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REVIEW ARTICLE

Outcome of conservative and surgical treatment of pyogenic spondylodiscitis: a systematic literature review

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Abstract
Background Spondylodiscitis is a spinal infection affecting primarily the intervertebral disk and the adjacent vertebral bodies. Currently many aspects of the treatment of pyogenic spondylodiscitis are still a matter of debate.
Purpose The aim of this study was to review the currently available literature systematically to determine the outcome of patients with pyogenic spondylodiscitis for conservative and surgical treatment strategies.
Methods A systematic electronic search of MEDLINE, EMBASE, Cochrane Collaboration, and Web of Science regarding the treatment of pyogenic spondylodiscitis was performed. Included articles were assessed on risk of bias according the Cochrane Handbook for Systematic Reviews of Interventions, and the quality of evidence and strength of recommendation was evaluated according the GRADE approach.
Results 25 studies were included. Five studies had a high or moderate quality of evidence. One RCT suggest that 6 weeks of antibiotic treatment of pyogenic spondylodiscitis results in a similar outcome when compared to longer treatment duration. However, microorganism-specific studies suggest that at least 8 weeks of treatment is required for *S. aureus* and 8 weeks of Daptomycin for MRSA. The articles that described the outcome of surgical treatment strategies show that a large variety of surgical techniques can successfully treat spondylodiscitis. No additional long-term beneficial effect of surgical treatment could be shown in the studies comparing surgical versus antibiotic only treatment.
Conclusion There is a strong level of recommendation for 6 weeks of antibiotic treatment in pyogenic spondylodiscitis although this has only been shown by one recent RCT. If surgical treatment is indicated, it has been suggested by two prospective studies with strong level of recommendation that an isolated anterior approach could result in a better clinical outcome.

Keywords Spondylodiscitis · Pyogenic · Treatment · Systematic review · Outcome

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Introduction

Spondylodiscitis, also known as vertebral osteomyelitis or bacterial spondylitis, is the most common spinal infection, which affects the intervertebral disk, adjacent vertebral bodies, and occasionally also the posterior elements of the spine [1, 2]. The incidence of spondylodiscitis ranges from 0.2 till 2.4 per 100.000 per year in the Western countries [2, 3]. Generally three types of spondylodiscitis are recognized; pyogenic, granulomatous (tuberculous, brucellar, aspergillar, and fungal), and parasitic [2, 4]. In the mid twentieth century, the majority of the reported cases in literature consisted of granulomatous infections with up to 59 % of the cases caused by Mycobacterium tuberculosis [3, 5, 6]. The name granulomatous spondylodiscitis is somewhat misleading since spinal tuberculosis typically involves the vertebral bodies and to lesser extent the

intervertebral disks. Nowadays, only 24 % is caused by tuberculosis and the vast majority of the cases of spinal infections are pyogenic [3, 5, 6]. Besides a relative increase in pyogenic spondylodiscitis, there also appears to be an increase in the total incidence [1, 3, 7, 8]. This increase in incidence is thought to be caused by the aging population, by the rise of immunosuppressed patients, of intravenous drug use and of improved diagnostic possibilities [1, 3, 7, 8].

Although diagnostic and therapeutic possibilities have drastically improved during the past decades, pyogenic spondylodiscitis remains a diagnostic and therapeutic challenge. Since it is often a complication of a distant process causing bacteremia, the relatively nonspecific array of symptoms of spondylodiscitis may be initially dominated by the primary infection [9]. Consequently, clinical presentation is often unclear and a considerable delay in diagnosis frequently occurs [2, 3, 10]. Spondylodiscitis remains a life-threatening disease with a mortality rate of 2–20 % [10, 11]. Although some therapeutic guidelines are available, treatment of spondylodiscitis is certainly not standardized and is mostly based on local preferences resulting in physician-related variability [12–15]. Conservative treatment, comprising of long-term antibiotics optionally combined with bed rest and/or an orthosis, appears to be the treatment of choice for the majority of the patients [3]. However, there is still debate about the optimal duration of intravenous and oral antibiotic treatment. Furthermore is it unclear whether there is a relation between treatment duration and relapse or treatment failure.

