

Postoperative Spinal Implant Infections (PSII)—A Systematic Review: What Do We Know So Far and What is Critical About It?

Global Spine Journal
2022, Vol. 12(6) 1231–1246
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DOI: 10.1177/21925682211024198
journals.sagepub.com/home/gsj



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Abstract

Study Design: Systematic review.

Objectives: Postoperative spinal implant infections (PSII) are an increasing challenge in the daily clinical routine. This review summarizes existing knowledge in the field of PSII, including definitions, epidemiology, classifications, risk factors, pathogenesis, symptoms, diagnosis, and treatment.

Methods: A systematic review was performed using a structured PubMed analysis, based on the PRISMA criteria. The search terminology was set as: “spinal implant associated infection OR spinal implant infection OR spinal instrumentation infection OR peri spinal implant infection.” PubMed search was limited to the categories randomized controlled trials (RCT), clinical trials, meta-analysis and (systematic) reviews, whereas case reports were excluded. Studies from January 2000 to December 2020 were considered eligible. A total of 572 studies were identified, 82 references included for qualitative synthesis, and 19 for detailed sub analysis (12 meta-analysis, 7 prospective RCT).

Results: Structural problems in the field of PSII were revealed, including (1) limited level of evidence in clinical studies (missing prospective RCT, metanalyses), (2) small patient numbers, (3) missing standardized definitions, (4) heterogeneity in patient groups, and (5) redundancy in cited literature.

Conclusion: Evidence-based knowledge about spinal implant-associated infections is lacking. All involved medical fields should come together to define the term PSII and to combine their approaches toward research, training, and patient care.

Keywords

PSII, spinal implant infection, surgical site infection, algorithm, definition

Introduction

Rationale

While several review articles describe characteristics of general spinal infections like spondylodiscitis or non-specified surgical site infections (SSI), up to date reviews specifically designed for postoperative spinal implant infections (PSII), for example following posterior instrumentation, are limited. The 3 most frequently cited reviews giving an overview over the entire field of spinal implant infections, including epidemiology, pathogenesis, diagnosis, and therapy include Kasliwal (2013),¹ Gerometta (2012)² and Quaile et al (2012).³ However, no review has summarized the latest research (2013-2020) with a focus on all potential level of evidence I and II studies

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(randomized controlled trials (RCT) and meta-analysis), while describing PSII characteristics in total, and using a systematically analysis following a standardized protocol like the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) criteria.

Objectives

This systematic review aims (1) to summarize the clinically most important characteristics of PSII, (2) to include the latest research results in the field, (3) systematically include all RCT and meta-analysis in the field, and (4) to critically challenge existing results and concepts.

Methods

Eligibility Criteria

RCT, clinical trials, meta-analysis, reviews and systematic reviews were eligible study categories, while case reports were excluded. Publications from January 2000 to December 2020 were considered eligible. English and German articles were accepted language categories. English abstracts of studies written in different languages were individually considered eligible based on whether all necessary information were included in the abstract.

Information Sources

The review was performed on the basis of a systemic analysis using the PRISMA criteria and algorithm. PubMed was used as only data base. In addition to the initial search results, studies were included that were found in the reference part of other reviews and papers, but not in the initial search itself.

Search

The PubMed search criteria included: “spinal implant associated infection OR spinal implant infection OR spinal instrumentation infection OR peri spinal implant infection.” Using the PubMed NCBI filters, RCT, clinical trials, meta-analysis, reviews and systematic reviews were accepted study categories, while case reports and undetermined study categories were excluded. The last search date was January 30th of 2021.

Study Selection

The individual article suitability was based on: (1) description of implant associated infections in specific, not of unspecified infections like general SSI or wound healing delay without differentiation between implant and non-implant associated cases (unspecified terms like “infection” were analyzed in the context of the present study and considered equivalent to PSII, if applicable); (2) relevance toward clinical routine, with exclusion of solely experimental studies; (3) narrative (not systematic) reviews covering duplicated/similar research results were compared based on patient numbers, year of publication and/or

potential level of evidence, and the best match included accordingly. Exclusion criteria included: (1) primary spondylodiscitis/spondylitis treated with instrumentation, (2) spinal tuberculosis infections, (3) infections of spinal cord stimulators, and (4) non English or non German articles.

Data Collection Process

The search was performed by 2 independent reviewers. Duplicated search results were removed, and the remaining articles analyzed, first based on the abstract, then if considered suitable, as a full text.

Data Items

Data was sought in all fields of PSII, including definition, epidemiology, pathogenesis, risk factors, symptoms, diagnosis, treatment and prophylaxis. Unspecific terms like “deep spinal infection” were considered equivalent to the term PSII depending on the context of the study.

Risk of Bias in Individual Studies and Risk of Bias Across Studies

Potential bias of RCTs was evaluated via the revised Cochrane risk of bias tool for randomized trials (RoB 2.0).⁴ Five different categories (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results) were accessed for risk of bias, and studies graded as “low risk of bias” (1; low risk in all domains), “some concerns” (2; at least 1 domain raising concerns), or “high risk of bias” (3; high risk of bias for at least 1 domain or concerns in multiple domains). Bias analysis was independently performed by 2 reviewers (DK and MP). Non-RCT were evaluated via the “risk of bias in non-randomized studies of interventions” (ROBINS-I) tool.⁵ Evaluated bias categories include confounding factors, selection of participants, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported results. Categories were classified in no information (0), low bias (1), moderate bias (2), serious bias (3), and critical bias (4).

Additional Analyzes

All prospective RCT and meta-analysis were summarized separately, to give an overview over all potential level of evidence category I and II studies.

Summary Measures and Synthesis of Results

As no meta-analysis was performed no principal summary measures and no synthesis of results were reported.

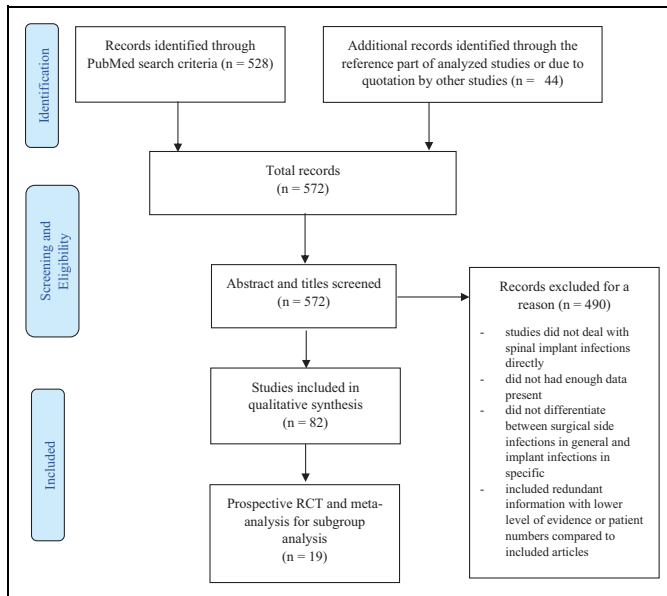


Figure 1. Prisma flow chart.

Results

Study Selection

A total of 572 studies were identified, 528 through the initial search criteria, and an additional 44 records through the reference part of analyzed studies or quotation by analyzed studies (Figure 1).

Study Characteristics

Overall, 82 references, including a detailed analysis of 12 meta-analysis and 7 prospective RCT, were included, as demonstrated by the flow chart (Figure 1).

Results of Individual Studies

Definition and epidemiology. A PSII is not yet defined on an international basis, and is oftentimes not differentiated from the term SSI, especially in older articles.¹⁻³ Trampuz et al (2018) suggested a possible definition based on the EBJIS (European Bone and Joint Infection Society) periprosthetic joint infection (PJI) criteria, and thus considers microbiology, histopathology and clinical signs as possible defining criteria (Table 1)^{6,7} (reference 5 was not included in the systemic PRISMA search). A PSII can either be classified concerning (1) acuity of symptoms or (2) based on the origin of infection. Trampuz et al have suggested a PSII <6 weeks following a surgical intervention an acute, >6 weeks a chronic infection. In cases without a directly prior operation (hematogenous or contiguous), <6 weeks of symptom duration is defined an acute, >6 weeks a chronic PSII.⁶ Alternatively, Pawar et al have suggested <3 weeks an acute, >4 weeks a chronic infection based on results used for SSI.⁸

Table 1. PSII Based on PJI Definition.

