Aus dem Centrum für Muskuloskeletale Chirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

„Diagnostik und Therapie Spondylodese-assoziierter Infektionen“

“Diagnosis and Treatment of Spinal Implant-associated Infections”

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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Datum der Promotion: 03.12.2021

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Abbreviations

SIAI..... Spinal implant-associated infections
SAI..... Spondylodese-assoziierte Infektionen
CRP..... C-reactive protein
WBC..... White blood count

I. Abstract

Abstract (English)

Introduction

Spinal implant-associated infections (SIAI) are among the most significant complications after spinal stabilization. The diagnosis of SIAI is complex and treatment strategies require further standardization. The aim of this work was to evaluate the clinical, laboratory, microbiological, radiological and treatment characteristics in patients with SIAI, using uniform definition criteria and diagnostic procedures as well as a standardized treatment approach.

Material and methods

Between 2015 and 2019 all patients diagnosed with SIAI were prospectively included in our study. A SIAI was defined by following criteria: (i) secondary wound dehiscence, exposed implant or intraoperative visible pus; (ii) relevant microbial growth in peri-implant tissue samples or in sonication; (iii) peri-implant inflammation in histopathology. SIAI were classified in early-onset (≤6 weeks) and late-onset (>6 weeks) after index surgery. All patients were treated according to a standardized algorithm.

Results

From 250 included patients, 61% had an early-onset and 39% a late-onset infection. The most common clinical manifestation in early-onset infections was local inflammatory signs. Late-onset infections manifested with persisting local pain. Particularly in late-onset infections, sonication fluid culture showed higher pathogens detection rates than peri-implant tissue samples (92% vs. 75%, p=0.005). Overall, the most common pathogens were coagulase-negative staphylococci (38%), *Staphylococcus aureus* (24%) and *Cutibacterium* spp. (19%). In early-onset infections the predominant surgical approach was debridement and implant retention, whereas partial or complete implant exchange was mainly performed in late-onset infections. In twenty percent of the patients more than one surgical revision was performed. After initial intravenous antibiotic therapy, oral biofilm-active antibiotics were administrated in 88%. The median treatment duration was 11.7

weeks. Ninety-eight percent of patients have been discharged with a dry wound; six patients died during their hospital stay.

Conclusion

The most frequent SIAI were early-onset infections. This suggests a perioperative acquisition of infection. Early-onset infections presented mainly with local inflammatory signs whereas late-onset infections manifested with persisting or increasing local pain. The most sensitive microbiological diagnostic method in SIAI was sonication of explanted material, particularly in late-onset infections. Independently of the moment of onset of the infection, debridement and implant retention was used in well-integrated implants without loosening.

Abstrakt (Deutsch)

Einleitung

Spondylodese-assoziierte Infektionen (SAI) gehören zu den bedeutendsten Komplikationen nach Stabilisierungsoperationen der Wirbelsäule. Die Diagnosestellung dieser Infektionen ist komplex und eine weitere Standardisierung ist erforderlich. Ziel dieser Arbeit war es, die klinischen, laborchemischen, mikrobiologischen und radiologischen Charakteristika sowie die Behandlungsstrategien bei Patienten mit SAI unter Anwendung von einheitlichen Definitionskriterien, diagnostischen Verfahren sowie standarisierten Behandlungsstrategien zu bewerten.

Material und Methoden

Zwischen 2015 und 2019 wurden 250 Patienten mit SAI prospektiv in diese Studie eingeschlossen. Eine SAI wurde durch die folgenden Kriterien definiert: (i) sekundäre Wunddehiszenz, freiliegendes Implantat oder intraoperativ sichtbarer Eiter; (ii) signifikanter Erregernachweis in periimplantären Gewebeproben oder im Sonikat; (iii) Entzündung im periimplantären Gewebe in der histopathologischen Untersuchung. Die SAI wurden in akute (≤ 6 Wochen) und chronische (> 6 Wochen) Infektionen, bezogen auf die Indexoperation, unterteilt. Alle Patienten wurden nach einem standardisierten Algorithmus behandelt.

Ergebnisse

Von 250 eingeschlossenen Patienten hatten 61% eine akute und 39% eine chronische SAI. Die häufigste klinische Manifestation akuter SAI war das Auftreten von lokalen Entzündungszeichen. Chronische SAI manifestierten sich mit anhaltenden lokalen Schmerzen. Insbesondere bei den chronischen Infektionen zeigte sich die Kultur der Sonikationsflüssigkeit häufiger positiv als die periimplantären Gewebeproben (92% gegenüber 75%, p = 0,005). Die häufigsten nachgewiesenen Erreger waren koagulase-negative Staphylokokken (38%) gefolgt von *Staphylococcus aureus* (24%) und *Cutibacterium* spp. (19%). Die chirurgische Therapie bei akuten Infektionen beinhaltete ein Débridement mit Implantaterhalt. Bei chronischen SAI wurden gelockerte Implantate ausgetauscht, feste Implantate wurden belassen. 20% der Patienten benötigten mehr als eine chirurgische Revision zur Behandlung der Infektion. Nach anfänglicher intravenöser Antibiotikatherapie

wurden in 88% der Fälle orale, biofilmaktive Antibiotika verabreicht. Die mediane Behandlungsdauer betrug 11,7 Wochen. Achtundneunzig Prozent der Patienten wurden mit einer trockenen Wunde entlassen; sechs Patienten verstarben während des Krankenhausaufenthaltes.

Schlussfolgerung

Die häufigsten SAI dieser Kohorte waren Frühinfektionen. Dies suggeriert eine perioperative Genese. Akute SAI manifestierten sich hauptsächlich mit lokalen Entzündungszeichen, während chronische Infektionen sich mit anhaltenden oder zunehmenden lokalen Schmerzen präsentierten. Die sensitivste mikrobiologische Diagnostik war die Sonikation des explantierten Materials, insbesondere bei den chronischen Infektionen. Unabhängig vom Zeitpunkt des Infektionsbeginns bestand der chirurgische Ansatz aus einem Débridement und Erhalt integrierter Implantate und dem alleinigen Austausch von gelockerten Implantaten.

