Early periprosthetic infection - one-year follow-up after DAIR procedure

Byser Bonchev[1], Teodor Ivanov[1], Teodor Yordanov[1], Luben Stokov[2], Georgi P. Georgiev[3](✉), Luben L. Stokov[4]

[1]Department of Orthopedics and Traumatology, UMHAT Sofiamed, Sofia, Bulgaria
[2]Clinic of Orthopedics and Traumatology, UMHAT "St. Anna", Sofia, Bulgaria
[3]Department of Orthopedics and Traumatology, University Hospital "Queen Giovanna - ISUL", Medical University of Sofia, Sofa, Bulgaria
[4]Clinic of Orthopedics and Traumatology, MHAT "St. Sofia", Sofia, Bulgaria

georgievgp@yahoo.com

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Abstract—During the period of 2022 and 2023, 10 patients with early infection following joint arthroplasty were admitted to the Clinic of Orthopedics and Traumatology at Sofiamed. Among them were 8 women and 3 men, with an average age of 69 years. All patients were readmitted between 18-21 days after the primary joint arthroplasty. Laboratory and microbiological investigations were conducted for all patients, followed by surgical intervention and prolonged antibiotic therapy. At a mean follow-up of 1 year and 2 months, all patients showed excellent results, except for one who died and one who was lost to follow-up.

Keywords—periprosthetic infections, endoprosthesis, DAIR.

1 Introduction

Periprosthetic infections (PPI) are fundamentally different from bone and joint infections. Even a minimal number of microbes is sufficient to trigger a PPI infection[1-5]. Pathogens causing PPI are usually found on the skin surface and can easily be transmitted during surgery and implantation of components[5,6]. Microorganisms can also infect prosthesis components hematogenously or through infected adjacent soft tissues[5].

There is no exact definition for periprosthetic infections. Classical symptoms of infection, such as fever, leukocytosis, and signs of sepsis, are often absent in PPI. Implants are foreign bodies, and the microbial load required to generate an infection is much lower[6].

The most accurate indicator of PPI is microbiological examination of intraoperative joint aspirate or tissue sample taken either intraoperatively or by biopsy. Other signs may include the presence of a fistula, dehiscence of the surgical wound or erythema

around it, prolonged secretion from the surgical wound in the early postoperative period, increased levels of inflammatory markers, and prosthetic loosening. The inability to isolate microorganism from joint fluid does not mean that periprosthetic infection is absent[6-8].

With the constant increase in the number of primary joint arthroplasties, the number of periprosthetic infections (1-2% of primary arthroplasties) is also increasing and becoming one of the main reasons for revision[8-10]. Periprosthetic infection significantly increases morbidity and mortality and becomes one of the main reasons for joint arthroplasty revision[8-10].

Successful treatment of PPI should be carried out by an interdisciplinary team including orthopedists, infectious disease specialists, and microbiologists.

Early recognition, diagnosis, and surgical treatment of periprosthetic infections increase the likelihood of success[1].

Etiology and Pathogenesis

The most common causative agents of periprosthetic infections are bacteria and fungi-coagulase-negative staphylococci, Staphylococcus epidermidis, Cutibacterium, and Enterobacter[11]. Highly virulent strains such as S. aureus, aerobic gram-negative bacilli, beta-hemolytic streptococci, and Enterococcus species are usually associated with early PPI. Meanwhile, low-virulence strains and opportunistic pathogens like Bacteroides, Acinetobacter, Cutibacterium, and others are more frequently isolated in late periprosthetic infections.

The formation of biofilm is a key pathophysiological process in the development of PPI[12] and represents the main cause of treatment failures. Several bacteria are capable of synthesizing extracellular polysaccharides that facilitate the attachment of microorganisms to the surface of implants.

Understanding the nature of biofilm and the stages of its formation are crucial for the success of treatment. Approximately 3 to 4 weeks after bacterial division begins on the implant surface, the biofilm is fully formed and represents a significant barrier to antibiotic therapy. This greatly increases the minimum bactericidal concentration, often unattainable with safe dosing regimens of oral and intravenous antibiotics[13].

Risk factors

Factors that can lead to periprosthetic infection can be divided into three groups: perioperative, intraoperative, and environmental factors.

Preoperative factors may include a history of previous infections or surgeries in the area. Patients with prior arthroplasty have a 20% higher risk of periprosthetic infection[14].