PSII (PRO-IMPLANT foundation) ⁶	PJI (EBJIS) ⁷
≥ 1 criterion must be present for diagnosis	≥ 1 criterion must be present for diagnosis
Symptoms: fistula <u>or</u> purulence <u>or</u> probe to implant test	Symptoms: fistula <u>or</u> purulence
Peri-implant inflammation in histology (not specified yet)	Peri-implant inflammation in histology (≥23 granulocytes per 10 high-power fields)
Positive microbiology: ≥ 2 out of at least 3 tissue samples <u>or</u> sonication fluid (≥ 50 CFU/ml)	Positive microbiology: ≥ 2 out of at least 3 tissue samples <u>or</u> sonication fluid (≥ 50 CFU/ml) <u>or</u> synovial fluid
n.a.	Leukocyte count in synovial fluid: > 2000/μl leukocytes <u>or</u> > 70% granulocytes

An infection rate of 0.7 to 20% after spinal instrumentation procedures, based on the review of Kasliwal et al (2013), is cited as a possible range by nearly all authors.¹ In the only systemic analysis present, Patel et al have calculated a pooled average SSI rate of 1.9 (0.1-22.6) % following spinal surgery (196 study cohorts, 425,180 patients), and of 3.8 (0.4-20) % following instrumented spinal fusion (39 study cohorts, 28,628 patients).⁹ Jung et al compared patients treated with (1,176) and without spinal implants (699) in the course of open lumbar surgery within a 15-year period and within 1 single institution. The infection rate within the spinal implant group was significantly higher compared to the non-implant group (2.64% vs. 1%; $P < .05$).¹⁰ Ishii et al reported of a rate of 1.1% of “deep surgical-site infection” within a group of 3,462 instrumented spinal surgeries.¹¹ To the authors best knowledge, the study with the highest patient numbers in the context of “postoperative spinal site infection” is the 1 of Horn et al (2019) using the 2005 to 2013 results of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. 90,551 elective spine surgery patients, of whom 1.4% developed SSI, were identified.¹²

Pathogenesis and risk factors. A differentiation of PSII types can also be based on the focus of infection as local, hematogenous or contiguous.¹³ A prospective study by Margaryan et al (2020) was able to show that 98% of all PSII were acquired during surgery, with the majority of them being acute infections.¹⁴ The most frequently identified microbes include *Staphylococcus aureus*, *Coagulase negative Staphylococci* and *Cutibacterium spp.*¹⁴⁻¹⁶ However, in up to 50% of the cases no microbe can be detected.¹⁷ Following an operation, a local focus should always be suspected first.¹⁴ In chronic cases a hematogenous focus should be considered, with genitourinary as its leading cause.¹⁸ Per continuitatem infections are extremely rare and primarily described in the context of an infected aorta graft.^{19,20} The pathogenesis is based on biofilm formation, with subsequent implant loosening and fistula formation, especially in chronic cases.⁶

Table 2. Risk Factor Classification for PSII / Spinal Site Infection Based on Kasliwal and Blood et al.^{1,21}

Category	Explanation	Risk factors
Unspecific patient related factors	General risk factors that increase the morbidity and mortality in the health care setting, and that are comparable with other surgical fields like hip or knee arthroplasty.	Advanced age, diabetes mellitus, high ASA, obesity, immunosuppression, medications (steroids, alcohol, tobacco), malignancy, (male sex)
Unspecific surgery related factors	General risk factors that increase the morbidity and mortality during surgery, but are not specific for PSII.	Prolonged operation time, prior operation / trauma, malignancy, preoperative hospital stays, use of blood transfusions and cell savers, postoperative complications
Specific surgery related factors	Surgery related risk factors, specific for PSII.	Posterior and open surgical approach, number of involved spinal segments, stainless-steel as implant material

Based on the risk factors for SSI described by Kasliwal et al (2013)¹ and Blood et al, (2017),²¹ a simplified classification of risk factors is possible (Table 2). In the beginning, any foreign spinal material is a risk factor for a spinal infection itself, as compared to non-instrumented cases.¹⁵ In this context, Olsen et al were able to show that a posterior approach was associated with a significantly higher SSI rate in a combined group of patients undergoing laminectomy and/or spinal fusion (OR 8.2, 95% CI 2-33.5).²² In contrast, an anterior approach is associated with a lower infection risk, likely due to less muscle destruction, blood loss and anatomic dead space formation, as hypothesized by Kasliwal et al.¹ Titanium as instrumentation material has demonstrated promising results and is discussed later as part of the prophylaxis section.²³⁻²⁵ Ho et al identified a more distal level of posterior fusion with instrumentation (thoracic as compared to lumbar) as risk factor for infection. However, the infection group only included 30 patients and a multivariate logistic regression analysis could not show significance.²⁶ Schimmel et al identified a higher number of spinal levels as a risk factor for infection in a patient group of 1.568 patients treated with spinal fusion, developing a total of 36 infections.²⁷

Symptoms and diagnosis. To this point there are no clinical studies present that describe the sensitivity, specificity, positive or negative predicative value of specific symptoms in the context of PSII. In addition to classical symptoms of a local infection (redness, pain, swelling, loss of function, warmth), a progression of symptoms following an operation is characteristically, differentiating PSII from physiological / normal postoperative pain.²⁸ Wound drainage (seroma, purulence) is the most common local, fever the most common systemic presentation.²⁹ High-grade microbes (*Staphylococcus aureus*, *Streptococcus* spp.) are primarily responsible for acute postoperative cases (high fever, sepsis, postoperative wound healing), low-virulent microbes like Coagulase-negative staphylococci or *Cutibacterium* are causing chronic PSII, resembled by implant loosening, gradual development of fistulas and neurological deficiencies.⁶

The initial diagnosis of PSII should include a detailed anamnesis, including prior spinal operations and a full body

clinical examination.⁶ In suspected PSII, CRP can be determined next. A CRP < 5mg/l should never be considered an absolute exclusion criterion for a PSII, especially when considering patients with chronic and low-grade infections.^{30,31} Procalcitonin, ESR and a leukocytosis might be alternative diagnostical tools, although their predictive value specifically in the context of PSII has not systematically determined yet.³² Blood cultures should be taken in any patients showing signs of systemic infections or sepsis.³³ An MRI with Gadolinium enhancement is the gold standard for imaging in suspected PSII, and might show epidural fluid collections, bone destructions and marrow inhomogeneity.²⁸ However, CT and plane X-Ray can be used as a faster and cheaper way to rule out or show additional pathologies like fractures or implant loosening, and might show lytic lesions, loosening or pseudarthrosis as indirect signs of an infection.³⁴ Positron emission tomography might be an alternative in undetermined cases following the prior mentioned diagnostical tools.³⁵ In undetermined cases, CT guided biopsy might offer a possible solution.³⁶ Alternative or additional diagnosis, including aseptic implant loosening, spinal tissue infection without implant involvement and skin infections like erysipelas should be excluded at any stage. Identification of possible infection areas is essential and should include hematogenous foci (teeth, heart, lung, urinary tract, foreign devices), local foci (skin, surrounding tissue, bone) or trigger (operations, dental procedures, immunosuppressive medications). Following preoperative diagnosis, intraoperative diagnosis should be performed similar to PJI, and thus should include sonication of removed implants, microbial detection out of the intraoperative samples, and histopathology.³⁷ Akbar et al estimated the probability of microbe detection to be 50% using 2 to 3 intraoperative tissue, and up to 70% using 5 samples, based on results from PJI.³⁸ While present studies indicate high rates of microbe detection using spinal implant sonication,³⁹ histopathology demonstrated poor results in identifying infection. A study by Bürger et al calculated a sensitivity of 51% for the detection of PSII using histopathology in a study cohort of 47 patients, and concluded that histopathology is insufficient, especially when detecting low-grade microbes such as *Cutibacterium*.⁴⁰

Treatment and prophylaxis. The treatment of PSII remains controversial. In 2014 Lall et al systematically analyzed all PubMed studies comparing/discussing the principle of spinal implant retention versus removal. He could not identify a single level of evidence I or II study.⁴¹ In general, a common rather than an isolated surgical and antimicrobial approach is considered a preferred strategy, combined with an interdisciplinary team of microbiologist, orthopedic-/neurosurgeons, and pathologist in a specialized and centralized department.^{42,43} While unstable implants and patients presenting with (impending) neurological damage should undergo imminent implant removal, patients unable to undergo surgery (cardiovascular, anesthesiologic and surgical contraindications, limited life expectancy, personal refusal) can be covered by long term suppressive antibiotic therapy,⁶ although long term results of suppressive antibiotic strategies are still undetermined. Cases involving completed biofilm formation on spinal implants (chronic infections)⁴⁴ and specific microbes that cannot be eradicated by antimicrobial therapy alone (difficult to treat (DTT) microbes)⁶ should undergo implant exchange due to high failure rates.^{45,46} DTT microbes are considered microbes resistant to biofilm active antimicrobial therapy, and include Rifampin resistant gram-positive bacteria, fluoroquinolone resistant gram-negative bacteria, and fungi/candida.⁶ The spinal stability is the critical factor limiting complete and multilevel implant removal, especially considering instable fractures and the following patient mobilization. Thus, exchange for stabilization rather than removal is necessary in instable cases. Debridement and implant retention with antibiotics (DAIR) is a possible treatment strategy for acute infections.⁴⁷⁻⁴⁹ Thereby, a second look surgery might improve the therapeutic outcome in DAIR.⁵⁰ In this context, the role of DAIR in chronic cases unable to undergo implant removal / exchange due to instability or perioperative factors remains unknown.