Apart from the antibiotic treatment, some of the cases with pyogenic spondylodiscitis may require surgical debridement and stabilization. The indications for surgery are compression of neurological structures, mechanical instability, spinal deformity, and failure of adequate conservative treatment. However, there is an enormous variation in surgical techniques described for the treatment of pyogenic spondylodiscitis [1–3, 10, 11]. Classically anterior debridement and stabilization has been the preferred treatment, since the anterior part of the spine is the most commonly involved in spondylodiscitis [2]. In recent literature, however, both more elaborated combined anterior–posterior approaches, less invasive posterior stabilization, or transpedicular curettage and drainage have been described [16–18]. Whereas the open surgical procedures are thought to reduce the loss of sagittal balance and minimize the risk of relapse, less invasive strategies are a lower burden for the patients with potentially fewer complications [16, 17].

Many fundamental aspects of the treatment of pyogenic spondylodiscitis are still a matter of debate. Therefore, the aim of this study was to systematically review the currently available literature to determine the outcome; defined as relapse rate, treatment failure and mortality; in patients with pyogenic spondylodiscitis after the different antibiotic and/or surgical treatments.

Methods

This systematic literature review regarding the outcomes of treatment of pyogenic spondylodiscitis was preformed according the PRISMA guidelines for systematic reviews and was registered at Prospero; the international register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO) [19, 20], registration number: CRD42015020618.

Literature search

We conducted an electronic search of databases of MEDLINE, EMBASE, Cochrane Collaboration, and Web of Science on the 1st of January 2015 for articles in English language regarding treatment of spondylodiscitis that were published since 2000 [21–24]. We used a standardized search strategy including search keywords (spondylodiscitis, vertebral osteomyelitis, osteodiscitis, discitis, treatment, therapy, antibiotics, and surgery). In addition, to prevent omission of relevant articles from before 2000, the references of the included articles and recent reviews regarding the treatment of spondylodiscitis were screened for relevant literature [1–3, 10, 11]. Literature before 2000 was not systematically assessed since research before 2000 was predominantly focused on infections caused by tuberculosis. Details about the used search strategy are presented in Table 1.

Study selection

A stepwise procedure to identify relevant studies was used. First, the title and abstract of all articles were systematically assessed using the inclusion and exclusion criteria as described in Table 2. Second, all included articles were assessed full text by two independent reviewers (JR and DK). This critical appraisal was performed according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [25]. In order to determine the extent of selection bias, the selection procedures and the homogeneity of the patient populations were examined. The studies were also assessed on the standardization of antibiotic treatment, operative procedure and peri- and postoperative care in order to determine the risk on performance bias. Attrition bias was scored on the basis of percentage follow-up and exclusion criteria. The risk on detection bias was based on the description of how the data was acquired (for example blinding) and how statistical analysis was performed.

Table 1 Search strategy

Database	Search	Limits
Medline	(Spondylodiscitis [title/abstract] OR vertebral osteomyelitis [title/abstract] OR osteodiscitis [title/abstract] OR (discitis [title/abstract] AND spondylitis [title/abstract])) AND (Treatment [title/abstract] OR therapy [title/abstract] OR antibiotics [title/abstract] OR surgery [title/abstract])	2000–2015 English
Embase	(spondylodiscitis:ab,ti OR (vertebral AND osteomyelitis:ab,ti) OR osteodiscitis:ab,ti OR (discitis:ab,ti AND spondylitis:ab,ti)) AND (treatment:ab,ti OR therapy:ab,ti OR antibiotics:ab,ti OR surgery:ab,ti) AND [2000–2014]/py	2000–2015 English
Cochrane library	Spondylodiscitis OR (vertebral AND osteomyelitis) OR osteodiscitis OR (discitis AND spondylitis)) AND (treatment OR therapy OR antibiotics OR surgery)	2000–2015 English
Web of science	TS = (Spondylodiscitis OR vertebral osteomyelitis OR osteodiscitis OR (discitis AND spondylitis)) AND TS = (Treatment OR therapy OR antibiotics OR surgery)	2000–2015 English

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Study on the treatment of pyogenic spondylodiscitis in adult patients
	Study design: meta-analysis, RCT, prospective trails, comparative studies, and large case series ≥100 patients
Exclusion criteria	Study design: Case reports, case series <100 patients, and review articles
	>50 % tuberculosis, aspergillosis, brucellosis, and postoperative infections
	Studies on solitary epidural abscesses
	Children (<18 years)

Quality assessment

The quality of evidence and strength of recommendation was assessed according to the GRADE approach [26]. Details regarding treatment strategy (for example: antibiotics, thoracolumbosacral orthosis (TLSO) or surgery) and outcome parameters (treatment duration, required additional surgery, treatment failure, relapse, and mortality) were registered by two independent reviewers (JR and DK). Relapse was defined as every event that required additional conservative or surgical treatment after finishing the initial treatment. Treatment failure was defined as active infectious disease 1 year after start of the treatment. Differences in risk of bias, quality of evidence, strength of recommendation, and outcome parameters were discussed in a consensus meeting.