II. Synopsis

a. Introduction

Indications for spinal surgery have rapidly increased over the past decades. Internal spinal fixations are used in a variety of indications such as the treatment of acute fractures, degenerative pathologies or in congenital deformities such as scoliosis [1]. Despite a better comprehension of risk factors and the implementation of preventive measures, infections after spinal instrumentation are among the most severe complications in the field of musculoskeletal surgery. The incidence of infections after spinal instrumentation varies between 0.5% to 10% [2-4]. Spinal implant-associated infections (SIAI) are known to cause chronic pain, increase the morbidity and mortality, and significantly alter the quality of life [3, 5-7]. The principal goal in the treatment of SIAI is the eradication of the infection. Beside this, the stability of the spine and pain reduction are among the most relevant goals [3, 8]. The choice of the optimal treatment modality, whether to retain or remove the spinal implant and the right choice and duration of antibiotic therapy remain controversial. Most authors recommend debridement and retention of the spinal implant in early-onset infections [9] while in late infections a complete removal of the hardware is suggested. Considering the significant morbidity associated with the radical surgical procedure it remains unclear whether only loose components should be removed, and well-fixed parts can be retained, or the entire implant should be exchanged [10-12]. Once bacteria reach the implant surface, they attach to the surface and form a biofilm. In the biofilm, bacteria are protected from natural immune defense mechanisms as well as conventional antibiotics. In addition, the diagnosis is hindered, making sonication an important diagnostic tool. In the antibiotic treatment, the role of biofilm-active antibiotics is substantial.

b. Definition and classification of SIAI

Until today, there is no international consensus on standardized definition criteria for SIAI. Kowalski et al. [9] classified a SIAI in three categories: (i) definite case: patient with signs and symptoms of SIAI and positive results of spine site cultures or >2 sets of blood cultures; (ii) probable case: patient with signs and symptoms of SIAI and suggestive histopathology, gross intraoperative purulence, presence of a sinus tract, or a positive Gram stain result from tissue specimens; (iii) possible case: patients

with signs and symptoms of SIAI and clinical and radiographic diagnosis without microbiologic or histopathologic confirmation.
Dubée et al. [8] evaluated the diagnosis and management of early-onset SIAI and defined an acute infection as clinical signs of surgical site infection with at least 2 deep microbiological samples (bone or tissue surrounding the material) growing the same bacterium.
Both authors considered early-onset infection when the symptoms occurred and/or the diagnosis of SIAI was made within 30 days after implant placement. Late-onset infections were those arising 30 days after implant placement.

c. Pathogenesis of SIAI

An implant can be infected in three different ways:
a) Intraoperatively through direct colonization of the foreign material via the wound or contamination from ambient air.
b) By hematogenous or lymphogenic spread of the pathogen from another source of infection, i.e. from a urinary tract infection, skin infection or pneumonia.
c) Colonization through direct contact with an adjacent infected site or per continuitatem due to external skin defect and surrounding soft tissues.

The assignment to exogenous and haematogenic infections is not always clear. Infection localized elsewhere and isolated bacterial species often allow a correct assignment of the infection's pathogenesis. Most infections emerge intraoperatively and via postoperative wound healing disorders [13, 14]. Spinal instrumentation represents an avascular surface that bacteria can attach to. A small number of bacteria (whether they get on the implant perioperative, contiguous or hematogenous) can be enough to initiate the infectious process [14]. Once a biofilm has formed, bacteria gain a resistance against both, endogenous immune defense and antibiotics. Preventive measures such as perioperative antibiotic prophylaxis as well as technical and hygiene measures lead to a significant reduction of these infections.

d. Treatment of SIAI

Surgical treatment

The choice of the optimal treatment modality is still controversial and varies between different authors. Most authors agree that debridement with implant retention is the recommended surgical treatment in early-onset infections [1, 3, 8, 9, 15-17]. In case of debridement and implant retention the wound is explored, multiple samples are collected, necrotic and infected tissues are excised and the surgical site is washed with pulsed normal saline.

In late-onset infections, the treatment algorithm depends on whether the prior instrumented segments of the spine can be considered as stable at the time of the diagnosis of the infection. In late-onset infections stability and fusion is more likely and the implant can be removed [9]. If unfused, most authors suggest a complete exchange of the hardware [8-12].

Antimicrobial treatment

In combination with an adequate surgical treatment, antimicrobial therapy is mandatory in the management of SIAI. Empiric antibiotic regime is administered initially intravenously to cover the most common and expected pathogens, including staphylococci, streptococci, enterococci and Gram-negative bacilli [1]. SIAI are reported to be polymicrobial infections in up to 50%, with equal incidence in early-onset and late-onset infections [1, 8, 9, 18]. Due to this high rate of polymicrobial infections, combined initial antibiotic therapy is suggested by most authors [1]. Once the responsible pathogen is identified, targeted antimicrobial treatment is given according to susceptibility pattern. After the wound is dry and drainages are removed, which occurs typically in 1-2 weeks after surgery, oral antibiotics with biofilm activity are given. In a recent study with 93 SIAI, biofilm-active therapy showed a significant better outcome and less postoperative pain compared to a treatment without biofilm- active antibiotics (hazard ratio, 0.23, 95% CI, 0.07-0.77) [16]. Biofilm-active antibiotics include rifampin combination against staphylococci, depending on the susceptibility of the pathogen, combined with quinolones, cotrimoxazole, doxycycline or fusidic acid [1, 19], against *Cutibacterium* species [1, 20] and in culture-negative infections. In streptococcal infections, oral amoxicillin is recommended as a long-

term suppressive therapy for 6-12 months. With a shorter treatment duration, high relapse rates are observed in periprosthetic joint infections [21]. In case of penicillin allergy, doxycycline or levofloxacin can be used. In enterococcal infections, amoxicillin is recommended for 3 months [21, 22]. Ciprofloxacin is the biofilm-active antibiotic recommended against Gram-negative bacilli [1, 23, 24].

e. Current issues in the diagnostic and treatment of SIAI

Currently, there are only few data regarding the diagnosis and management of SIAI. There is a lack of validated, defined criteria to uniformly diagnose, classify and treat SIAI in the clinical practice. The main studies on SIAI used a period of 30 days to differentiate between acute- and late-onset infections without considering that hardware loosening is unlikely to occur at this stage.