The exact length of administered antibiotics (AB) remains controversial. Trampuz et al have suggested AB administration for a total of 12 weeks in cases of implant retention and one-stage exchange. According to the authors, a possible empiric intravenous (i.v.) therapy is Vancomycin (2 x 1 g) together with Ampicillin/Sulbactam (3 x 3 g), or together with Piperacillin/Tazobactam (3 x 4.5 g) in cases of multiple previous revisions.⁶ In contrast, Bullmann et al have suggested only 6 weeks of AB following the surgery.⁵¹ All authors agree that, as soon as a specific microbe or a combination is detected, a targeted eradication therapy must be started immediately. The exact combination depends on the microbe's susceptibility, patient weight, renal and liver function. In a 10-year cohort study, Köder et al (2020) were able to show that PSII treated with biofilm active AB demonstrated a significantly higher infection free survival rate as opposed to non-biofilm active AB.⁵²

Despite general trends toward specific treatment paradigms, alternative treatment strategies are still present and should be considered dependent on the individual case. For example, a study by Yin et al (2018) was able to show that aggressive debridement combined with vacuum closed-suction drain and

AB was able to resolve late onset PSII with implant retention in 41 of 42 cases.⁵³ A further study by Bosch-Nicolau et al was able to show that 8 weeks of AB was not inferior to 12 weeks in acute PSII treated with DAIR.⁵⁴

Given the complexity of PSII treatment, an adequate prophylaxis avoiding an infection in the first place is necessary. Prospective RCTs by Meneske and Bible et al covering spinal implants before and during surgery,^{55,56} as well as metanalysis by Stepanow and Khan et al using Vancomycin powder,^{57,58} demonstrated significantly lower infection rates in spinal implant surgeries. However, the risk for development of resistant bacteria is a possible downside in the long run, and thus the indication for prophylactic local AB administration should be critically reviewed.⁵⁹ Further strategies reducing the rate of PSII include AB prophylaxis,⁶⁰ an anterior surgical approach,⁶¹ regular glove changing,^{62,63} minimal invasive surgery,⁶⁴ and AB-impregnated fibrin sealant.⁶⁵

Antibiotic prophylaxis is a critical factor when avoiding PSII in the first place and should be based on the patient's weight, liver and renal function, possible allergies, incision to closure time, blood loss, and previous surgeries. Table 3 is showing an overview over all included clinical original studies dependent on antibiotic prophylaxis and implant type (exclusion of narrative reviews; systematic reviews and prospective RCT are listed separately in Table 4 and 5).⁶⁶⁻⁶⁹ All authors cited in this systematic review, except Tofuku et al⁶⁵ (proposing a synthetic penicillin), used a first- (cefazolin, cephalothin) or second-generation (cefuroxime, cefamandole, cefonicid) cephalosporin as first line preoperative antibiotic prophylaxis.^{10,15,22,26,27,29,39,49,50,54,61} Some authors additionally used a second combined preoperative antibiotic prophylaxis such as an aminoglycoside in selected cases.^{22,70,71} In cases of known allergy to penicillin or cephalosporin, vancomycin was used/suggested by all authors,^{10,15,29,50,61,72} except Bosch-Nicolau et al that suggested a combination of clindamycin and gentamycin in known beta-lactam allergy instead.⁵⁴ While this cephalosporin and aminoglycoside-based prophylaxis is able to reduce the rate of low-virulent organisms such as *S. aureus*, resistant nosocomial microbes as *Pseudomonas aeruginosa* and MRSA are resistant to this first-line prophylaxis.⁷¹

While the selection of first line prophylaxis and first line alternative in allergies is relatively consistent among authors, both dosage and time interval of prophylaxis presents itself inconsistently. Some authors suggest a constant amount of prophylaxis (usually 1-2 g cefazolin),¹⁰ while some propose a body weight adapted dosage (e.g., 50 mg/kg).⁴⁹ All authors agree that cephalosporin prophylaxis should be started at a maximum of 1 hour prior to incision.^{10,29,39,49,50,61,65} A repeated prophylaxis was performed by Collins et al when surgery was more than 2 hours,³¹ by Liu, Lamberet and Litrico et al in operations longer than 4 hours,^{10,49,72} by Fang et al after 6 hours of surgery or significant blood loss,¹³ and by Pull ter Gunne et al after 4 hours or 1.5-liter blood loss.^{29,61}

In contrast, some authors suggest a prolonged antibiotic prophylaxis not only in selected cases but rather as a postoperative standard in all cases, independently of surgery time or

Table 3. Overview Over All Included Clinical Original Studies (Prospective RCT Are Listed Separately in Table 4).

Infection term	Patient characteristics	Spine implant type	Antibiotic prophylaxis (excluding antibiotic treatment in infection)	Outcome
Liu et al, 2015 ¹⁰	31 infections out of 1,176 patients with open lumbar spinal surgery and implant	Arthrodesis, syrinx shunting; material not précised	1-2 g cefazolin or 1 g vancomycin in allergy to penicillin or cephalosporin; additional shot in operations >4h	Total infection rate of 2.64%
Ishii et al, 2013 ¹¹	37 infections out of 3,462 instrumented spinal surgeries	Fusion material, cages, screws, plates, wires; not précised	Not specified	Total infection rate of 1.1%
Horn et al, 2019 ¹²	90,551 elective spine surgery patients; ACS-NSQIP database	Implant type not specified	Not specified	Total infection rate of 1.1%
Margaryan et al, 2020 ¹⁴	250 infections treated with an algorithm	Implant type not specified	no prophylaxis statement; 88% received biofilm-active antibiotics (11.7 weeks median duration)	20% with more than 1 revision, 2.4% died
Fang et al, 2005 ¹⁵	48 infections out of 1,095 patients	Implant type not specified	In all patients first-generation cephalosporin; if allergy, vancomycin; re-dosed after 6 hours of surgery or significant blood loss; continued for 48 hours after surgery, except for simple decompressions (here only until discharge)	Total infection rate of 4.4%
Cahill et al, 2010 ¹⁶	57 infections out of 1,543 pediatric patients who underwent spinal deformity surgery	Implant type not specified	Antibiotic prophylaxis information was not available according to authors and varied among surgeons	Total infection rate of 3.7%
Olsen et al, 2003 ²²	41 cases with SSI or meningitis, 178 uninfected control patients	Laminectomy and/or spinal fusion	Cefazolin alone in 71% and in 10% combined with an aminoglycoside; 11% vancomycin, 5% vancomycin combined with an aminoglycoside, 5% all other	Total infection rate of 2.8%
Soultanis et al, 2008 ²³	50 idiopathic scoliotic patients treated with first-generation stainless steel vs. 45 similar patients treated with titanium	Stainless steel versus titanium implants	Antibiotic prophylaxis information could not be obtained	12% infection rate vs. 2% infection rate
Ho et al, 2007 ²⁶	Posterior spinal fusion in adolescent idiopathic scoliosis (infection group n = 36; no infection n = 90)	TSRH as primary instrumentation except for 1	Antibiotic regimen was not associated with delayed infection; cefazolin was used in all patients except 8 with penicillin allergy	Parameters associated with infection: significant medical history, blood transfusion, no postoperative drain
Schimmel et al, 2010 ²⁷	36 cases with deep SSI; 135 uninfected patients	Lumbar or thoracolumbar spinal fusion	Author recommendation for prophylactic antibiotic therapy to at least 72 h post-surgery (1 g cefazolin every 8h) in history of spinal surgery	Total infection rate 2.2%
Pull ter Gunne et al, 2009 ²⁹	3,174 patients; 132 infections	Implant type not specified	First-generation cephalosporin; 30 minutes before skin incision, redosing every 4 hours or after 1.5l blood loss during the procedure; every 6 for 24 hours after surgery; in allergy, clindamycin when no metallic implants and vancomycin when implant placement	Total infection rate of 4.2%

(continued)

Table 3. (continued)

	Infection term	Patient characteristics	Spine implant type	Antibiotic prophylaxis (excluding antibiotic treatment in infection)	Outcome
Alkun et al, 2019 ³⁰	Postoperative spinal implant infection modified according to EBJS	257 patients with revision surgery after instrumented spinal fusion, 61 infections	Implant type not specified	Not specified	24% infection proportion
Collins et al, 2008 ³¹	Infection following instrumented spinal fusion	1,980 instrumented spinal fusions, 74 infections (years 1993 to 2003)	Stainless steel, since 2003 titanium implants only	Broad-spectrum prophylactic antibiotic, after 2002 repeated 2 hourly antibiotics doses when surgery was more than 2h	Total infection rate of 3.7%
Syvanen et al, 2014 ³²	Acute deep wound infection	50 adolescent scoliosis patients	Implant type not specified	Not specified	Evaluation of procalcitonin's diagnostic value
Prinz et al, 2019 ³⁹	Infection	22 of 82 patients had a positive sonication result	Pedicle screws	Cefazolin 30-60 minutes before surgery	40.7% with positive sonication results
Burger et al, 2020 ⁴⁰	PSII	224 revision spinal cases with implant removal, 64 implant infections	Implant type not specified	Not specified	Low sensitivity of histopathological examination in PSII
Oikonomidis et al, 2020 ⁴³	Implant-associated infection	46 infections	Long-segment spinal instrumentation	Not specified	Treatment outcome: 50% postoperative complication rate, 8.7% mortality rate
Cho et al, 2018 ⁴⁶	Spinal implant infection	102 patients with Staph. aureus spinal implant infection	Titanium cages, plates, screws, rods, hooks	Not specified	Treatment failure in 36%
Moyano et al, 2020 ⁴⁷	SSI	29 pediatric infections with spinal fusion for scoliosis and M. Scheuermann	Implant type not specified	Not specified	3.4% reinfection rate after treatment
Chen et al, 2014 ⁴⁸	Postoperative spinal implant infection	51 infections in the posterolateral thoracolumbar region	Implant type not specified	Not specified	Implant retention in 41 of 51 cases
Lamberet et al, 2018 ⁴⁹	Postoperative spinal implant infection	450 children, 26 infections	Fusion with titanium rods, screws, hocks, ligaments and bone grafts	Up to 1 hour prior to surgery (cefamandole, since 2012 cefazolin), 50 mg/kg (max 2g), repeated in surgery > 4 hours	Total infection rate of 5.8%
Manet et al, 2018 ⁵⁰	Deep SSI	1694 instrumentations, 46 infections	Implant type not specified	33 patients with cefuroxime (median 13 minutes before skin incision), 12 times vancomycin (penicillin allergy; median 12 minutes prior surgery)	Total infection rate of 2.7%
Koder et al, 2020 ⁵²	Spinal implant-associated infection	93 infections	Implant type not specified		Infection-free survival after 1 and 2 years 94% and 84% with, and 57% and 49% without biofilm-active antibiotics (P = .009)
Yin et al, 2018 ⁵³	Late-onset deep SSI	4057 patients, 44 infections	Implant type not specified	Not specified	Total infection rate of 1.0%
Bosch-Nicolau et al, 2019 ⁵⁴	Acute deep spinal implant infection	76 patients treated with debridement and implant retention	Titanium rods, plates, screws, intervertebral cages	Cefazolin or clindamycin plus gentamycin in known beta-lactam allergy	8 weeks of antibiotics are not inferior to 12 weeks