Results

Study selection

A total of 1662 articles were found in the four electronic databases (Fig. 1). After screening the titles and abstracts, 65 full-text articles were reviewed. Of these full-text manuscripts, 25 articles were excluded since they did not meet de inclusion criteria. Most common reason for exclusion was description of non-pyogenic spondylodiscitis (13 articles) such as postoperative or tuberculosis infection. Furthermore, 16 abstracts of scientific conferences were found which were not included in the critical appraisal. Relevant abstracts were incorporated in the discussion section of the review. One article published before 2000 was included after reference tracking of included articles and de recent reviews regarding the treatment of spondylodiscitis [6]. This resulted in 25 included studies (Table 3). Ten studies containing only a minority of tuberculosis or postoperative infection cases (2.9–38 %) were included in the review [16–18, 27–33]. At total of 75 patients in the current review had tuberculosis and 52 patients had a postoperative infection, which represented, respectively, 3.1 and 2.2 % of all included patients. Similarly, four included study populations consisted of 0.9–13.5 % children and adolescent patients [4, 6, 27, 34]. Additionally 3 other studies contained patients between 16 and 18 years of age; however, the number of these patients is not described [32, 35, 36]. A total number of 31 children and adolescents have described in the included studies and represent 1.3 % of the study population in this review [4, 6, 27, 34].

Characteristics of included studies

The majority of 25 included studies were retrospective ($n = 20$) and only five were prospective. The retrospective studies consisted of 11 retrospective comparative studies (RCoS) and nine retrospective case series (RCS). Additionally, there were three prospective comparative studies (PCS) and 2 randomized controlled trails (RCT) (Table 4).

The combined number of patients in all included studies was 2407 and ranged from 20 to 351 patients per study.