Intraoperative factors may include longer duration of surgery, influenced by the surgeon's skills, inherent bone deformities, and the equipment in the operating room[1,14].

Environmental factors include alcohol use, smoking, and increased BMI.

Classification

Classification of periprosthetic infections (*Table 1*) is primarily based on two principles[15]:

Pathogenetic - according to the mechanism of microbial penetration to the prosthesis.

Time interval from surgery to the onset of the first symptoms.

Pathogenesis	**Acute PPI** **Immature biofilm**	**Chronic PPI** **Mature biofilm**
Perioperative	Early postoperative <4 weeks postoperatively	Late (≥4 weeks postoperatively) Most commonly 3 months to 3 years
Hematogenous or contiguous	Duration of symptoms <3 weeks	Duration of symptoms ≥3 weeks

Table 1: *Classification of PPI by time.*

With the current article, we present early periprosthetic infection as one of the main issues following primary knee and hip arthroplasty, its diagnosis, and contemporary treatment trends.

2. Materials and Methods

All patients underwent the following diagnostic algorithm:

Physical examination: Presence of fever, redness around the surgical wound with or without a fistula (*Figure 1*).

Laboratory tests: Complete blood count (**CBC**), C-reactive protein (**CRP**), erythrocyte sedimentation rate (**ESR**). Leukocytosis > 2000/μL or > 70% granulocytes, CRP > 8 mg/dL, and ESR > 20 mm/h were considered indicative of periprosthetic infection. (CRP levels can be elevated during the first weeks after arthroplasty, making it a non-specific marker).

Microbiological examination: Joint aspiration.

Surgical treatment: Revision arthroplasty, sampling for microbiological examination (3-5 samples), thorough debridement of avascular tissues, lavage with aseptic solutions using "jet lavage" technique, replacement of mobile components, local application of antibiotics.

Postoperative antibiotic treatment: Combination of antibiotics according to the microbiological culture results - 14 days intravenously and 10 weeks orally.

All ten patients were readmitted between 18-21 days after primary arthroplasty. All patients exhibited erythema around the surgical scar, and four of them had a fistula opening.

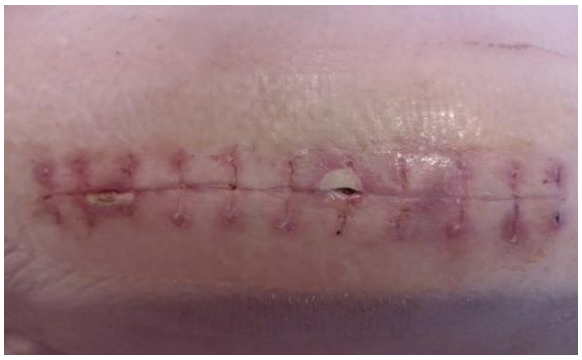

Figure 1. Fistula opening in a patient with early periprosthetic infection.

In all patients, laboratory tests showed elevated levels of leukocytes, granulocytes, CRP, and ESR, with CRP >20 mg/dL and ESR >30 mm/h.

Since patients are diagnosed within the first weeks after arthroplasty, CRP levels may be elevated, making it a nonspecific marker for infection[16].

The main criteria for hospitalization and subsequent revision for us remain the physical examination and macroscopic appearance of the surgical wound.

All patients underwent surgical intervention, including surgical debridement of avascular and infected tissues, sampling for microbiological examination from various anatomical sites, irrigation lavage with antiseptic solutions using an automated irrigation system, and replacement of mobile components. Local application of Vancomycin 4g directly applied to the tissues and implants was used in all 10 patients[17].

Microbiological examination isolated *Staphylococcus aureus* in 5 patients, *Klebsiella* in one case, *Pseudomonas aeruginosa* in one case, and no causative agent was isolated in 3 cases (*Table 2*).

Isolated microorganism	Number of patients (n)
Staphylococcus aureus	5
Klebsiela	1
Pseudomonas aeruginosa	1
Negative	3

Table 2: *Isolated microorganism.*

Empirical antibiotic therapy was initiated intraoperatively with a combination of Amoxicillin/Clavulanic acid 3x3g intravenously (i.v.) + Vancomycin 2x1g i.v. After microbiological results were available, therapy was adjusted based on specific antibiotic susceptibility.

All patients received two weeks of intravenous antibiotic administration, followed by oral antibiotic therapy with at least two antibiotics, one of which had biofilm activity. The total duration of antibiotic treatment for all patients was 12 weeks.