(continued)

Table 3. (continued)

	Infection term	Patient characteristics	Spine implant type	Antibiotic prophylaxis (excluding antibiotic treatment in infection)	Outcome
Pull ter Gunne et al, 2010 ⁶¹	SSI	132 infections	Implant type not specified	First generation cephalosporin; 30 minutes before skin incision, redosing every 4 hours or after 1.5l blood loss during the procedure; every 6 for 24 hours after surgery; in allergy, clindamycin when no metallic implants and vancomycin when implant placement	Deep SSI with debridement and intravenous antibiotics, superficial SSI with local wound care and oral antibiotics.
Tofuku et al, 2012 ⁶⁵	SSI	188 spinal instrumentations without and 196 patients with antibiotic-impregnated fibrin sealant	Implant type not specified	30 min before and after the spinal surgery for 2 more days (synthetic penicillin)	5.8% vs. 0% infection rate
Nota et al, 2015 ⁶⁶	ICD-9 SSI criteria, CDC criteria for deep infection, incision as isolated criterion	5761 adults with spine surgery	Implant type not specified	Not specified	Infection rate 6% with ICD definition, 4% CDC criteria,
Mirovsky et al, 2007 ⁶⁷	Deep wound infection	8 infections out of 111 patients with PLIF	Cages	Cefazolin and Cefonicid in 4 cases each	6 cases with retention, 2 exchanges; no reinfection at 2-year follow-up
Pons et al, 1993 ⁶⁸	Infection	Ceftizoxime (2 g) (n = 422) or vancomycin (1 g) and gentamicin (80 mg) (n = 404) 1 hour before surgery in neurosurgical cases	Exclusion of implants	Ceftizoxime versus vancomycin and gentamicin in neurosurgical prophylaxis	Both groups are the same effective, ceftizoxime is less toxic
Grossi et al, 2020 ⁶⁹	Spinal implant-associated infection	59 patients with <i>C. acnes</i> infection, 93 with different infection, 302 controls without infection	Implant type not specified	Not specified	<i>C. acnes</i> infections in young thin patients with instrumentation of the thoracic spine

Table 4. Overview Over All Identified Prospective RCT Concerning Spinal Implant Infections.

Study	Patient characteristics	Results	Spine implant type	Antibiotic prophylaxis (excluding antibiotic treatment in infection)
Menekse et al (2015) ⁵⁵	22 intervention; 20 control	Spinal implants covered with sterile surgical towel (intervention group) are showing a significantly ($P < .005$) lower contamination rate after >30min compared to uncovered spinal implants (control)	Polyaxial titanium pedicle screws	Not specified
Bible et al (2013) ⁵⁶	51 intervention; 54 control	Implant type (plate, rods, polyetheretherketone) and number of implants are not significantly associated with implant contamination; coverage of implants (intervention group) significantly reduced the implant contamination rate ($P = .016$)	Screws with plates and/or rods, polyetheretherketone	Not specified
Darouiche et al (2017) ⁷⁰	148 intervention; 146 control	Air barrier system devices (intervention group) creating a positive pressure air shield significantly reduce the number of airborne colonies forming units ($P < .001$)	Not specified	Cefazolin or vancomycin (alone 49%, both together 6.5%, combined with another antibiotic 43%) intraoperatively and for 1 to 4 days postoperatively (weight adapted).
Chang et al (2006) ⁷¹	120 intervention; 124 control	Instrumented lumbosacral posterolateral fusion for degenerative spinal disorder: wounds irrigated with 0.35% povidone-iodine solution and normal saline before the instrumentation (intervention) vs. only normal saline solution (control); no infection in intervention group, 6 "deep infections" (in this context considered implant infection) in control group ($P < .05$)	Primary instrumented lumbosacral posterolateral fusion	Pre-operative cefazolin (1g) and gentamicin (60 mg), additional cefazolin (1g/6h) and gentamicin (60 mg/12 h) for 48 h after surgery, and then oral cefazolin (0.5g/6h) for 3 days
Litrico et al (2016) ⁷²	49 intervention; 100 control	One infection with single-use instrumentation in posterior lumbar fusion, 6 infections in control group with reusable instrumentation (no P value given)	Titanium pedicle screws	2g cephalothin before skin incision and every 4h until wound closure; in penicillin allergy 2g vancomycin before skin incision and every 6h until closure
Hellbusch et al (2008) ⁷³	116 intervention; 117 control	No significant difference between single and multiple dose AB prophylaxis in instrumented lumbar fusion concerning infection rates ($P > .25$); exclusion of patients with cephalosporin or severe penicillin allergies	94 TLIF/PLSF, 21 PLIF/PLSF, 5 ALIF, 97 PLSF, 16 minimally invasive sextant fusion	Preoperative only (cefazolin IV) vs. preoperative (cefazolin IV) with an extended postoperative protocol (plus postoperative cefazolin IV every 8 hours for 3 days followed by oral cephalixin every 6 hours for 7 days).
Dromzee et al (2012) ⁷⁵	28 intervention; 28 control	No significant difference between postoperative implant infection in patients with and without a sterile film-forming cyanoacrylate liquid for scoliosis surgery ($P = .096$)	Instrumentation with hybrid constructs including pedicular screws, pedicular and laminar hooks, and rods	Not specified

Table 5. Overview Over All Identified Meta-Analyses Concerning Spinal Implant Infections.

Meta-analysis	Results
Stepanov et al (2020) ⁵⁷	Vancomycin powder reduces the incidence of infection in cases of stabilizing implant surgeries ($P = .004$); 28 studies; 17,469 patients
Keorochana et al (2019) ⁷⁶	Iliac screw fixation with statistically significant higher chance of infection by relative risk of 3.03 (95% CI, 1.62-5.66) compared to sacral 2 alar iliac screw fixation; 7 studies; 377 patients
Luo et al (2017) ⁷⁷	Pedicle screw (PS) compared to hybrid instrumentation (HI) for adolescent idiopathic scoliosis demonstrated no statistically significant difference ($P > .05$) concerning infection (PS 1,068 patients; HI 963 patients). However, a significantly higher rate of reoperations due to “deep infections” (in this context considered implant infection) ($P = .016$) in the PS group (969) was identified compared with the HI group (663)
Khan et al (2014) ⁵⁸	Patients with implants had a reduced risk of infection with vancomycin powder ($P = .023$), compared with those without spinal implants ($P = .226$); 10 studies; 2,574 cases in the control, 2,518 in the treatment group
Phillips et al (2020) ⁷⁴	No statistically significant difference concerning PSII development between extended postoperative and preoperative antimicrobial prophylaxis in instrumented surgery ($P = .93$); 888 patients
Wang et al (2019) ⁷⁸	No statistically significant difference concerning infection between ($P = .24$) cortical bone trajectory and pedicle screw in posterior lumbar fusion surgery; 14 studies; 954 patients
Zhang et al (2018) ⁷⁹	No significant difference concerning postoperative infections between combined pedicle screw fixation at the fracture vertebrae compared to conventional method cross the fracture vertebrae ($P = .39$); 7 studies; 388 patients
Tong et al (2018) ⁸⁰	No statistically significant difference concerning infection rate between intersegmental pedicle screws (4-screw fixation) and addition of intermediate fixation screws (6-screw fixation) for thoracolumbar fractures; 6 studies; 310 patients
Liu et al (2017) ⁸¹	No statistically significant difference concerning infection rate between unilateral and bilateral pedicle screw fixation with PLIF; 6 studies; 500 patients ($P = .32$)
Vertuani et al (2015) ⁸²	Minimal invasive TLIF with lower infection rate (0.09) than an open based TLIF (0.12); no P value calculated
Ye et al (2013) ⁸³	No significant difference between PLF and PLIF group with transpedicular screw fixation for isthmic spondylolithesis concerning infection rate ($P = .191$); 4 studies; 226 cases
Lykissas et al (2013) ⁸⁴	Infection rates following instrumented posterior spinal fusion for adolescent idiopathic scoliosis: Harrington rods (5.5%), cotrel-dubousset (4.3%), pedicle screws (1.1%); 14 studies; 721 patients

blood loss. Pull ter Gunne et al continued the antibiotics for 1 day after surgery,^{29,61} Fang and Tofuku et al for 2 days after surgery,^{15,65} Darouiche et al for 1 to 4 days,⁷⁰ and Chang et al for up to 5 days.⁷¹ Prospective RCT and systematic analysis covering antibiotic prophylaxis are limited. A prospective RCT by Hellbusch et al could not identify a significant difference between single (preoperative i.v. cefazolin only; $n = 117$) and multiple doses of antibiotic prophylaxis (preoperative i.v. cefazolin plus postoperative cefazolin i.v. every 8 hours for 3 days followed by oral cephalexin every 6 hours for 7 days; $n = 116$) in instrumented lumbar fusion concerning infection rates ($P > .25$).⁷³ Similar to that, a systematic review by Phillips et al (2020)⁷⁴ could not identify a statistically significant difference concerning PSII development between extended postoperative and preoperative antimicrobial prophylaxis in instrumented surgery ($P = .93$; 888 patients).