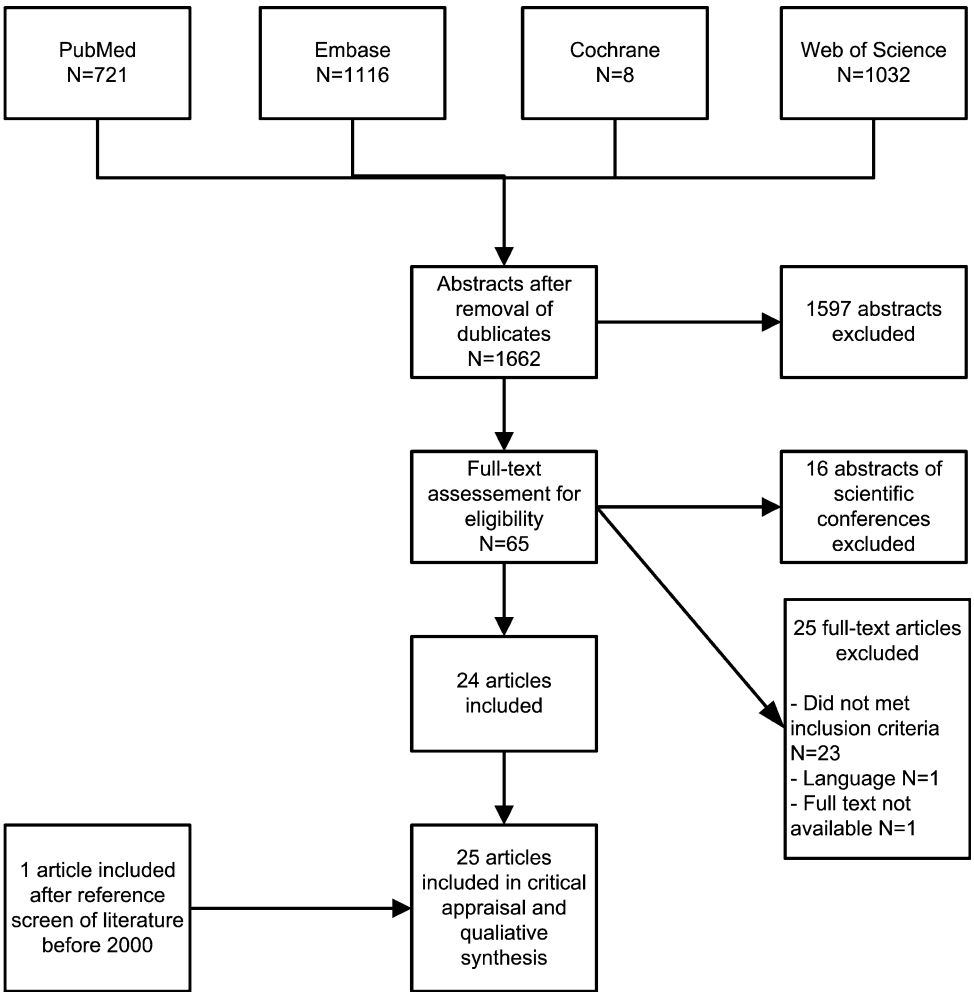

Fig. 1 Flow chart literature search

The average age of the included patients was 59 years (range 1–90 years). Sixty-one percent of the patients were male. Mean follow-up time of the patients was 24 months and ranged from 3 to 144 months (Table 3).

The reported treatment strategy was systemic antibiotics alone in six studies and a combination of surgery and systemic antibiotics in nine studies. In three studies, systemic antibiotic treatment alone was compared to a combination of surgery and antibiotics. Additionally, five studies focused on the treatment of a specific type of microorganism and two on a specific patient category consisting of HIV patients and intravenous drug users (IVDU).

Quality of included studies

According to the GRADE approach, the quality of evidence was high in one study, moderate in four studies, and very low in 20 studies (Table 4). The strength of recommendation was strong for five studies and weak for the 20 other studies.

Outcomes of systemic antibiotic treatment

Six studies have evaluated the effect of systemic antibiotic treatment alone (Table 5) [4, 30, 31, 35, 37, 38]. Antibiotics therapy could be targeted on the causative bacteria in 792 (89 %) of the cases. Four studies were of a more descriptive nature and reported the outcome after antibiotic therapy [4, 30, 35, 37]. The reported systemic antibiotic treatment duration ranged between 6 and 40 weeks [4, 30, 35]. Despite antibiotic treatment, additional surgery was required in 25–55 % of the reported cases [4, 30]. Relapse rates of 2 and 4 % after antibiotics treatment only were reported in two studies. Whereas one study did not report the microorganisms causing the relapse, the other reported three cases of *S. aureus* (one case of MRSA), and one case of Proprionibacterium acnes. The in-hospital mortality ranged from 1–10 % [4, 30, 35]. A recent RCT by Bernard et al. compared 6–12 weeks of antibiotic treatment and showed that the therapy can be safely shortened to a total of 6-week treatment without increasing

Table 3 Characteristics of the included studies

Author and year of publication	Treatment	Number of patients	Sex	Age (range/SD)	Follow-up
Aagaard 2013 [1]	AB and ST	100	67 male 33 female	60 (54–69)	1 year
Bernard 2014 [2]	AB	351	242 male 109 female	61 (SD 17)	1 year
Hadjipavlou 2000 [3]	AB and ST	101	75 male 26 female	46 (8–71) one 8 year old patient	ND
Jensen 1998 [4]	AB	133	70 male 63 female	65 (6–86) 10 patients <20 years	ND
Karadimas 2008 [5]	AB and ST	163 (141 pyogenic, 22 tuberculosis)	101 male 62 female	56 (1–83) 12 patients <20 years	1 year
Lee 2014 [6]	ST	26 (24 pyogenic, 2 tuberculosis)	17 male 9 female	62 (32–80)	57 months (16–109)
Legrand 2011 [7]	AB	110	67 male 43 male	60.6 (17–86) number of patients <18 ND	3 months
Lin 2014 [8]	ST	45	25 male 20 female	62.4 (ND)	2 years
Linhardt 2006 [9]	ST	22 (17 pyogenic, 5 tuberculosis)	16 male 4 female	58.2 (20–75)	5.4 years
Loibl 2014 [10]	AB and ST	105 (102 pyogenic, 3 tuberculosis)	55 male 50 female	66.1 (28–88)	31.5 months (2–198)
Mulleman 2006 [11]	AB and ST	136	83 male 53 female	59.8 (16–87) Number of patients <18 ND	ND
Nasto 2014 [12]	AB and ST	27	18 male 9 female	57.8 (31–77)	9 months
Ozturk 2007 [13]	AB and ST	56 (40 pyogenic 16 tuberculosis)	25 male 31 female	60.8 (38–74)	6.5 years (3–11)
Park 2013 [14]	AB and ST	139	79 male 60 female	65 (55–71)	At least 12 months after completing Antibiotic treatment (AB)
Parra 2012 [15]	AB and ST	108 (67 pyogenic, 30 post-operative, 11 tuberculosis)	49 male 59 female	67.5 (SD 17)	6.1 years (2–12)
Rangaraja 2014 [16]	AB	61	39 male 22 female	57 (ND)	At least 12 months
Roblot 2007 [17]	AB	120 (98 pyogenic, 22 post-operative)	78 male 42 female	64 (18–90)	6 months $N = 120$, 41 months $N = 91$
Rossbach 2014 [18]	AB and ST	135 (127 pyogenic, 8 tuberculosis)	85 male 50 female	59.9 (16–87) Number of patients <18 ND	ND

