and alcohol, disorders that compromise the immune system, drug use, and nasal carriage of S aureus are only a few patient-specific variables. After general surgery and orthopedic treatments, diabetes increases the risk of infection; nonetheless, total joint arthroplasty results can vary. According to some studies, diabetes individuals have infection rates that are seven times greater than those of non-diabetic patients. Obese patients' post-arthroplasty results are frequently described as having poor wound healing, persistent drainage, and high infection rates [20]. Long operating hours, more allogeneic blood transfusions, and comorbidities are all linked to greater risks.

Additionally, patients who are obese have reduced antibiotic tissue penetration, which may fall below minimal inhibitory limits, increasing their risk of infection. Weight-based perioperative antibiotic adaptation is spread due to problems with antibiotic administration in obese patients. Poor surgical results are brought on by smoking and drinking. Deficient wound healing has been attributed mostly to nicotine-mediated vasoconstriction. Tissue hypoxia and a rise in infection susceptibility are the effects of poor circulation. Preoperative smoking cessation advantages have been highlighted in multiple meta-analyses spanning several surgical subspecialties, which reduce postoperative infections by more than 50%. After arthroplasty, drinking excessively increased the risk of postoperative complications and periprosthetic joint infections. Drug use related to immune-compromising disorders is a separate risk factor. Patients who are infected with both HIV and hepatitis C may be in danger. Fortunately, long-term survivability comparable to that of healthy patients may be achieved with undetectable viral loads and CD4 cell counts of more than 400 cells per ml. Glucocorticoids, cytostatic, interferon, and tumor necrosis factor inhibitors are examples of immunosuppressive medications that have a deleterious impact on postoperative results [21, 22].