Titanium as instrumentation material has demonstrated promising results. A clinical study by Soultanis et al compared 50 scoliosis patients treated with posterior stainless-steel instrumentation, and 45 patients treated with titanium implants. In the course of the follow-up, 6 patients in the stainless-steel, and 1 patient in the comparison group demonstrated signs of late infection.²³ The superiority of titanium has additionally been shown in several in vitro studies.^{24,25} According to Arens and Meneske et al titanium is the spinal implant of choice due to MRI compatibility, higher biocompatibility, and less risk of infections compared to stainless steel.^{25,55} For that reason,

titanium has become the standard spinal implant in many hospitals. For example, stainless steel was replaced by titanium implants only since 2003 in the hospital reported of by Collins et al.³¹ In contrast, Polyethyleneetherketone (PEEK) is showing a higher infection rate compared to titanium, likely due to its surface allowing for better biofilm formation.¹ However, as demonstrated by Table 4 and Table 5 studies directly comparing titanium, stainless steel and PEEK are limited to the cited study of Soultanis et al and in vitro studies. As many studies do not report a specific material type at all, and the studies are highly heterogenous concerning patient characteristics and intervention, a further comparison of different material among studies is not possible.

Additional Analysis

Existing meta-analysis and prospective RCT. A total of 82 results of the 572 overall identified articles were sub analyzed for prospective RCT and meta-analyses. As demonstrated by Table 4, only 4 RCT were able to show statistically significant results: air barrier system reduces the number of airborne colonies forming units during spinal implant surgery, covering with surgical towels reduces the rate of spinal implant contamination, and 0.35% povidone-iodine solution reduces the rate of infection following instrumentation.^{55,56,70,71} The remaining RCT dealing with PSII could not show significant differences between single-use and reusable instrumentation, postoperative

Table 6. Potential Bias of RCTs (RoB 2.0).

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Darouiche et al (2017) ⁷⁰	1	1	1	1	2	2
Menekse et al (2015) ⁵⁵	1	1	1	2	2	2
Bible et al (2013) ⁵⁶	1	1	2	2	2	2
Chang et al (2006) ⁷¹	1	1	1	2	1	2
Litricio et al (2016) ⁷²	3	2	2	2	2	3
Dromzee et al (2012) ⁷⁵	2	1	1	2	1	2
Hellbusch et al (2008) ⁷³	2	2	1	1	1	2

Table 7. Risk of Bias in Non-RCT (ROBINS-I).

	Deviations							Overall
	Confounding	Selection of participants	Classification of interventions	from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	
Margaryan et al, 2020 ¹⁴	2	2	1	2	1	1	1	2
Soultanis et al, 2008 ²³	3	2	2	2	3	3	2	3
Köder et al, 2020 ⁵²	2	2	1	2	2	2	2	2
Bosch-Nicolau et al, 2019 ⁵⁴	3	2	2	3	2	3	2	3
Tofuku et al, 2012 ⁶⁵	2	2	1	2	3	3	2	3
Pons et al, 1993 ⁶⁸	2	2	2	2	2	1	2	2

infection in patients with and without a sterile film-forming cyanoacrylate liquid, and between single and multiple dose AB prophylaxis.^{72,73,75}

Like with RCT, only 4 meta-analyzes were able to demonstrate statistically significant results (Table 5): Vancomycin powder reduces the rate of spinal implant infection, sacral 2 alar iliac screw fixation showed a lower risk of infection compared to iliac screw fixation, and pedicle screws demonstrated a significantly higher rate of reoperations for reinfection than hybrid instrumentation.^{57,58,76,77} In contrast significantly reduced risk for infection was not identified with extended postoperative and preoperative antimicrobial prophylaxis, or different screw fixation techniques.^{74,78,79,80-84}

After analyzing the context of the study, the term “deep spinal infection”^{71,77} and the unspecified term “infection (rate)”^{57,58,72,76,78} were considered equivalent to the term PSII in the included RCT and meta-analyzes, as opposed to solely wound healing delay and superficial infection. In addition, although not directly reporting of implant infection, studies dealing with “contamination rates” of spinal implants were considered eligible for inclusion, given the limited absolute number of studies.^{55,56,70}

Risk of bias Potential bias was assessed in 7 RCTs via the RoB 2.0 tool (Table 6), the ROBINS-I tool for was used for 6 non-randomized studies. “Some concerns of bias” were identified in all RCTs, except Litricio et al,⁶⁸ in which “high risk of bias” was accessed due to an inadequate randomization process. In contrast, “serious bias” was identified in 3 of the 6 non-randomized studies, primarily due to the measurement of outcome and missing data (Table 7). However, no critical bias could be identified following the evaluation. Overall, no study

fulfilled all criteria for low bias. While an overall number of 32 original studies (excluding RCTs) could be included in Table 3, only 6 of them included an intervention, as most studies were solely descriptive, analyzing specific patient and diagnostically characteristics.

Synthesis of Result

As no metanalysis was performed no confidence intervals and measures of consistency were calculated.

Discussion

Limitations

Up to this point, level of evidence I and II studies in the field of PSII, especially prospective controlled and double blinded studies, as well as meta-analyzes are limited. To the authors best knowledge, not a single prospective double blinded level of evidence I study addressing different treatment strategies for PSII with more than 100 patients is existing at this point. In addition to a limited level of evidence, the absolute numbers are a limiting factor compared to other fields like arthroplasty in which data sets with a few 1.000 patients are present⁸⁵ (reference 79 was not included in the systemic PRISMA search). This problem is aggravated by non-standardized definitions of spinal implant infections. Different articles are using different terms like “spinal site infection,” “superficial / deep infection” or “wound infection.” In 2015 Nota et al already noted that different definitions of the term “surgical site infection” were present, and that the different terms lead to varied frequencies of infection rates after spinal surgery within the same

population.⁶⁶ The term “postoperative spinal implant infection” as used in this article still needs to be defined on an international level. Similar to arthroplasty were several internationally accepted definitions and even a consensus process is present⁸⁶ (reference 86 was not included in the systemic PRISMA search), an international consensus for the term “spinal implant infection” is necessary. The initially mentioned definition of Trampuz et al might be a first step toward this direction.⁶ However, the definition has neither been evaluated in clinical studies, nor been accepted as an international standard, like its EBJIS counterpart. In addition, it remains unknown, if results and definitions initially developed in the field of PJI are directly transferable toward the field of PSII after all. For example, instability within knee and hip joint are of less direct importance compared to the spine where imminent neurological damage can result as a consequence. Thus, implant exchange or even a complete removal like a girdlestone resection arthroplasty might be an option in hip PJI, but are not directly transferable toward the field of PSII. An additional problem includes the heterogeneity even within the group of spinal implant infections, with some infections referring to pedicle screws, others exclusively to cages⁶⁷ and further studies to plates. In this context, it remains unknown if cement is considered a spinal implant. Besides, special patient groups, for example scoliosis surgery patients, known to demonstrate comparable high rates of late-onset infections,⁸⁷ are oftentimes analyzed together with elderly patient groups treated for fractures caused by osteoporosis or trauma.