For culture-negative patients, empirical therapy was continued for 2 weeks intravenously, followed by a transition to oral therapy with biofilm-active antibiotics Rifampicin + Ciprofloxacin for a period of 10 weeks.

In selecting antibiotic agents, we relied on both microbiological treatment and the latest version of the Pocket Guide to PPI Treatment issued by the PRO-IMPLANT Foundation[2] (*Figure 2*).

Empirical antibiotic therapy:
- Ampicillin/sulbactam 3 x 3 g IV or amoxicillin/clavulanic acid 3 x 1.2 g IV (+/- vancomycin 2 x 1 g IV in septic patients, known MRSA carriers, multiple previous surgeries, suspected low-grade infection)

Interval/suppressive therapy

Micro-organism	Antibiotic (according to susceptibility, dose see table below)
Staphylococcus spp.	Cotrimoxazole, doxycyclin, clindamycin
Streptococcus spp.	Amoxicillin, clindamycin, levofloxacin
Enterococcus spp.	Amoxicillin, (linezolid)
Anaerobes (gram-positive)	Clindamycin, amoxicillin, doxycycline
Anaerobes (gram-negative)	Metronidazole, clindamycin
Gram-negative organisms	Ciprofloxacin, cotrimoxazole
Fungi (*Candida spp.*)	Fluconazole

Targeted eradication therapy (de-escalate as soon as the pathogen is known)

Micro-organism (red: difficult-to-treat)	Antibiotic[a] (check pathogen susceptibility before)	Dose[b]	Route
***Staphylococcus* spp.**			
- Oxacillin-/methicillin-susceptible	Flucloxacillin[c]	4 x 2 g	IV
	(+/- Fosfomycin[d])	(3 x 5 g)	IV
	for 2 weeks, followed by (according to susceptibility)		
	Rifampin[e] +	2 x 450 mg	p.o.
	- Levofloxacin or	2 x 500 mg	p.o.
	- Cotrimoxazole or	3 x 960 mg	p.o.
	- Doxycyclin or	2 x 100 mg	p.o.
	- Fusidic acid	3 x 500 mg	p.o.
- Oxacillin-/methicillin-resistant	Daptomycin or	1 x 8 mg/kg	IV
	Vancomycin[f]	2 x 1 g	IV
	(+/- Fosfomycin[d])	(3 x 5 g)	IV
	for 2 weeks, followed by an oral rifampin combination as above		
- Rifampin-resistant	Intravenous treatment according susceptibility for 2 weeks (as above), followed by long-term suppression for ≥ 1 year		
***Streptococcus* spp.**	Penicillin G[c] or	4 x 5 million U	IV
	Ceftriaxon	1 x 2 g	IV
	for 2–3 weeks, followed by:		
	Amoxicillin or	3 x 1000 mg	p.o.
	Levofloxacin	2 x 500 mg	p.o.
	(consider suppression for ≥1 year)		
***Enterococcus* spp.**			
- Penicillin-susceptible	Ampicillin[c]	4 x 2 g	IV
	Gentamicin[g]	1 x 120 mg	IV
	(+/- Fosfomycin[d])	(3 x 5 g)	IV
	for 2–3 weeks, followed by:		
	Amoxicillin	3 x 1000 mg	p.o.
- Penicillin-resistant	Vancomycin[f] or	2 x 1 g	IV
	Daptomycin	1 x 10 mg/kg	IV
	+		
	Gentamicin[g]	1 x 120 mg	IV
	(+/- Fosfomycin[d])	(3 x 5 g)	IV
	2–4 weeks, followed by		
	Linezolid (max. 4 weeks)	2 x 600 mg	p.o.
- Vancomycin-resistant (VRE)	Individual; removal of the implant or life-long suppression necessary		