Regarding the microbiological diagnosis, available studies on SIAI are only based on spine site cultures or blood cultures. Taking into account the presence of a biofilm on implant surfaces, peri-implant tissue culture may fail to detect the responsible pathogen, especially for low-virulent pathogens. Studies on prosthetic joint infections demonstrated that sonication of removed prosthesis significantly improved the microbiological diagnosis compared to periprosthetic tissue cultures. Therefore, sonication should be considered as an important diagnostic tool for the management of SIAI.

In late-onset SIAI, most authors recommend a complete removal or exchange of the instrumentation to eradicate the infection. But this recommendation does not consider important aspects such as poor bone stock in some patients, previously cemented screws or well-integrated intersomatic cages which can lead to an extensive revision surgery.

The use of biofilm-active antibiotics in the treatment of SIAI is essential, as a biofilm is present on implant surfaces. In available studies, partly oral non-biofilm-active antimicrobial suppression therapy was used for a prolonged period of ≥ 6 months [9].

f. Aim of the study

The aim of this multicenter, cohort study was to investigate the clinical, laboratory, microbiological, radiological, patient and treatment characteristics in patients with

early- and late-onset SIAI. Uniform definition criteria and diagnostic and treatment algorithms were applied.

g. Definition criteria and classification of SIAI

We used standardized institutional definition criteria for SIAI modifying the previously published criteria by Kowalski et al. and Dubée et al. [8, 9]. SIAI was diagnosed in patient with spinal implants in place and presence of at least one clinical, microbiological or histological feature.

Clinical signs were secondary wound dehiscence, exposed implant or sinus tract and intraoperative visible purulence around the implant.

Microbiological results were relevant microbial growth in ≥2 peri-implant tissue samples or in sonication fluid (≥50 CFU/ml) of explanted instrumentation. Histopathological criteria were the presence of acute and/or chronic inflammation in the peri-implant tissue.

Suggestive signs and symptoms for infection, leading to further diagnostic investigations were persisting or increasing local pain, neurologic impairment or radiological evidence of inflammation

Early-onset infection was defined as a symptom onset ≤6 weeks after the index surgery. Symptom onset >6 weeks after the index surgery was defined as late-onset infection. Index surgery was defined as the latest spinal instrumentation before infection.

A detailed overview of the diagnostic criteria of SIAI was prepared for the publication and is fully cited for an extensive information in the following Table 1.

Table 1. Spinal implant-associated infection was defined in patients with spinal implants in place and presence of ≥1 of the following 3 features [7].

Feature	Characteristic
Clinical signs	Presence of: • Secondary wound dehiscence or • Visible exposed implant ("implant on view") or • Intraoperative visible purulence
Microbiology	Relevant microbial growth[a] in: • ≥2 peri-implant tissue samples or • Sonication fluid (≥50 CFU/ml)
Histopathology	Presence of acute and/or chronic inflammation in peri-implant tissue

[a] For highly virulent organisms (e.g. *S. aureus, E. coli*, streptococci) or patients currently receiving antibiotics, one positive peri-implant tissue sample or <50 CFU/ml in sonication fluid was relevant. If a non-microbiological criterion was fulfilled, any growth was considered relevant.

h. Material and Methods

This clinical study was conducted in the department of orthopedics and trauma surgery and department of neurosurgery of Charité - Universitätsmedizin Berlin. Institutional review board approval was obtained prior to the initiation of the study (EA4/101/14). The study was performed in accordance with the Declaration of Helsinki. The need of the patient informed consent was waived due to the observational character of this study.

Patients diagnosed with any type of infection after spinal instrumentation are prospectively documented in the institutional electronic database since 2015. The medical records of all potential patients with infection after spinal surgery from the mentioned database were reviewed for inclusion in the study by the principal investigator. Between 1 January 2015 and 31 December 2019, we retrospectively identified and included 250 patients, aged > 7 years, meeting the above-mentioned diagnostic criteria for SIAI. To elaborate our observational, descriptive, cohort study

on SIAI, the following data of each included patient were extracted: age, sex, indication for primary spinal surgery, number of previous spinal surgeries, anatomic site of spinal surgery, local and systemic clinical findings, presumed pathogenesis of SIAI, radiological findings, preoperative laboratory parameters (including C-reactive protein (CRP) and leucocytes), intraoperative microbiological and histopathological findings, surgical treatment, and antimicrobial treatment.

For further analysis of the in-hospital outcome, during the hospitalization for SIAI, additional features were recorded: need for admission to the intensive care unit, number of revision surgeries, length of hospital stay and cause of in-hospital death (where applicable).

At discharge, patients were evaluated for systemic and local clinical signs of infection, laboratory parameters including CRP, leucocytes, and radiology imaging (where indicated).

Each episode of SIAI was evaluated by an interdisciplinary team consisting of a surgeon (orthopedic spine surgeon or neurosurgeon), infectious disease specialist and microbiologist. During the study period, definition criteria, diagnostic procedures, surgical techniques, implants, or antimicrobial treatment regime remained unchanged.

Detailed description of performed surgical and antimicrobial treatment:

Surgical treatment

In patients with early-onset infections, with stable and well positioned implants, the surgical treatment consisted of debridement and implant retention. Intraoperatively, multiple microbiological and histological samples were collected, and the infected tissue was excised.

The surgical procedure in late-onset infections depended on a previously interdisciplinary discussed decision based on patient-specific factors including relevant comorbidities and local particularities such as poor bone stock, previously cemented screws and well-integrated intersomatic cages. In those patients, and with unfused vertebral segments or further necessity for spinal stabilization, well-fixed implants remained in place and loose implant components were exchanged. In case of fused and/or stable spine segments, patients underwent a complete implant removal. An entire exchange of the spinal implant was performed in patient without relevant comorbidities, with good bone stock, uncemented screws or with loose intersomatic cages.

Similar to the surgical procedure of acute onset infections, the infected site was debrided, and several tissue samples were collected for microbiology and histopathology. Removed implants were sent for sonication.

Antimicrobial treatment

Empiric treatment was a combined or single beta-lactam treatment and was administered after the revision surgery for 1-2 weeks, followed by an oral treatment to complete a course of 6 weeks (if foreign material was removed) or 12 weeks (if foreign material remained in place or was exchanged, using biofilm-active antibiotics) [1].