A final problem, which however also might be a general problem of research in orthopedics, includes the redundancy of cited literature. For example, nearly all articles describing or discussing the field of PSII, including this article, cite the 2-20% infection rate stated by Kasliwal et al without even mentioning different results.¹

Summary of Evidence

As criticized by prior authors, it seems necessary to define the term “spinal implant associated infection / spinal implant infection / spinal instrumentation infection / postoperative spinal implant infection.” While Trampuz et al have already proposed concrete definition criteria, this article suggests an additional more abstract definition of the term. A possible definition can be adapted on the basis of the term “(postoperative) surgical site infection” and has in return to be differentiated by the term in the way that not any spine operation is necessarily using foreign material (e.g., microsurgical nucleotomy following a mediolateral disc prolapse). Based on review results¹⁻³ we therefore suggest the following general definition. A PSII is: (1) an infection of any foreign spinal implant, (2) excluding autologous/allogeneous bone material and cement, (3) independently of the original cause of surgical integration, onset of symptoms and route of infection, (4) with the possibility of peri implant biofilm formation. A possible downside of the presented term PSII includes a strong focus on a recent operation, and thus the term “spinal peri-implant infection” might

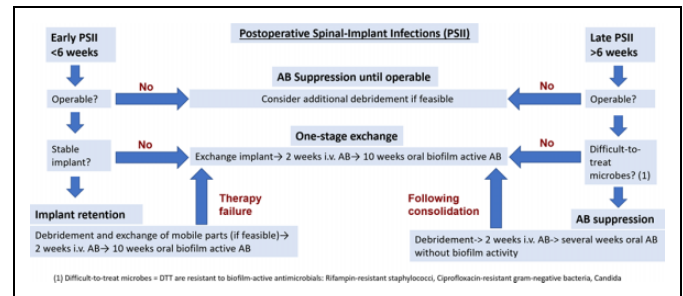


Figure 2. A simplified therapy algorithm for PSII.

be another option to put an additional focus on hematogenous infections without direct prior surgery. In addition, the role of cement and autologous/allogeneous bone material as part of the definition was discussed controversially in our working group. Ultimately the authors decided to exclude bone material and cement from the definition, because (1) the PSII definition was primarily based on existing definitions of PJI, (2) biofilm formation on prosthesis surface differs from the 1 on cement, and (3) isolated infections of integrated bone material and (antibiotic augmented) cement is rare compared to instrumentation.³⁷

Based on the classification of PSII into acute or chronic infections, the operability, the stability of the implant, the types of involved microbes, and the paradigms mentioned in the results part, an additional simplified algorithm-based treatment model was developed for this article (Figure 2). In general, acute PSII with implant stability should be treated with implant retention and debridement, chronic cases without the involvement of difficult to treat microbes (DTT) with a one-stage exchange, given completed biofilm formation on implants, and subsequently reduced options to eradicate bacteria with isolated debridement and AB. AB suppression therapy is an option for inoperable cases and cases involving DTT microbes, until an implant exchange is possible.

Future Approaches

Future training, research and patient care in spinal implant infections should include a combined approach by neurosurgeons, microbiologists, infectiologists, and orthopedic surgeons. Such an approach might not only offer better clinical results, but would also increase the number of patients for studies. Additionally, implications from other fields like arthroplasty and neurosurgery should be critically reviewed and transferred in an adapted way to the field of PSII. For example, RCT should compare existing knowledge about AB prophylaxis in neurosurgery with current concepts in PSII.⁶⁸ An example of such a knowledge transfer is the usage of sonication, initially developed in the field of arthroplasty, which has been successfully established in spinal surgery in recent years.³⁷ Finally, personalized medicine might play a stronger role in the future, as specific risk factors now can be contributed toward specific patient groups, like for example a stronger association of *Cutibacterium acnes* in young, thin patients with instrumentation of the thoracic spine.⁶⁹

Conclusion

International consensus on a standardized definition of the term “spinal implant infection” is necessary. Existing concepts should be critically reviewed, given their limited level of evidence and small patient numbers. A combined approach by neurosurgeons, orthopedic surgeons and infectiologists is essential when dealing with complex patient cases. Both a possible definition and standardized treatment algorithm has been proposed by this article.

Authors' Note

(I) Conception and design: DK, MP

(II) Administrative support: MP

(III) Provision of study materials or patients: review article / n.a.

(IV) Collection and assembly of data: All authors

(V) Data analysis and interpretation: All authors

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors.

ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals were considered.

Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

- Kasliwal MK, Tan LA, Traynelis VC. Infection with spinal instrumentation: review of pathogenesis, diagnosis, prevention, and management. *Surg Neurol Int.* 2013;4(suppl 5):S392-S403. doi:10.4103/2152-7806.120783
- Gerometta A, Rodriguez Olaverri JC, Bitan F. Infections in spinal instrumentation. *Int Orthop.* 2012;36(2):457-464. doi:10.1007/s00264-011-1426-0
- Quaile A. Infections associated with spinal implants. *Int Orthop.* 2012;36(2):451-456. doi:10.1007/s00264-011-1408-2
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:I4898. doi:10.1136/bmj.I4898
- Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919. doi:10.1136/bmj.i4919
- Pocket Guide to Diagnosis & Treatment of Spinal Infections. Version 1: PRO-IMPLANT Foundation. Dr. Andrej Trampuz, Chairman. Published 1 March 2018. Accessed December 2020. Updated December 2020. <https://www.pro-implant-foundation.org/>
- Ochsner P, Borens O, Bodler P, Broger I, Maurer T, Nötzli H. *Infections of the Musculoskeletal System. Basic Principles, Prevention, Diagnosis and Treatment.* Swiss Orthopaedics and the Swiss Society for Infectious Diseases Expert Group; 2014.
- Pawar AY, Biswas SK. Postoperative spine infections. *Asian Spine J.* 2016;10(1):176-183. doi:10.4184/asj.2016.10.1.176. PMID: 26949475; PMCID: PMC4764532.
- Patel H, Houry H, Girgenti D, Welner S, Yu H. Burden of surgical site infections associated with select spine operations and involvement of staphylococcus aureus. *Surg Infect (Larchmt).* 2017;18(4):461-473. doi:10.1089/sur.2016.186. PMID: 27901415; PMCID: PMC5466015.
- Liu JT, Liao WJ, Chang CS, Chen YH. Management of deep infection after instrumentation on lumbar spinal surgery in a single institution. *Biomed Res Int.* 2015;2015:842010. doi:10.1155/2015/842010. PMID: 26273650; PMCID: PMC4529929.
- Ishii M, Iwasaki M, Ohwada T, et al. Postoperative deep surgical-site infection after instrumented spinal surgery: a multicenter study. *Global Spine J.* 2013;3(2):95-102. doi:10.1055/s-0033-1343072. PMID: 24436857; PMCID: PMC3854595.
- Horn SR, Pierce KE, Oh C, et al. Predictors of hospital-acquired conditions are predominately similar for spine surgery and other common elective surgical procedures, with some key exceptions. *Global Spine J.* 2019;9(7):717-723. doi:10.1177/2192568219826083
- Babic M, Simpfendorfer CS. Infections of the spine. *Infect Dis Clin North Am.* 2017;31(2):279-297. doi:10.1016/j.idc.2017.01.003
- Margaryan D, Renz N, Bervar M, et al. Spinal implant-associated infections: a prospective multicenter cohort study. *Int J Antimicrob Agents.* 2020;106116. doi:10.1016/j.ijantimicag.2020.106116. PMID: 32726675.
- Fang A, Hu SS, Endres N, Bradford DS. Risk factors for infection after spinal surgery. *Spine (Phila Pa 1976).* 2005;30(12):1460-1465.
- Cahill PJ, Warnick DE, Lee MJ, et al. Infection after spinal fusion for pediatric spinal deformity: thirty years of experience at a single institution. *Spine (Phila Pa 1976).* 2010;35(12):1211-1217. doi:10.1097/BRS.0b013e3181c212d1.
- Jeong SJ, Choi SW, Youm JY, Kim HW, Ha HG, Yi JS. Microbiology and epidemiology of infectious spinal disease. *J Korean Neurosurg Soc.* 2014;56(1):21-27. doi:10.3340/jkns.2014.56.1.21
- Tsantes AG, Papadopoulos DV, Vrioni G, et al. Spinal infections: an update. *Microorganisms.* 2020;8(4):476. doi:10.3390/microorganisms8040476
- Mavrogenis AF, Triantafyllopoulos GK, Kokkinis K, Stefanos A, Sipsas NV, Pneumaticos SG. Continuous L3 spondylitis caused by an infected endovascular aortic graft. *Surg Infect (Larchmt).* 2014;15:861-862. doi:10.1089/sur.2013.219
- Megaloiakonimos P, Antoniadou T, Dimopoulos L, et al. Spondylitis transmitted from infected aortic grafts: a review. *J Bone Jt Infect.* 2017;2:96-103. doi:10.7150/jbji.17703
- Blood AG, Sandoval MF, Burger E, Halverson-Carpenter K. Risk and protective factors associated with surgical infections among spine patients. *Surg Infect (Larchmt).* 2017;18(3):234-249. doi:10.1089/sur.2016.183. PMID: 28394747.