Micro-organism (red: difficult-to-treat)	Antibiotic[a] (check susceptibility before)	Dose[b]	Route
Gram-negative			
- Enterobacteriaceae (*E. coli, Klebsiella, Enterobacter* etc.)	Ciprofloxacin[h]	2 x 750 mg	p.o.
- Non-fermenters	Piperacillin/tazobactam or	3 x 4.5 g	IV
(*Pseudomonas aeruginosa, Acinetobacter* spp.)	Meropenem or	3 x 1 g	IV
	Ceftazidim	3 x 2 g	IV
	+ Tobramycin	1 x 300 mg	IV
	(or gentamicin)	1 x 240 mg	IV
	for 2–3 weeks, followed by:		
	Ciprofloxacin	2 x 750 mg	p.o.
- Ciprofloxacin-resistant	Depending on susceptibility: meropenem 3 x 1 g, colistin 3 x 3 million U and/or fosfomycin[d] 3 x 5 g IV, followed by oral suppression.		
Anaerobes			
- Gram-positive (*Cutibacterium, Peptostreptococcus, Finegoldia magna*)	Penicillin G[c] or	4 x 5 million U	IV
	Ceftriaxon	1 x 2 g	IV
	for 2 weeks, followed by:		
	Rifampin[e] +	2 x 450 mg	p.o.
	- Levofloxacin or	2 x 500 mg	p.o.
	- Amoxicillin	3 x 1000 mg	p.o.
- Gram-negative (*Bacteroides, Fusobacterium*)	Ampicillin/sulbactam[c]	3 x 3 g	IV
	for 2 weeks, followed by		
	Metronidazol	3 x 400 mg or 500 mg	p.o.
Candida spp.			
- Fluconazole-susceptible	Caspofungin[i] or	1 x 70 mg	IV
	Anidulafungin	1 x 100 mg (1[st] day: 200 mg)	IV
	for 1–2 weeks, followed by:		
	Fluconazole	1 x 400 mg	p.o.
	(suppression for ≥ 1 year)		
- Fluconazole-resistant	Individual (e.g. with voriconazole 2 x 200 mg p.o.); removal of the implant or long-term suppression		
Culture-negative	Ampicillin/sulbactam[c]	3 x 3 g	IV
	for 2 weeks, followed by:		
	Rifampin[e] +	2 x 450 mg	p.o.
	Levofloxacin	2 x 500 mg	p.o.

Notes. IV, intravenously; p.o., per os; MRSA, Methicillin-resistant Staphylococcus aureus; CRP, C-reactive protein.
[a]Total duration of therapy: 12 weeks, usually 2 weeks intravenously, followed by oral route. [b]Laboratory testing 2 x weekly: leukocytes, CRP, creatinine/eGFR, liver transaminases. Dose-adjustment according to renal function and body weight (< 40 / > 100 kg). [c]Penicillin allergy of NON-type 1 (e.g. skin rash): cefazolin (3 x 2 g IV). In case of anaphylaxis (= type 1-allergy such as Quincke's edema, bronchospasm, anaphylactic shock) or cephalosporin allergy: vancomycin (2 x 1 g IV) or daptomycin (1 x 8 mg/kg IV) Ampicillin/sulbactam is equivalent to amoxicillin/clavulanic acid (3 x 2.2 g IV). [d]For fosfomycin the 5 g dosage form is only available in Germany. In all other countries 2, 4 and 8 g dosage forms for IV fosfomycin are available. A daily dosage of 12 to 24 g IV fosfomycin is licensed. [e]Rifampin is administered only after the new prosthesis is implanted. Add it to intravenous treatment as soon as wounds are dry and drains removed; in patients aged > 75 years, rifampin is reduced to 2 x 300 mg p.o. [f]Check Vancomycin through concentration (take blood before next dose) at least 1 x weekly; therapeutic range: 15–20 µg/ml. [g]Give only if gentamicin high-level (HL) is tested susceptible (consult the microbiologist). In gentamicin HL-resistant *E. faecalis* gentamicin is exchanged with ceftriaxone (1 x 2 g IV). [h]Add IV treatment (piperacillin/tazobactam 3 x 4.5 g or ceftriaxon 1 x 2 g or meropenem 3 x 1 g IV) in the first post-operative days (until wound is dry). [i]After a loading dose of 70 mg on day 1, reduce dose to 50 mg in patients weighing < 80 kg from day 2.

Figure 2. Pocket Guide to Diagnosis & Treatment of Periprosthetic Joint Infection (PJI) Version 9: October 2019.

Intra-articular drainage was not used. Dressings were applied as needed. Sutures of the surgical wound were removed on the 14th postoperative day for all patients (*Figure 3*).