After the removal of all drainages and provided dry wound conditions, oral biofilm-active antibiotics were administered. Biofilm-active antibiotics included rifampin-combination and ciprofloxacin. Rifampin combination was used against staphylococci, *Cutibacterium* species and culture-negative infections. Ciprofloxacin was used as a biofilm-active antibiotic in patients with infections due to Gram-negative bacilli. In streptococcal infections, oral amoxicillin or, in case of penicillin allergy, doxycycline or levofloxacin was given for at least 6 months. This treatment was prolonged to 12 months in case of good antibiotic tolerance and no related side effects. For enterococcal infections, amoxicillin was administered for 3 months. Rifampin-resistant staphylococci, ciprofloxacin-resistant Gram-negative bacilli and fungi were considered as difficult-to-treat infections since for these pathogens no biofilm-active antibiotics are available. In this situation, oral antibiotics without biofilm activity, with good oral bioavailability and bone penetration were administered for at least 12 months, defined as suppressive antibiotic therapy.

Statistical analysis

Categorical variables were compared using Chi-Quadrat-Test or Fisher's exact test, as appropriate. To test for the difference between two medians, the Mann-Whitney U test was used. A p-value (two-sided) <0.05 was considered significant. For statistical analysis the program R (version 3.1.3) and for graphics the software Prism (version 8.2; GraphPad, La Jolla, CA, USA) was used.

i. Results

Two hundred and fifty patients with SIAI met the definition criteria and were included in the study; 152 patients (61%) had early-onset and 98 (39%) had late-onset SIAI. The median age was 67 years (range, 8–90); 131 (52%) were female. The median length of hospital stay was 14 days (range, 6-84 days). During the hospital stay, 22 patients (9%) required admission to the intensive care unit. Six patients (2%) died during inpatient treatment, four of them (2%) due to a non-infectious related reason and two patients (1%) because of infection (septic shock and hospital-acquired pneumonia). The remaining 244 patients (98%) were discharged with a dry wound, 97% of them with a serum CRP <20 mg/l (normal < 5 mg/L). Degenerative spinal disease (145 patients, 58%) was the most common indication for the index spine surgery.

In our cohort, perioperative colonization of the foreign material via the surgical wound or contamination from ambient air was the most common pathogenesis of SIAI. In 98% of patients the infection occurred perioperatively. Hematogenous spread from a distant infection focus or a contiguous extension from an adjacent infection were described in 5 patients (2%).

A detailed overview of the baseline infection characteristics of included patients withs SIAI was worked out for the publication and is fully cited for an extensive information in the Table 2.

Table 2. Infection characteristics of 250 spinal implant-associated infections, stratified by early-onset and late-onset infection [7].

Characteristic	All patients (n = 250)	Early-onset infection (n = 152)	Late-onset infection (n = 98)	P-value
Clinical findings				
Local inflammatory signs [a]	142 (57)	128 (84)	14 (14)	<0.0001
Neck or back pain	92 (37)	22 (14)	70 (71)	<0.0001
Focal neurological impairment [b]	59 (24)	22 (14)	37 (38)	<0.0001
Body temperature >38 °C	37 (15)	28 (18)	9 (9)	0.044
Exposed implant	9 (4)	1 (1)	8 (8)	0.001
Sinus tract	5 (2)	0	5 (5)	0.004
Radiological findings on spine CT or MRI				
Abscess [c]	63/188 (34)	41/97 (42)	22/91 (24)	0.008
Implant failure [d]	42/188 (22)	22/97 (23)	20/91 (22)	0.908
Implant loosening	38/188 (20)	8/97 (8)	30/91 (33)	<0.0001
Laboratory findings before surgery				
WBC count >10 $\times$ 10^9/L	91 (36)	58 (38)	33 (34)	0.442
Serum CRP value >10 mg/L	191 (76)	129 (85)	62 (63)	0.004
Histopathological findings in peri-implant tissue				
Presence of acute and/or chronic inflammation	80/95 (84)	47/51 (92)	33/44 (75)	0.022

NOTE: Data are n (%) of patients, unless otherwise indicated. Whenever a denominator is shown, data are not available for all patients.

CT, computed tomography; MRI, magnetic resonance imaging; WBC, white blood cell; CRP, C-reactive protein.

[a] Wound dehiscence or discharge, redness, or warmth at the surgical site.

[b] Including paraesthesia and paresis.

[c] Including epidural (n = 30), subcutaneous (n = 17), paravertebral (n = 8) and intraspinal (n = 8) abscesses.

[d] Including implant fracture and dislocation.

Four relevant differences between early- and late-onset SIAI could be observed:

First, 128 (84%) of patients with early-onset SIAI showed local signs of inflammation such as redness and swelling at the incision site, suggesting an infection. For late-onset SIAI, the most important clinical sign suggesting infection was persisting or increasing local pain in 70 (71%) patients.

Second, serum CRP values of >10 mg/L were significantly more frequent in early-onset SIAI compared to late-onset SIAI (85% vs 63%, p= 0.004). The serum white blood count (WBC) was an unspecific parameter. WBC count of >10 × 10^9/L was observed in 58 (38%) patients with early-onset SIAI and in 33 (34%) patients with late- onset SIAI.

Third, radiological findings (computed tomography or magnetic resonance imaging) also differed notably between early- and late-onset SIAI. Abscesses were more commonly observed in early-onset infections (42% vs. 24%, p=0.008). Late-onset SIAI showed predominantly implant loosening (8% vs. 33%, p <0.0001).

Fourth, spectrum of responsible pathogens varied depending on the type of SIAI. Gram-negative bacilli caused mostly early-onset SIAI (19% vs. 3%, p=0.002) whereas *Cutibacterium spp.* were responsible particularly for late-onset SIAI (8% vs. 33%, p<0.001). The isolation of *Stapylococcus spp.* was similar in early- and late- onset SIAI. We observed a characteristic distribution of the microorganisms between different spine segments. Staphylococci were mainly found in the cervical spine, *Cutibacterium spp.* in thoracic and lumbosacral segments and Gram-negative bacilli mostly in the lumbosacral spine. A detailed overview of microbiological findings was worked out for the publication and is fully cited for an extensive information in the Table 3.

Table 3. Microbiological findings of spinal implant-associated infections stratified in early-onset and late-onset infection [7].