22. Olsen MA, Mayfield J, Laurysen C, et al. Risk factors for surgical site infection in spinal surgery. *J Neurosurg*. 2003;98(2 suppl): 149-155. PMID: 12650399.
23. Soultanis KC, Pyrovolou N, Zahos KA, et al. Late postoperative infection following spinal instrumentation: stainless steel versus titanium implants. *J Surg Orthop Adv*. 2008;17(3):193-199. PMID: 18851806.
24. Schildhauer TA, Robie B, Muhr G, Köller M. Bacterial adherence to tantalum versus commonly used orthopedic metallic implant materials. *J Orthop Trauma*. 2006;20(7):476-484. doi:10.1097/00005131-200608000-00005. PMID: 16891939.
25. Arens S, Schlegel U, Printzen G, Ziegler WJ, Perren SM, Hansis M. Influence of materials for fixation implants on local infection. An experimental study of steel versus titanium DCP in rabbits. *J Bone Joint Surg Br*. 1996;78(4):647-651. PMID: 8682836.
26. Ho C, Sucato DJ, Richards BS. Risk factors for the development of delayed infections following posterior spinal fusion and instrumentation in adolescent idiopathic scoliosis patients. *Spine (Phila Pa 1976)*. 2007;32(20):2272-2277. doi:10.1097/BRS.0b013e31814b1c0b. PMID: 17873822.
27. Schimmel JJ, Horsting PP, de Kleuver M, Wonders G, van Limbeek J. Risk factors for deep surgical site infections after spinal fusion. *Eur Spine J*. 2010;19(10):1711-1719. doi:10.1007/s00586-010-1421-y. PMID: 20445999; PMCID: PMC2989231.
28. Zippelius T, Bürger J, Schömig F, Putzier M, Matziolis G, Strube P. Clinical presentation and diagnosis of acute postoperative spinal implant infection (PSII). *J Spine Surg*. 2020;6(4): 765-771. doi:10.21037/jss-20-587
29. Pull ter Gunne A, Cohen D. Incidence, prevalence, and analysis of risk factors for surgical site infection following adult spinal surgery. *Spine*. 2009;34:1422-1428. doi:10.1097/BRS.0b013e3181a03013.
30. Akgün D, Bürger J, Pumberger M, Putzier M. C-reactive protein misdiagnoses delayed postoperative spinal implant infections in patients with low-virulent microorganisms. *Eur Spine J*. 2019; 28(12):2990-2995. doi:10.1007/s00586-019-05889-3.
31. Collins I, Wilson-MacDonald J, Chami G, et al. The diagnosis and management of infection following instrumented spinal fusion. *Eur Spine J*. 2008;17(3):445-450. doi:10.1007/s00586-007-0559-8
32. Syvänen J, Peltola V, Pajulo O, Ruuskanen O, Mertsola J, Helenius I. Normal behavior of plasma procalcitonin in adolescents undergoing surgery for scoliosis. *Scand J Surg*. 2014;103(1): 60-65. doi:10.1177/1457496913504910. PMID: 24520101.
33. Chahoud J, Kanafani Z, Kanj SS. Surgical site infections following spine surgery: eliminating the controversies in the diagnosis. *Front Med (Lausanne)*. 2014;1:7. doi:10.3389/fmed.2014.00007. PMID: 25705620; PMCID: PMC4335387.
34. Winegar BA, Kay MD, Chadaz TS, Taljanovic MS, Hood KA, Hunter TB. Update on imaging of spinal fixation hardware. *Semin Musculoskelet Radiol*. 2019;23(2):e56-e79. doi:10.1055/s-0038-1677468. PMID: 30925634.
35. Georgakopoulos A, Pneumaticos SG, Sipsas NV, Chatziioannou S. Positron emission tomography in spinal infections. *Clin Imaging*. 2015;39(4):553-558. doi:10.1016/j.clinimag.2015.04.002. PMID: 25914050.
36. Sertic M, Parkes L, Mattiassi S, Pritzker K, Gardam M, Murphy K. The efficacy of computed tomography-guided percutaneous spine biopsies in determining a causative organism in cases of suspected infection: a systematic review. *Can Assoc Radiol J*. 2019;70(1):96-103. doi:10.1016/j.carj.2018.09.003.
37. Karczewski D, Pumberger M, Müller M, Andronic O, Perka C, Winkler T. Implications for diagnosis and treatment of peri-spinal implant infections from experiences in periprosthetic joint infections—a literature comparison and review. *J Spine Surg*. 2020; 6(4):800-813. doi:10.21037/jss-20-12
38. Akbar M, Lehner B, Ryang YM, Pepke W. Low-grade-infektionen in der wirbelsäulenchirurgie—ein chamäleon?: neuste erkenntnisse und behandlungsstrategien. Low-grade-infections after spondylodeses—a chameleon?: current findings and therapeutic strategies. *Orthopade*. 2020;49(8):669-678. German. doi:10.1007/s00132-020-03947-z. Erratum in: *Orthopade*. 2020 Sep;49(9):823-824. PMID: 32676718.
39. Prinz V, Bayerl S, Renz N, et al. High frequency of low-virulent microorganisms detected by sonication of pedicle screws: a potential cause for implant failure. *J Neurosurg Spine*. 2019; 31(3):424-429. doi:10.3171/2019.1.SPINE181025
40. Bürger J, Palmowski Y, Strube P, Perka C, Putzier M, Pumberger M. Low sensitivity of histopathological examination of peri-implant tissue samples in diagnosing postoperative spinal implant infection. *Bone Joint J*. 2020;102-B(7):899-903. doi:10.1302/0301-620X.102B7.BJJ-2019-1725.R2
41. Lall RR, Wong AP, Lall RR, Lawton CD, Smith ZA, Dahdaleh NS. Evidence-based management of deep wound infection after spinal instrumentation. *J Clin Neurosci*. 2015;22(2):238-242. doi:10.1016/j.jocn.2014.07.010. PMID: 25308619.
42. Quiñones-Hinojosa A, Jun P, Jacobs R, Rosenberg WS, Weinstein PR. General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. *Neurosurg Focus*. 2004;17(6):E1. doi:10.3171/foc.2004.17.6.1. PMID: 15636566.
43. Oikonomidis S, Altenrath L, Westermann L, Bredow J, Eysel P, Scheyerer MJ. Implant-associated infection of long-segment spinal instrumentation: a retrospective analysis of 46 consecutive patients. *Asian Spine J*. 2020;15(2):234-243. doi:10.31616/asj.2019.0391. PMID: 32703924.
44. Agarwal A, Kelkar A, Agarwal AG, et al. Implant retention or removal for management of surgical site infection after spinal surgery. *Global Spine J*. 2020;10(5):640-646. doi:10.1177/2192568219869330. PMID: 32677561; PMCID: PMC7359681.
45. Lora-Tamayo J, Senneville É, Ribera A, et al. The not-so-good prognosis of streptococcal periprosthetic joint infection managed by implant retention: the results of a large multicenter study. *Clin Infect Dis*. 2017;64(12):1742-1752. doi:10.1093/cid/cix227. PMID: 28369296.
46. Cho OH, Bae IG, Moon SM, et al. Therapeutic outcome of spinal implant infections caused by *Staphylococcus aureus*: a retrospective observational study. *Medicine (Baltimore)*. 2018; 97(40):e12629. doi:10.1097/MD.00000000000012629. PMID: 30290637; PMCID: PMC6200525.
47. Moyano CA, Tello CA, Piantoni L, et al. Infection recurrence in instrumented spinal fusion in children. *Global Spine J*. 2020. doi: 10.1177/2192568220935818. PMID: 32783471.