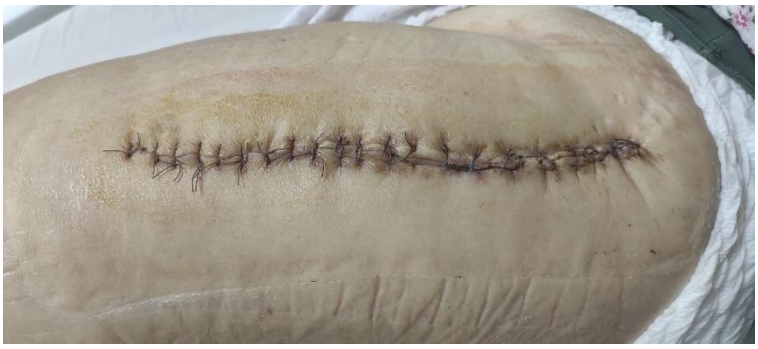

Figure 3. On the 14th postoperative day, there was no erythema or secretion.

3. Results

In the early postoperative period, there was a regression of local erythema and increased local temperature. Prolonged wound secretion was not observed for more than 3 days.

The average follow-up period is 1 year and 2 months. One patient died, and one was lost to follow-up due to failure to attend follow-up visits after the 45th postoperative day. The remaining eight patients show no clinical or laboratory evidence of infection recurrence. Follow-up continues with check-up visits every 3 months.

4. Discussion

Although relatively rare (1-2%), early infection following hip and knee arthroplasty remains one of the major and challenging complications. Successful treatment of PPI infections requires an interdisciplinary team, including orthopedists, infectious disease specialists, and microbiologists.

Early recognition and diagnosis of periprosthetic infections increase the likelihood of success. Of paramount importance for successful PPI treatment is the development of a diagnostic and therapeutic algorithm to be applied at the slightest suspicion of PPI development. A unified therapeutic and treatment algorithm ensures a high success rate and protects the surgeon from overdiagnosis or, in most cases, underestimation of the situation. Underestimating the situation and "burying one's head in the sand" often leads to chronic PPI or a series of diagnostic and therapeutic errors, resulting in treatment failures and poor outcomes.

5. Conclusion

Periprosthetic infections, as a whole, pose a challenge that requires an interdisciplinary approach. Every surgeon should have a developed diagnostic and therapeutic algorithm that is applied immediately in patients suspected of developing PPI. Surgical treatment is the main and indispensable method of treatment. Any delay in surgically removing infected tissues and initiating antibiotic therapy without surgical treatment are the main prerequisites for treatment failure in early PPI.

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Authors

Byser Bonchev, M.D., Ph. D. is member of the **Bulgarian Orthopedic and Traumatology Association (BOTA).** He works as an ortopaedic surgeon at Clinic of Orthopedics and Traumatology, UMHAT "UMHAT Sofiamed", Sofia, Bulgaria.

Teodor Ivanov, M.D. is member of the **Bulgarian Orthopedic and Traumatology Association (BOTA).** He works as an ortopaedic surgeon at Clinic of Orthopedics and Traumatology, UMHAT "UMHAT Sofiamed", Sofia, Bulgaria.

Tsvetoslav Yordanov, M.D. is member of the **Bulgarian Orthopedic and Traumatology Association (BOTA).** He works as an ortopaedic surgeon at Clinic of Orthopedics and Traumatology, UMHAT "UMHAT Sofiamed", Sofia, Bulgaria.

Luben Stokov, M.D., Ph.D. is a member of the **Bulgarian Orthopedic and Traumatology Association (BOTA).** He works as an ortopaedic surgeon at Clinic of Orthopedics and Traumatology, UMHAT "St. Anna", Sofia, Bulgaria. He is professor at the Department of Orthopedics and Traumatology, Medical University of Sofia, Sofia, Bulgaria. He is a member of the Editorial Board of the Journal of the Bulgarian Orthopaedics and Trauma Association (JBOTA).

Georgi P. Georgiev, M.D., Ph.D., D.Sc. is member of the **Bulgarian Orthopedic and Traumatology Association (BOTA)**. He works as an orthopaedic surgeon at the Department of Orthopedics and Traumatology, University Hospital "Queen Giovanna - ISUL", Medical University of Sofia, Bulgaria. He is Associated Professor at the Department of Orthopedics and Traumatology, Medical University of Sofia, Bulgaria. He is a member of the Editorial board of BMC Musculoskeletal Disorders and Clinical Anatomy.

Luben Lubenov Stokov, is a member of the **Bulgarian Orthopedic and Traumatology Association (BOTA)**. He works as volunteer at Clinic of Orthopedics and Traumatology, MHAT "St. Sofia", Sofia, Bulgaria. He is medical student, Medical University of Sofia, Sofia, Bulgaria.