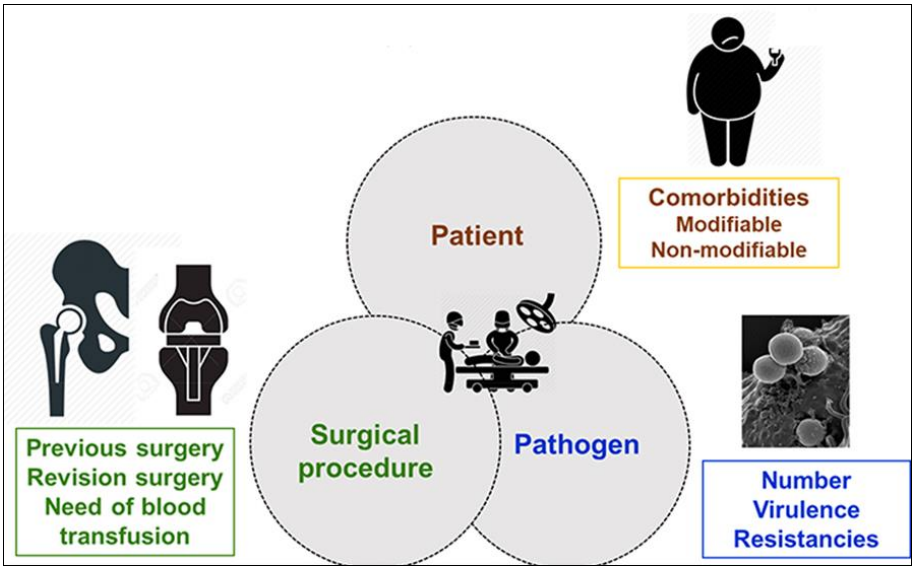

Fig 2: Risk factors of periprosthetic joint infections

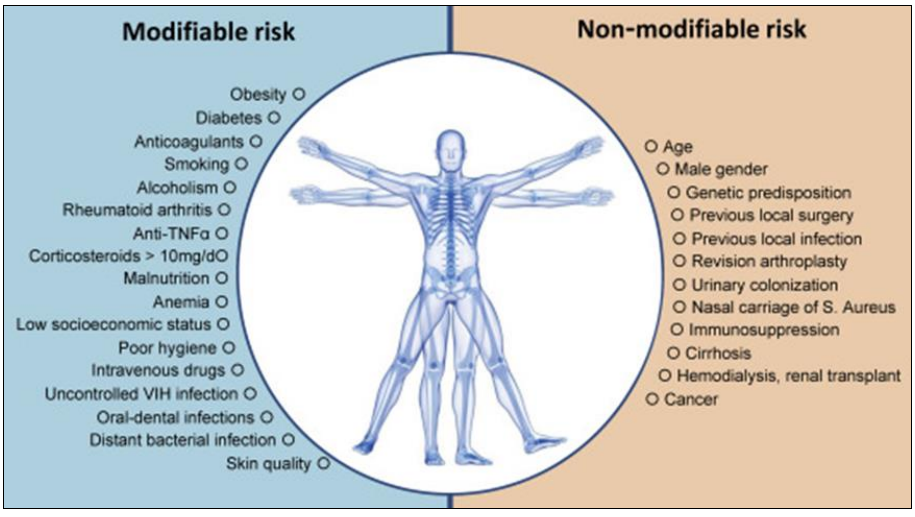

Fig 3: Patient-specific risk factors for infection in arthroplasty procedure

The understanding that every illness condition has a genetic basis is one of the latest advances. Numerous genome-wide association studies have been conducted since the human genome was sequenced, revealing the genetic underpinnings of disease. Periprosthetic joint infection may have a hereditary component. Recognizing this genetic foundation for infection could therefore be a positive step [22].

Preventive actions

In the USA, 12-23% of all periprosthetic joint infections are caused by methicillin-resistant S aureus. Nasal and cutaneous decontamination, which attempts to reduce endogenous bacterial burdens and prevent infections, has been questioned regarding its efficacy. Nasal carriers of high concentrations of S aureus are three to six times more likely to get an infection

than non- or low-level carriers. The application methods used in different research vary, particularly in terms of the timing of the treatment, which produces inconsistent findings. A randomized, double-blinded, multicenter experiment compared the effectiveness of nasal mupirocin ointment and chlorhexidine for screening and decolonization to a placebo. S aureus infections occurred more frequently in the placebo group than in the research group, according to reports [23]. Mupirocin has not been associated with an infection reduction in other studies evaluating it for orthopedic and general surgery patients. Preoperative mupirocin was evaluated for cost-effectiveness in patients who had total joint arthroplasty. The costs and advantages were evaluated for three fictitious cohorts: preoperative screening, empirical preoperative therapy with mupirocin without screening, and neither preoperative nor treatment for patients with S aureus culture positivity. The treat everyone strategy and the screen and treat everyone found to be a carrier strategy were less expensive than not treating anyone [24]. To determine the effectiveness of screening followed by decolonization, controlled randomized trials are required. The Centers for Disease Control and Prevention support the use of preoperative antiseptics.

Bathing, antiseptic soaps, iodine-based antiseptics, and medications based on chlorhexidine gluconate are only a few examples of skin treatments that have been explored. Studies reveal that chlorhexidine gluconate is more effective than solutions based on povidone-iodine. The relative risk of infection is decreased with antibiotic prophylaxis by up to 81%, while the absolute risk is decreased by 8%. According to the recommendations of the Surgical Care Improvement Project, antibiotics should be started at least 1 hour before surgery and stopped within 24 hours. Additionally, to lower expenses, pharmacological toxicity, and the emergence of antibiotic resistance, surgeons ought to think about utilizing single-dose or short-term antibiotics [25, 26].