48. Chen SH, Lee CH, Huang KC, Hsieh PH, Tsai SY. Postoperative wound infection after posterior spinal instrumentation: analysis of long-term treatment outcomes. *Eur Spine J*. 2015;24(3):561-570. doi:10.1007/s00586-014-3636-9. PMID: 25351841.
49. Lamberet A, Violas P, Buffet-Bataillon S, et al. Postoperative spinal implant infections in children: risk factors, characteristics and outcome. *Pediatr Infect Dis J*. 2018;37(6):511-513. doi:10.1097/INF.0000000000001812. PMID: 29088025.
50. Manet R, Ferry T, Castelain JE, et al. Relevance of modified debridement-irrigation, antibiotic therapy and implant retention protocol for the management of surgical site infections: a series of 1694 instrumented spinal surgery. *J Bone Jt Infect*. 2018;3(5):266-272. doi:10.7150/jbji.28765. PMID: 30662819; PMCID: PMC6328300.
51. Bullmann V. Evidenzbasierte Implantatwahl bei Infektionen der Wirbelsäule: Ist es doch eine Bauchsache? Evidence-based implant choice in infections of the spine: is it a gut thing, after all? *Orthopade*. 2020;49(8):685-690. German. doi:10.1007/s00132-020-03955-z. PMID: 32661896.
52. Köder K, Hardt S, Gellert MS, et al. Outcome of spinal implant-associated infections treated with or without biofilm-active antibiotics: results from a 10-year cohort study. *Infection*. 2020;48(4):559-568. doi:10.1007/s15010-020-01435-2. PMID: 32372396; PMCID: PMC7395063.
53. Yin D, Liu B, Chang Y, Gu H, Zheng X. Management of late-onset deep surgical site infection after instrumented spinal surgery. *BMC Surg*. 2018;18(1):121. doi:10.1186/s12893-018-0458-4. PMID: 30577832; PMCID: PMC6303994.
54. Bosch-Nicolau P, Rodríguez-Pardo D, Pigrau C, et al. Acute spinal implant infection treated with debridement: does extended antibiotic treatment improve the prognosis? *Eur J Clin Microbiol Infect Dis*. 2019;38(5):951-958. doi:10.1007/s10096-019-03537-8. PMID: 30904996.
55. Menekse G, Kuscu F, Suntur BM, et al. Evaluation of the time-dependent contamination of spinal implants: prospective randomized trial. *Spine (Phila Pa 1976)*. 2015;40(16):1247-1251. doi:10.1097/BRS.0000000000000944. PMID: 25929209.
56. Bible JE, O'Neill KR, Crosby CG, Schoenecker JG, McGirt MJ, Devin CJ. Implant contamination during spine surgery. *Spine J*. 2013;13(6):637-640. doi:10.1016/j.spinee.2012.11.053. PMID: 23321148.
57. Stepanov IA, Beloborodov VA, Borisov VE, Aliev MA, Shepelev VV, Pestryakov YY. Effektivnost' lokal'nogo primeneniya poroshka vankomitsina v profilaktike infektsii oblasti khirurgicheskogo vmeshatel'stva v spinal'noi khirurgii: metaanaliz. The effectiveness of local application of vancomycin powder in the prevention of surgical site infections in spine surgery: a meta-analysis. *Khirurgiia (Mosk)*. 2020;(6):60-70. Russian. doi:10.17116/hirurgia202006160. PMID: 32573534.
58. Khan NR, Thompson CJ, DeCuypere M, et al. A meta-analysis of spinal surgical site infection and vancomycin powder. *J Neurosurg Spine*. 2014;21(6):974-983. doi:10.3171/2014.8.SPINE1445. PMID: 25259555.
59. Sartori M, Contartese D, Salamanna F, et al. Spinal fusion surgery and local antibiotic administration: a systematic review on key points from preclinical and clinical data. *Spine (Phila Pa 1976)*. 2020;45(5):339-348. doi:10.1097/BRS.0000000000003255. Erratum in: *Spine (Phila Pa 1976)*. 2020;45(10):E607. PMID: 31568186.
60. Barker FG. 2nd efficacy of prophylactic antibiotic therapy in spinal surgery: a meta-analysis. *Neurosurgery*. 2002;51:391-400.
61. Pull ter Gunne A, Mohamed A, Skolasky R, Laarhoven C, Cohen D. The presentation, incidence, etiology and treatment of surgical site infections after spinal surgery. *Spine*. 2010;35(13):1323-1328.
62. Schömig F, Perka C, Pumberger M, Ascherl R. Implant contamination as a cause of surgical site infection in spinal surgery: are single-use implants a reasonable solution?—a systematic review. *BMC Musculoskelet Disord*. 2020;21(1):634. doi:10.1186/s12891-020-03653-z. PMID: 32977778; PMCID: PMC7519515.
63. Agarwal A, Schultz C, Goel VK, et al. Implant prophylaxis: the next best practice toward asepsis in spine surgery. *Global Spine J*. 2018;8(7):761-765. doi:10.1177/2192568218762380. PMID: 30443488; PMCID: PMC6232723.
64. Vazan M, Gempt J, Meyer B, Buchmann N, Ryang YM. Minimally invasive transforaminal lumbar interbody fusion versus open transforaminal lumbar interbody fusion: a technical description and review of the literature. *Acta Neurochir (Wien)*. 2017;159(6):1137-1146. doi:10.1007/s00701-017-3078-3. PMID: 28160064.
65. Tofuku K, Koga H, Yanase M, Komiya S. The use of antibiotic-impregnated fibrin sealant for the prevention of surgical site infection associated with spinal instrumentation. *Eur Spine J*. 2012;21(10):2027-2033. doi:10.1007/s00586-012-2435-4. PMID: 22820952; PMCID: PMC3463706.
66. Nota SP, Braun Y, Ring D, Schwab JH. Incidence of surgical site infection after spine surgery: what is the impact of the definition of infection? *Clin Orthop Relat Res*. 2015;473(5):1612-1619. doi:10.1007/s11999-014-3933-y. PMID: 25212963; PMCID: PMC4385381.
67. Mirovsky Y, Floman Y, Smorgick Y, et al. Management of deep wound infection after posterior lumbar interbody fusion with cages. *J Spinal Disord Tech*. 2007;20:127-131.
68. Pons VG, Denlinger SL, Guglielmo BJ, et al. Ceftizoxime versus vancomycin and gentamicin in neurosurgical prophylaxis: a randomized, prospective, blinded clinical study. *Neurosurgery*. 1993;33(3):416-422. Discussion 422-3. doi:10.1227/00006123-199309000-00010. PMID: 8413872.
69. Grossi O, Lamberet R, Longis PM, et al. Risk factors for cutibacterium acnes spinal implant-associated infection: a case-case-control study. *Clin Microbiol Infect*. 2020;26(6):743-747. doi:10.1016/j.cmi.2019.10.018. PMID: 31669425.
70. Darouiche RO, Green DM, Harrington MA, et al. Association of airborne microorganisms in the operating room with implant infections: a randomized controlled trial. *Infect Control Hosp Epidemiol*. 2017;38(1):3-10. doi:10.1017/ice.2016.240. PMID: 27780479.
71. Chang FY, Chang MC, Wang ST, Yu WK, Liu CL, Chen TH. Can povidone-iodine solution be used safely in a spinal surgery? *Eur Spine J*. 2006;15(6):1005-1014. doi:10.1007/s00586-005-0975-6. PMID: 16133077; PMCID: PMC3489437.

72. Litrico S, Recanati G, Gennari A, Maillot C, Saffarini M, Le Huec JC. Single-use instrumentation in posterior lumbar fusion could decrease incidence of surgical site infection: a prospective bi-centric study. *Eur J Orthop Surg Traumatol*. 2016;26(1):21-26. doi:10.1007/s00590-015-1692-4. PMID: 26325248.
73. Hellbusch LC, Helzer-Julian M, Doran SE, et al. Single-dose vs multiple-dose antibiotic prophylaxis in instrumented lumbar fusion—a prospective study. *Surg Neurol*. 2008;70(6):622-627. Discussion 627. doi:10.1016/j.surneu.2007.08.017. PMID: 18207532.
74. Phillips BT, Sheldon ES, Orhurhu V, et al. Preoperative versus extended postoperative antimicrobial prophylaxis of surgical site infection during spinal surgery: a comprehensive systematic review and meta-analysis. *Adv Ther*. 2020;37(6):2710-2733. doi:10.1007/s12325-020-01371-5. PMID: 32415484; PMCID: PMC7467442.
75. Dromzee E, Tribot-Laspière Q, Bachy M, Zakine S, Mary P, Vialle R. Efficacy of integuseal for surgical skin preparation in children and adolescents undergoing scoliosis correction. *Spine (Phila Pa 1976)*. 2012;37(21):E1331-E1335. doi:10.1097/BRS.0b013e3182687d6c. PMID: 22814302.
76. Keorochana G, Arirachakaran A, Setrkraising K, Kongtharvonskul J. Comparison of complications and revisions after sacral 2 alar iliac screw and iliac screw fixation for sacropelvic fixation in pediatric and adult populations: systematic review and meta-analysis. *World Neurosurg*. 2019;132:408-420.e1. doi:10.1016/j.wneu.2019.08.104. PMID: 31465853.
77. Luo M, Li N, Shen M, Xia L. Pedicle screw versus hybrid instrumentation in adolescent idiopathic scoliosis: a systematic review and meta-analysis with emphasis on complications and reoperations. *Medicine (Baltimore)*. 2017;96(27):e7337. doi:10.1097/MD.0000000000007337. PMID: 28682881; PMCID: PMC5502154.
78. Wang J, He X, Sun T. Comparative clinical efficacy and safety of cortical bone trajectory screw fixation and traditional pedicle screw fixation in posterior lumbar fusion: a systematic review and meta-analysis. *Eur Spine J*. 2019;28(7):1678-1689. doi:10.1007/s00586-019-05999-y. PMID: 31087165.
79. Zhang C, Liu Y. Combined pedicle screw fixation at the fracture vertebrae versus conventional method for thoracolumbar fractures: a meta-analysis. *Int J Surg*. 2018;53:38-47. doi:10.1016/j.ijssu.2018.03.002. PMID: 29535015.
80. Tong MJ, Tang Q, Wang CG, et al. Efficacy of using intermediate screws in short-segment fixation for thoracolumbar fractures: a meta-analysis of randomized controlled trials. *World Neurosurg*. 2018;110:e271-e280. doi:10.1016/j.wneu.2017.10.157. PMID: 29113901.
81. Liu H, Xu Y, Yang SD, et al. Unilateral versus bilateral pedicle screw fixation with posterior lumbar interbody fusion for lumbar degenerative diseases: a meta-analysis. *Medicine (Baltimore)*. 2017;96(21):e6882. doi:10.1097/MD.0000000000006882. PMID: 28538379; PMCID: PMC5457859.
82. Vertuani S, Nilsson J, Borgman B, et al. A cost-effectiveness analysis of minimally invasive versus open surgery techniques for lumbar spinal fusion in Italy and the United Kingdom. *Value Health*. 2015;18(6):810-816. doi:10.1016/j.jval.2015.05.002. PMID: 26409608.
83. Ye YP, Xu H, Chen D. Comparison between posterior lumbar interbody fusion and posterolateral fusion with transpedicular screw fixation for isthmic spondylolysis: a meta-analysis. *Arch Orthop Trauma Surg*. 2013;133(12):1649-1655. doi:10.1007/s00402-013-1868-5. PMID: 24136445; PMCID: PMC3828496.
84. Lykissas MG, Jain VV, Nathan ST, et al. Mid- to long-term outcomes in adolescent idiopathic scoliosis after instrumented posterior spinal fusion: a meta-analysis. *Spine (Phila Pa 1976)*. 2013;38(2):E113-E119. doi:10.1097/BRS.0b013e31827ae3d0. PMID: 23124268.
85. Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev*. 2014;27(2):302-345. doi:10.1128/CMR.00111-13. PMID: 24696437; PMCID: PMC3993098.
86. Cats-Baril W, Gehrke T, Huff K, Kendoff D, Maltenfort M, Parvizi J. International consensus on periprosthetic joint infection: description of the consensus process. *Clin Orthop Relat Res*. 2013;471(12):4065-4075. doi:10.1007/s11999-013-3329-4. PMID: 24155178; PMCID: PMC3825924.
87. Bose B. Delayed infection after instrumented spine surgery: case reports and review of the literature. *Spine J*. 2003;3(5):394-399. doi:10.1016/s1529-9430(03)00023-8. PMID: 14588952.