Pathogen	All patients (n=250)	Early-onset infection (n=152)	Late-onset infection (n=98)	P-value
Monomicrobial infection	156 (62)	89 (57)	67 (43)	0.141
CoNS[a]	60 (38)	35 (39)	25 (37)	0.869
Staphylococcus aureus[b]	38 (24)	23 (26)	15 (22)	0.708
Cutibacterium spp.[c]	29 (19)	7 (8)	22 (33)	<0.001
Gram-negative bacilli[d]	19 (12)	17 (19)	2 (3)	0.002
Enterococcus spp.[e]	4 (3)	3 (3)	1 (1)	0.635
Streptococcus spp.[f]	2 (1)	2 (2)	0	0.507
Other pathogen[g]	4 (3)	2 (2)	2 (3)	1.000
Polymicrobial infection[h]	61 (24)	37 (25)	24 (25)	0.978
Culture-negative infection	33 (13)	23 (15)	10 (10)	0.115

NOTE. Data are n. (%) of patients. The percentages were rounded and may not sum 100%. CoNS, coagulase-negative staphylococci.

[a] Including *S. epidermidis* (n=51), *S. hominis* (n=2), *S. warneri* (n=2), *S. capitis* (n=1), *S. lugdunensis* (n=1), *S. cohnii* (n=1), *S. saccharolyticus* (n=1), *S. caprae* (n=1)

[b] Among 38 *S. aureus* isolates, 2 (5,3%) were methicillin resistant.

[c] All isolates were identified as *Cutibacterium acnes*.

[d] Including *Pseudomonas aeruginosa* (n=6), *Enterobacter cloacae* (n=6), *Escherichia coli* (n=3), *Proteus mirabillis* (n=3), *Enterobacter aerogenes* (n=1)

[e] Including *Enterococcus faecalis* (n=3), *E. faecium* (n=1)

[f] Including *Streptococcus agalactiae* (n=1), *S. pyogenes* (n=1)

[g] Including *Finegoldia magna (* n=1), *Peptoniphilus asaccharolyticus* (n=1), *Corynebacterium* spp. (n=1), *Peptostreptococcus* spp. (n=1)

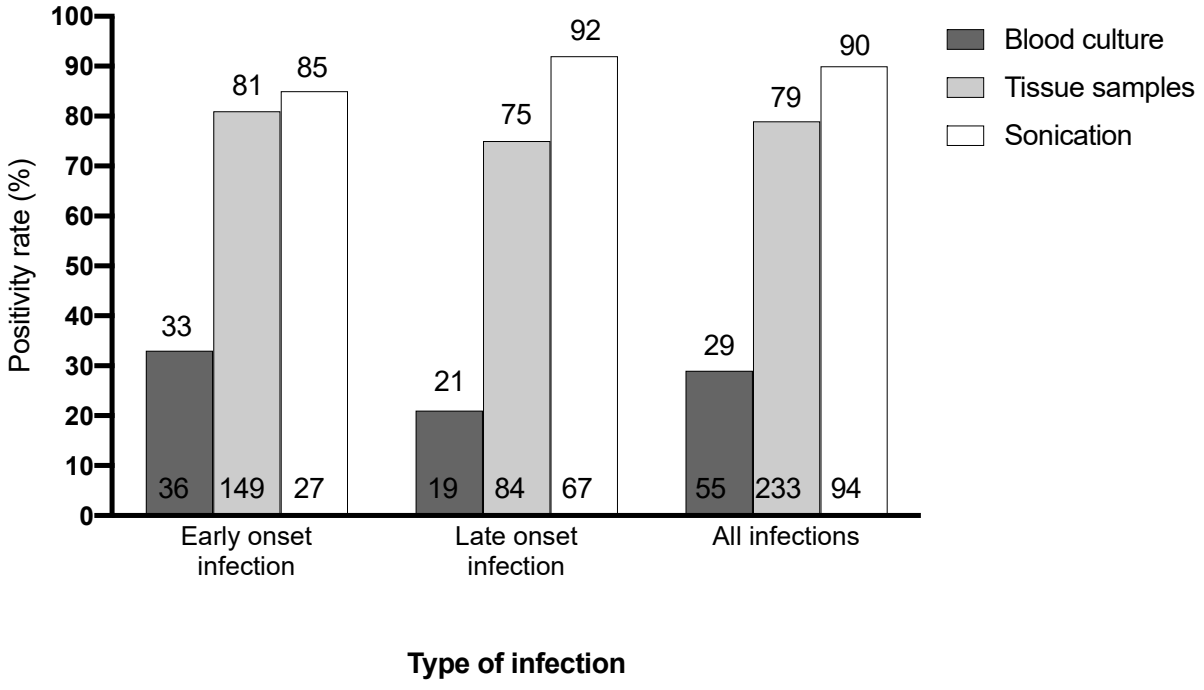
[h] Polymicrobial infections include CoNS (n=35), Gram-negative bacilli (n=28), *S. aureus* (n=14), *C. acnes* (n=13), *Enterococcus* spp. (n=13), *Streptococcus* spp. (n=8), other anaerobes (n=8), *Candida* spp. (n=7), *Corynebacterium spp.* (n=5), *Peptoniphilus asaccharolyticus* (n=2), *Lactobacillus* spp. (n=2), *Actinomyces* spp., *Dermabacter* spp., *Fusobacterium* spp. and *Stenotrophomonas maltophilia* (n=1 each).

Finally, of 95 patients (38%) with available histological peri-implant tissue samples, acute and/or chronic inflammation was described significantly more often in early-onset SIAI compared to late-onset SIAI (92% vs. 75%, p= 0.022).