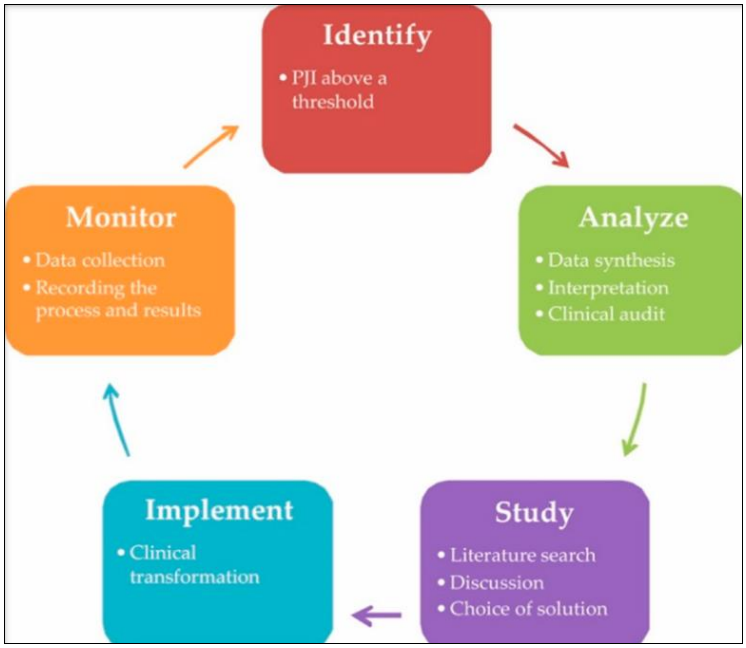

Fig 4: Preventive measures for periprosthetic joint infections

Cefazolin is advised for patients who have had total joint arthroplasty, according to the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. Vancomycin and clindamycin are recognized as suitable substitutes. Vancomycin must be utilized for MRSA-colonized patients and considered in settings where MRSA surgical site infections are common. Compared to shaving, clipper hair removal may reduce the risk of infection because shaving results in cutaneous micro lesions and promotes the colonization of endogenous flora. The general view is that using clippers; hair removal should be done right before surgery.

In various comparison studies, several perioperative skin preparations are used, such as alcohol-, povidone-, and chlorhexidine-based solutions. According to reports, iodine-impregnated drapes had no effect, whereas chlorhexidine-based solutions result in lower positive skin cultures than iodine-based groups with adhesive draping [27]. To dilute and minimize wound contamination particles, vertical-flow and horizontal-flow ventilation have been employed to maintain ultraclean operating room air. Laminar airflow was found to lower bacterial counts in operating rooms in early experiments. However, a review of the New Zealand Joint Registry revealed that laminar flow operating rooms had much more early infections than standard operating rooms.

Elevated infection risk was found in a systematic analysis of laminar airflow and surgical site infections following total joint arthroplasty. The surgeon has the option to use laminar airflow in the case of conflicting evidence. Arthroplasties sometimes involve the use of body exhaust suites; however, their efficacy has been questioned [28]. According to certain studies, the infection rate is the same whether wearing conventional clothing or not. Arthroplasties had noticeably increased infection rates, according to a combined registry review 63. 50–67% of surgical gloves are thought to be perforated during arthroplasty, which is linked to higher infection rates. Many surgeons have started using double-gloving techniques to stop this increase in infections. However, their effectiveness has not yet been established. Intraoperative lavage during arthroplasties has not been extensively studied. With diluted betadine lavage, which may be a cheap approach, infection rates were found to have decreased by six times in a retrospective analysis. The risk of infection during arthroplasty is increased by allogeneic and autologous blood transfusions. Low preoperative hemoglobin, female sex, longer surgical times, and a high Charlson

comorbidity index are all risk factors for transfusions [29]. Tranexamic acid, bipolar sealers, cell salvage systems, and reinfusion drains may all aid in reducing blood loss. After total joint arthroplasty, the use of tranexamic acid minimizes the need for transfusions, which may lower the risk of infection. The kind of prosthesis did not impact the prevalence of periprosthetic joint infections. There is no discernible difference between cement less and cemented prostheses in the likelihood of infection. But according to statistics from an international joint registry, antibiotic-laden cement may reduce the incidence of infection compared to uncemented or non-antibiotic-laden cement. Antibiotic resistance, higher costs, and allergic reactions are issues with using antibiotics in cement, though. Patients with immuno deficiencies and diabetics at higher risk for infection may benefit from this treatment [30].

Clinical characteristics

Within three months of surgery, early post-interventional infections appear and are thought to develop during implantation. Patients often complain of pain, edema or induration, wound drainage, erythema at the surgical site, and effusion. When a wound dehisces, infections can develop and spread from the cutaneous sites to deeper tissue. Early post-interventional infections should be treated right once; imaging and diagnostic procedures cannot wait [31]. These infections are believed to develop during implantation and manifest themselves 3 to 12 months after surgery. Infectious agents, including Propionibacterium acnes, enterococci, and coagulase-negative staphylococci, are typically less virulent. Less than 50% of individuals with delayed-onset infections have a fever, and the most common symptom is ongoing joint discomfort. While delayed infections and aseptic failures may present similarly, chronic discomfort and weight-bearing pain are signs of infection, while mobility is sign of aseptic failure. Twelve months following surgery, late infections start to appear and are typically brought on by hematogenous spread from another site. The presentation is the sudden onset of symptoms in a joint that was previously asymptomatic. According to some statistics, barely 50% of cases had their source of infection determined. S. aureus, Gram-negative bacteria, and -hemolytic streptococci are to blame for most of these instances [32].

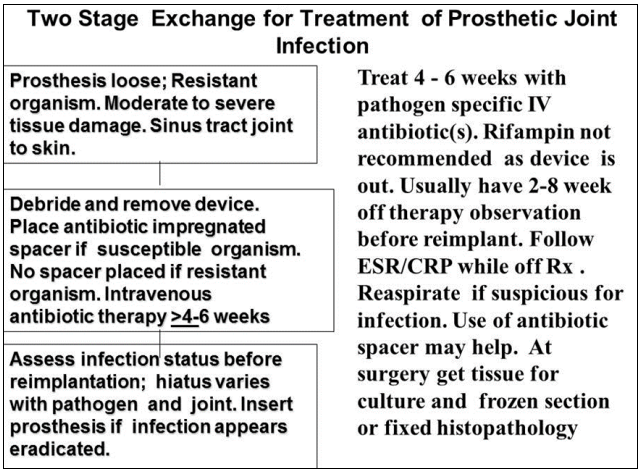

Fig 5: The periprosthetic joint infection – two stage treatment

Management prospects

Irrigation and debridement are the surgical approaches that may be used to treat early postoperative or late hematogenous periprosthetic joint infections. Success rates range from 0% to 89%, with early therapy with low virulence organisms and healthy individuals having the highest success rates. If the wound cannot be closed, irrigation and debridement should not be performed. The success rates have declined due to treating extremely pathogenic infections like MRSA [33]. According to certain research, switching to a polyethylene liner lowered the probability of failure by 33%. In a single institution's study, infection control rates were compared between a cohort of patients who had their components retained and those who had them removed and undergone two stages of revision. Final findings at a mean follow-up of 36 months revealed no differences in component retention rates. Failure was influenced by S aureus infections and polyethylene non-exchange. The most popular procedure for treating periprosthetic joint infections is two-stage exchange arthroplasty. Patients with sinus tracts, non-viable soft tissue covering, or infections with antibiotic-resistant microorganisms may benefit from two-stage modifications. Inadequate infection eradication frequently occurs when revision intervals are longer than six months. Although the length of antibiotic therapy is under question, evidence point to a 6-week course as perhaps enough in most situations [34, 35].

Before reimplantation, patients are typically maintained with a period without antibiotics to ensure that the infection is successfully treated. Even though there is limited information regarding the particular time frame, it is advised to wait 2–4 weeks before reimplantation is necessary. Since tissue-culture sensitivity was less than 50% if antibiotics were stopped less than 2 weeks before sampling, it appears that a minimum of 2 weeks is necessary. Since many germs can lay latent for years without an implant before re-emerging as an infection, some investigations have suggested that this gap may not play a significant role in recurrent infections. Success rates range from 65% to 100%, although the causes of this variation and the specific elements influencing results are unknown. According to certain researchers, negative reimplantation results are linked to positive reimplantation cultures. In contrast, only one of the five reimplantation cases that tested positive for culture in the study failed [36].

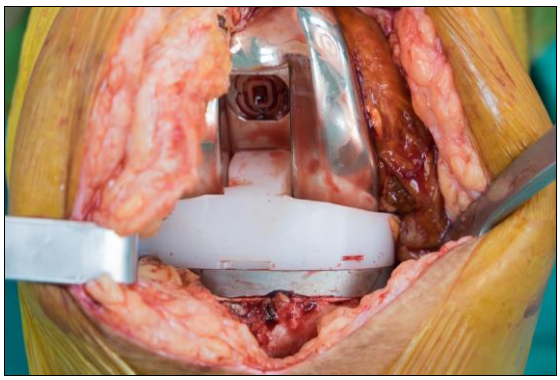

Fig 5: Periprosthetic joint infection

There aren't many reports that recommend using a one-stage exchange instead of two stages. When effective antibiotics are readily available for the organism, the one-stage exchange is seen to be a viable alternative. As much as 17% less can be spent compared to a two-stage revision. Fewer treatments are often thought to result in cheaper costs because of decreased patient morbidity, shorter operating room stays, and less need for medical supervision. The one-stage exchange may, however, result in increased rates of reinfection and higher overall expenses.