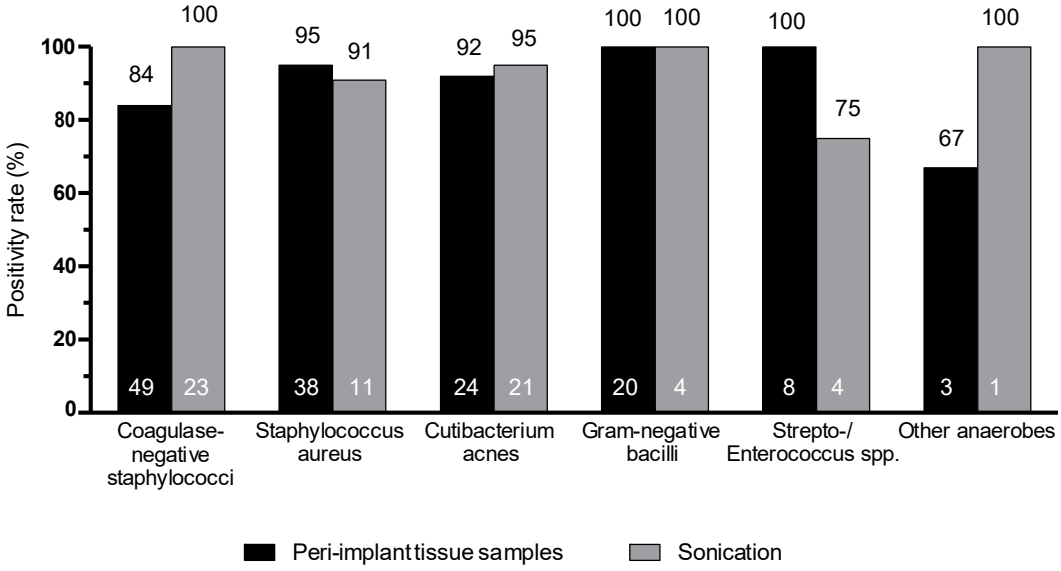
Concerning the microbiological diagnostic method of SIAI, our study showed that sonication of explanted spinal implants was more sensitive compared to peri-implant tissue samples or preoperative blood cultures, particularly in late-onset SIAI (92% vs. 75%, p=0.005). For graphical description of the obtained results, Figures 1 A and B from our publication are fully cited.

Figure 1. Culture positivity rate of blood culture, tissue samples and sonication for early-onset, late-onset and all infections (A) and stratified according to the respective causing pathogen (B). The numbers above the bars represent the positivity rate, the numbers at the bottom of the bars represent the absolute number of samples analyzed.

A.



B.



Regarding the performed surgery, debridement and implant retention was performed in 130 (85%) patients with early-onset SIAI. In late-onset SIAI, predominantly partial or complete implant exchange was performed (61 patients, 62%). Overall, the spinal implant was retained in 158 infections (63%), exchanged, partially or/and completely, in 83 (33%) and removed in 9 (4%). A total of 49 patients (20%) had more than one revision surgery.

Initial intravenous antibiotics were administered in a combination therapy in 183 patients (73%). Main used intravenous antibiotics were β-Lactams in 178 patients (71%), combined with vancomycin or daptomycin in 144 patients (58%). Oral biofilm-active substances such as rifampin or ciprofloxacin were given in 220 patients (88%). Rifampin was predominantly combined with levofloxacin (n=123) or cotrimoxazole (n=41). In 7 patients (3%), rifampin could not be administered due to interactions with comedication or important side effects, particularly nausea, vomiting and disturbed oral intake.

The median duration of biofilm-active antibiotic treatment was 11.7 weeks (range 6-12 weeks).

In 19 patients (8%) a suppressive antimicrobial treatment was given, from them 12 patients with difficult-to-treat microorganisms: rifampin-resistant staphylococci (n=3), ciprofloxacin-resistant Gram-negative bacilli (n=3) or fungi (n=6). The most common used antibiotic for suppression was cotrimoxazole, in 6 patients, followed by doxycycline (n=5), clindamycin (n=1) and amoxicillin/clavulanic acid (n=1). For the antimicrobial treatment of SIAI due to *Candida* spp. suppressive antifungal drugs were given in 6 patients, including oral fluconazole (n=5) and voriconazole (n=1). Amoxicillin, doxycycline or linezolid were used to treat 7 patients with enterococcal infections (1 with *Enterococcus faecium*) for a total of 3-12 months. In case of SIAI due to *Streptococcus spp.* (7 patients) oral amoxicillin for 6-12 months was given.

j. Discussion

This is the first study to investigate the diagnostic and treatment of SIAI according to uniform definition criteria. With this study we describe the largest cohort of SIAI, focusing on relevant clinical, microbiological and therapeutic differences between early-onset and late-onset infections.

Some authors consider 3 months within surgery to be the cut-off of early-onset infection [25]. Other authors used a period of 30 days after surgery to define early-onset infection, reporting similar clinical, laboratory and microbiological findings [8, 9, 16, 26]. Since hardware loosening is unlikely to occur in the first 30 postoperative days we considered early-onset infection as the manifestation within 6 weeks after surgical intervention.

Similarly to Murdoch et al. [27] who described a lower risk of hematogenous infection of internal fracture stabilization compared to arthroplasties, we showed that 98% of SIAI were acquired perioperatively. In contrast, about 30% of periprosthetic joint infections originate haematogenously from a distant focus of infection. The arthroplasty is exposed to continuous synovial fluid production and consequently to microbial filtration from the blood.

Clinical signs suggesting early-onset SIAI were local inflammation signs (84%). Late-onset SIAI often only presented with persisting or increasing local pain (71%). A relevant number of late-onset SIAI may remain unnoticed in this way.

Biofilms are localized on implant surfaces and peri-implant tissue cultures may miss the pathogen detection [28]. Several authors demonstrated that sonication is the most sensitive microbiological diagnostic method in peri-implant infections [29-37]. In our study, sonication of removed pedicle screws commonly detected *Cutibacterium spp.* and coagulase-negative staphylococci, especially in late-onset SIAI. Similarly, Prinz et al. showed microbial growth by sonication in 22 of 82 patients (41%) with screw loosening, compared to no growth of 28 patients without screw loosening ($p < 0.01$) [38]. This underlines the importance of sonication to diagnose low-grade infections.

The most common pathogens in early-onset SIAI were *S. aureus* and Gram-negative bacilli. Among lumbosacral segments the predominant pathogens were Gram-negative bacilli probably reflecting the anatomical vicinity to the urogenital and intestinal system. This observation underlines the importance of preoperative skin decolonization, optimized antimicrobial prophylaxis and the postoperative wound care.

Collins [39] and Wang [40] emphasized the importance of histopathological peri-implant tissue analysis in the diagnosis of SIAI. In this study, histopathological investigation of peri-implant tissue was performed in approximately one third of patients, showing inflammation in 84% of patients. Regarding the surgical management of SIAI, most authors agree to perform debridement and implant retention in early- onset SIAI [3, 8, 9, 17]. In late-onset SIAI, the recommendations are heterogenous. The most relevant studies recommend to completely exchange or remove the spinal implants, whenever possible [10-12].