When removing a prosthesis is inappropriate, one alternative is to take long-term suppressive oral antibiotics [37]. Poor overall health, situations in which removal might lead to subpar functional outcomes, and patient preferences are examples of potential indicators. An asymptomatic prosthetic that functions are the aim of suppressive therapy, not necessarily the complete eradication of infection. At mid-term follow-up, 86% of patients reported positive outcomes. Another study found that functional prostheses were retained in 15 of 18 patients who received antibiotic suppression for 489 months. 22% of patients experienced antibiotic-related problems. However, these did not necessitate stopping the medication. The second research found a 60% 2-year survival rate without treatment failure. Increased antibiotic suppression may also postpone rather than prevent failure, as studies have shown that stopping antibiotics increases the likelihood of failure. Prospective research on patients with reduced immune systems will be instructive. It may be prudent to switch from intravenous to oral antibiotic therapy since it can shorten hospital stays and cost-effectively treat patients. This choice is appealing because of the availability of oral formulations (which achieve serum concentrations comparable to those of intravenous antibiotics). The effectiveness of intravenous-to-oral antibiotic step-down therapy is not well studied. A study of those who had S aureus osteomyelitis, however, found no differences between those who had intravenous versus intravenous to oral antibiotics. Until more research is done to fully evaluate this treatment, the surgeon may use an intravenous-to-oral step-down. Clinical results following periprosthetic joint infection are anticipated to be further improved by interdisciplinary management teams. Patients should have weekly blood tests for serum C-reactive protein and erythrocyte sedimentation rate and clinical monitoring for infection symptoms. Marker monitoring is debatable since it does not always signal the end of an illness, yet serial trends are crucial indicators of how well a therapy will work [38, 39].

Prospects

The joint function must be preserved while the underlying infection is successfully treated, and this requires good patient-adapted diagnosis and treatment based on the algorithm and interdisciplinary collaboration. For the diagnosis of PJI, routine radiographic, laboratory, and clinical examinations show minimal sensitivity. Every uncomfortable or loose prosthetic joint must undergo joint aspiration to determine the synovial fluid leukocyte count and proportion of granulocytes before undergoing revision surgery. For culture, histology, and sonication, three to five intraoperative tissue samples should be collected adjacent to the implant, together with the explanted prosthesis. A careful debridement with removal of all devitalized material and foreign entities that contain mature biofilm is the cornerstone of optimal surgical treatment. Debridement, irrigation, replacement of movable elements, and retention of the prosthesis are standard procedures for acute infections. This less intrusive procedure's outcome is stated in a contentious manner. Trials qualifying and treating individuals following the suggested algorithm, however, have produced very positive results [40]. A complete prosthesis exchange in one step is the preferred treatment for chronic infections, patients with intact or little impaired soft tissue, and patients with easily treatable microorganisms. Compared to multiple-stage revisions, this treatment is associated with lower morbidity and a better functional outcome without a discernible change in the cure rate. The current notion for antimicrobial therapy calls for 12 weeks of treatment. For the greatest results, it is recommended to include antibiotics with biofilm-active properties. These antibiotics should be used as a targeted treatment and only introduced after re-implantation of the prosthesis when post-operative wounds are dry and drains are withdrawn to prevent the development of antimicrobial resistance. It is necessary to research and develop new diagnostic techniques that are more precise, easy to use, and convenient. For swift and early detection of PJI, pathogen-specific markers in synovial fluid, such as D-Lactate (a byproduct of bacterial fermentation), are currently being tested. 90 Active or passive implant coating, carefully regulated local antibiotic administration (using hydrogels, for example), and bacteriophages for bacterial biofilm elimination are further alternatives for preventing or treating biofilm-related infections [41, 42].

Conclusions

Patients and health care organizations worldwide face a significant challenge in the form of periprosthetic infections. Patients who suffer periprosthetic joint infections have been the focus of a great deal of research and development over the last few decades, which has led to the discovery of numerous novel approaches to the prevention, diagnosis, and treatment of these infections. On the other hand, the occurrence of this issue is on the rise in tandem with an increase in the number of arthroplasty surgeries performed and the emergence of a greater number of organisms that are resistant to drugs. In addition, there has been a shift in the demographics of patients, and the incidence of comorbid illnesses, such as obesity and diabetes, has been increasing. Both factors will continue to have a detrimental impact on patients undergoing arthroplasties in the leg. To overcome this obstacle, innovative approaches to diagnosis and therapy are required. Infection prevention strategies, on the other hand, should be enhanced for the sake of patients, and healthcare staff should make it a point to stick to the most effective procedures that have been created.

Conflict of Interest

None

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