This is the first study showing that only loose implants should be exchanged, whereas fixed implants can remain in situ reducing the patient's morbidity and mortality.

k. Limitations and future study questions

This study has several limitations. We only evaluated the in-hospital outcome and cannot provide a long-term follow-up so far (i.e. >5 years after surgery). Histopathological investigations of peri-implant tissue were only performed in one third of patients. This hinders a direct comparison with other diagnostic methods. We did not investigate the role of local antibiotics such as vancomycin powder or coated implants in the treatment of SIAI. Finally, we cannot exclude whether the treatment outcome in case of implant retention has been positively influenced by using 12-week biofilm-active antibiotics or where indicated, the long-term antibiotic suppression.

i. Conclusions

Several relevant findings can be deduced. Persisting or increasing local pain is the predominant clinical sign suggesting late-onset SIAI. 98% of SIAI occur perioperatively and most of them (61%) present within the first 6 postoperative weeks. Implant loosening as diagnosed in radiological imaging is a suggestive sign of late-onset SIAI. The most sensitive microbiological diagnostic method is sonication of removed spinal implants. Independently of the time of onset of the infection, in selected patients with well-fixed spinal implants, debridement and implant retention or only partial implant exchange can be performed.

III. References

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IV. Statutory Declaration

“I, Donara Margaryan, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Diagnosis and Treatment of spinal implant associated infections”; “Diagnostik und Therapie Spondylodese-assoziierter Infektionen”, independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

V. Declaration of own contribution to the publication

Donara Margaryan contributed the following to the below listed publication:

Donara Margaryan, Nora Renz, Maja Bervar, Robert Zahn, Julia Onken, Michael Putzier, Peter Vajkoczy, Andrej Trampuz. “Spinal implant-associated infections: a prospective multicenter cohort study”. International Journal of Antimicrobial Agents, 2020.

Contribution: first author

Contribution in detail:
The conception of the study was designed by me. I studied the previous relevant publications in detail, the current challenges and issues in the diagnosis and treatment of spinal implant associated infections and found out the heterogenicity of its management strategies. Then I created the study design in cooperation with PD. Dr. Andrej Trampuz and identify the parameters to be examined. In this study we recruited retrospectively all patients diagnosed with spinal implant-associated infections between 2015 and 2019 treated according to a standardized algorithm implemented in 2015 in the unit of septic surgery of the Center for musculoskeletal surgery at Charité - Universitätsmedizin Berlin. To create a database, a search was carried out in the clinic's own database, in the clinic's digital documentation system (SAP) and an evaluation of all patient documents available in the clinic archive.
The acquisition of all relevant clinical data was carried out by me.

The data analysis and statistical evaluation were carried out by me and the interpretation in collaboration with the senior author.
Tables 1-5, as well as, Figure 1 (A, B) and 2 were created on the basis of my statistical evaluation.

Initially, I wrote the draft of the manuscript, whose single sections were discussed with other co-authors. Afterwards I produced several revised versions which were intensively discussed an instantly supervised by PD Dr. Trampuz, Dr. Renz and Dr. Zahn. I submitted the manuscript in the journal agreed upon with the co-authors. As the article was initially accepted with minor revision, I prepared the new version and accurately replied to reviewers´ comments.

_____
Signature, date and stamp of first supervising university professor / lecturer

_____
Signature of doctoral candidate

VI. Journal Summary List (ISI Web of Knowledge)

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"INFECTIOUS DISEASES"** Selected Category
Scheme: WoS

Gesamtanzahl: 89 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET INFECTIOUS DISEASES	23,088	27.516	0.073350
2	Lancet HIV	2,417	14.753	0.014270
3	CLINICAL INFECTIOUS DISEASES	64,031	9.055	0.119010
4	Eurosurveillance	9,131	7.421	0.031660
5	EMERGING INFECTIOUS DISEASES	30,311	7.185	0.059420
6	CLINICAL MICROBIOLOGY AND INFECTION	17,929	6.425	0.036730
7	Journal of the International AIDS Society	4,530	5.192	0.018770
8	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	30,927	5.113	0.048620
9	JOURNAL OF INFECTION	6,946	5.099	0.014410
10	JOURNAL OF INFECTIOUS DISEASES	45,452	5.045	0.076010
11	ACS Infectious Diseases	1,459	4.911	0.005500
12	Travel Medicine and Infectious Disease	1,576	4.868	0.004660
13	Virulence	3,557	4.775	0.009120
14	INFECTIOUS DISEASE CLINICS OF NORTH AMERICA	2,765	4.757	0.005160
15	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	11,529	4.615	0.017010
16	AIDS	19,276	4.499	0.038330

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
17	Current HIV/AIDS Reports	1,559	4.382	0.004860
18	INTERNATIONAL JOURNAL OF HYGIENE AND ENVIRONMENTAL HEALTH	4,852	4.379	0.007830
19	Current Opinion in HIV and AIDS	2,426	4.268	0.008530
20	JOURNAL OF TRAVEL MEDICINE	2,229	4.155	0.003410
21	JOURNAL OF VIRAL HEPATITIS	4,816	4.016	0.009640
22	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	14,479	3.863	0.037150
23	CURRENT OPINION IN INFECTIOUS DISEASES	3,631	3.752	0.007600
24	AIDS PATIENT CARE AND STDS	3,526	3.742	0.006900
25	HIV MEDICINE	2,660	3.734	0.006570
26	JOURNAL OF HOSPITAL INFECTION	7,963	3.704	0.010250
27	Transboundary and Emerging Diseases	3,321	3.554	0.007140
28	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	7,119	3.538	0.016950
29	Open Forum Infectious Diseases	2,694	3.371	0.013970
30	SEXUALLY TRANSMITTED INFECTIONS	4,686	3.365	0.009490
31	Epidemics	806	3.239	0.003170
32	Clinical and Vaccine Immunology	5,772	3.233	0.010040
33	Antimicrobial Resistance and Infection Control	1,294	3.224	0.004910
34	INFECTION AND IMMUNITY	46,129	3.160	0.029050

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
35	Infectious Diseases of Poverty	1,284	3.123	0.005100
36	Influenza and Other Respiratory Viruses	2,044	3.094	0.006330
37	Ticks and Tick-Borne Diseases	2,693	3.055	0.006730
38	Infection and Drug Resistance	976	3.000	0.002730
39	INFECTION	3,607	2.927	0.006650
40	Antibiotics-Basel	701	2.921	0.002230
41	INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY	9,857	2.856	0.018120
42	MEDICAL MYCOLOGY	4,706	2.851	0.005460
43	MALARIA JOURNAL	13,128	2.798	0.029770
44	Current Infectious Disease Reports	1,263	2.755	0.002530
45	MICROBES AND INFECTION	6,469	2.669	0.004440
46	INFECTION GENETICS AND EVOLUTION	8,103	2.611	0.019150
47	EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES	8,584	2.591	0.015020
48	BMC INFECTIOUS DISEASES	15,284	2.565	0.045880
49	Journal of Infection and Public Health	1,449	2.487	0.003810
50	Journal of Global Antimicrobial Resistance	962	2.469	0.002960
51	JOURNAL OF MICROBIOLOGY IMMUNOLOGY AND INFECTION	2,163	2.455	0.003770
52	Microbial Drug Resistance	2,493	2.397	0.004440

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
53	AIDS REVIEWS	647	2.357	0.001190
54	PEDIATRIC INFECTIOUS DISEASE JOURNAL	11,681	2.317	0.019500
55	DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE	6,677	2.314	0.013080
56	ANTIVIRAL THERAPY	2,764	2.305	0.004990
57	SEXUALLY TRANSMITTED DISEASES	5,473	2.270	0.009980
58	Journal of the Pediatric Infectious Diseases Society	942	2.269	0.004450
59	AIDS Research and Therapy	813	2.240	0.002320
60	Brazilian Journal of Infectious Diseases	2,036	2.223	0.003680
61	Infectious Diseases	810	2.191	0.002690
62	Pathogens and Disease	1,517	2.182	0.005570
63	Zoonoses and Public Health	1,914	2.164	0.003960
64	Transplant Infectious Disease	2,691	2.112	0.005570
65	HIV CLINICAL TRIALS	659	2.089	0.001240
66	EPIDEMIOLOGY AND INFECTION	9,191	2.047	0.017140
67	INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE	7,751	2.024	0.014020
68	AMERICAN JOURNAL OF INFECTION CONTROL	7,923	1.971	0.015330
69	VECTOR-BORNE AND ZOONOTIC DISEASES	3,686	1.939	0.005990
70	Surgical Infections	2,018	1.921	0.004280

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
71	AIDS RESEARCH AND HUMAN RETROVIRUSES	4,009	1.805	0.007780
72	ENFERMEDADES INFECCIOSAS Y MICROBIOLOGIA CLINICA	1,533	1.685	0.001970
73	JOURNAL OF CHEMOTHERAPY	1,445	1.599	0.001680
74	Mediterranean Journal of Hematology and Infectious Diseases	746	1.586	0.001710
75	JOURNAL OF INFECTION AND CHEMOTHERAPY	2,519	1.539	0.004930
76	INTERNATIONAL JOURNAL OF STD & AIDS	2,984	1.501	0.006510
77	JOURNAL OF VECTOR BORNE DISEASES	788	1.473	0.001720
78	Sexual Health	1,279	1.421	0.002990
79	Canadian Journal of Infectious Diseases & Medical Microbiology	1,034	1.373	0.001740
80	SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE	205	1.372	0.000690
81	MEDECINE ET MALADIES INFECTIEUSES	1,185	1.289	0.002430
82	Journal of Infection in Developing Countries	2,378	1.175	0.004670
83	CURRENT HIV RESEARCH	981	1.115	0.001800
84	JAPANESE JOURNAL OF INFECTIOUS DISEASES	1,744	1.004	0.002430
85	LEPROSY REVIEW	813	0.541	0.000860
86	Revista Chilena de Infectologia	499	0.428	0.000750
87	SOUTHEAST ASIAN JOURNAL OF TROPICAL MEDICINE AND PUBLIC HEALTH	2,716	0.287	0.001720

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
88	Journal of Pediatric Infectious Diseases	65	0.197	0.000050
89	Boletin de Malariologia y Salud Ambiental	75	0.111	0.000040

VII. The selected publication

Publication:

Donara Margaryan, Nora Renz, Maja Bervar, Robert Zahn, Julia Onken, Michael Putzier, Peter Vajkoczy, Andrej Trampuz.

Spinal implant-associated infections: a prospective multicenter cohort study. Int J Antimicrob Agents. 2020 Oct;56(4):106116.

Link: https://doi.org/10.1016/j.ijantimicag.2020.106116

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

IX. List of publications

1. **Margaryan D**, Renz N, Bervar M, Zahn R, Onken J, Putzier M, Vajkoczy P, Trampuz A. Spinal implant-associated infections: a prospective multicenter cohort study. Int J Antimicrob Agents. 2020 Jul 26:106116. PMID: 32726675
   IF: 4,62

2. **Margaryan D**, Renz N, Gwinner C, Trampuz A. Septische Arthritis des nativen Gelenkes und nach Bandplastik: Diagnostik und Behandlung [Septic arthritis of the native joint and after ligamentoplasty: Diagnosis and treatment]. Orthopade. 2020 Aug;49(8):660-668. German. PMID: 32737513
   IF: 0,81

3. Li C, Ojeda-Thies C, Renz N, **Margaryan D**, Perka C, Trampuz A. The global state of clinical research and trends in periprosthetic joint infection: A bibliometric analysis. Int J Infect Dis. 2020 Jul; 96:696-709. PMID: 32434084.
   IF: 3,20

4. Li C, **Margaryan D**, Ojeda-Thies C, Perka C, Trampuz A. Meta-analysis of serum and/or plasma D-dimer in the diagnosis of periprosthetic joint infection. J Orthop Surg Res. 2020 Aug 6;15(1):298. PMCID: PMC7409706.
   IF: 1,90

X. Acknowledgments

I gratefully acknowledge the support of my advisor PD Dr. Andrej Trampuz who has been an outstanding mentor to me. I am thankful to him for giving me the opportunity to join his team after finishing my residency. Without his thoughtful encouragement and immense knowledge, this thesis never would have been conducted.

Furthermore, I am grateful to Dr. Nora Renz and PD Dr. med Robert Zahn who helped me and patiently supervised the development of this academic work.

I would also like to thank Jannis for inspiring me in achieving this milestone and pursuing my academic goals, as well as his endless support during this entire process.

Finally, a very special thanks go to my parents and my sisters Dianna and Anahit for their love, constant support and patience.

This work is dedicated to you.