Table 3 continued

Author and year of publication	Treatment	Number of patients	Sex	Age (range/SD)	Follow-up
Schomacher 2014 [19]	AB and ST	37	24 male 13 female	62.4 (42–81)	20.4 months (6–81)
Si 2013 [20]	AB and ST	23	13 male 10 female	38.8 (23–62)	38 months (24–67)
Sobottke 2009 [21]	AB and ST	20 (16 pyogenic, 4 tuberculosis)	14 male 6 female	43 (21–67)	13 months (1–84)
Valancius 2013 [22]	AB and ST	196	106 male 90 female	59 (1–89), 8 patients <18 years	1 year
Vcelak 2014 [23]	AB and ST	31 (27 pyogenic, 4 tuberculosis)	20 male 11 female	60.5 (21–81)	1 year
Wang 2012 [24]	AB and ST	102	60 male 42 female	49.5 (25–83)	1 year
Yong 2008 [25]	AB and ST	60	36 male 24 female	58 (26–87)	35.8 months (26–50)

AB antibiotic treatment, *ST* surgical treatment, *ND* not described

the risk for relapse, failure, and infection-related mortality (Table 5) [38]. An earlier RCoS by Roblot et al. supports this conclusion [31].

Outcomes of surgical treatment

Four studies compared anterior and/or posterior approaches [16, 17, 29, 39]. The RCT of Linhardt et al. and the PCoS of Si et al. both compared a combined anterior and posterior stabilization with an isolated anterior spondylodesis [29, 39]. They both reported less pain and statistically significant better clinical outcomes (SF36, Oswestry, ODI, and VAS) in the anterior only group [29, 39]. The RCoS by Vcelak et al. evaluated the differences between a combined anterior and posterior approach and an isolated posterior approach [17]. No statistically significant differences in reoperation rate, relapse, treatment failure, or mortality were found [17]. The isolated posterior approach group had a statistically significant greater loss of sagittal balance; however, this had no clinical consequences [17].

Lee et al. retrospectively evaluated the outcome of transpedicular curettage and drainage with posterior stabilization versus an combined anterior/posterior stabilization [16]. No differences in clinical outcome were found and the transpedicular curettage, and drainage with posterior stabilization was suggested to be a good treatment for patients with severe co-morbidities [16]. Lin et al. retrospectively assessed the difference between an open and a percutaneous approach in a combined anterior and posterior strategy [40]. They found no differences in the outcomes between the open and percutaneous groups [40]. The retrospective study by Ozturk et al. analyzed if there was a difference between a sequential versus a simultaneous anterior and posterior surgery [18]. No differences were found between the two study groups [18]. Two studies retrospectively compared the effectiveness of anterior fusion with different types of cages and cage versus strut graft [41, 42]. Schomacher et al. compared Polyetheretherketone (PEEK) cages with titanium (TTN) cages [41]. No differences between the two cage types were found [41]. The differences between iliac bone struts and titanium mesh cages were analyzed by Yong et al. [42]. Although there was no difference in clinical outcome, a higher subsidence rate in the strut group was reported [42]. The descriptive RCS by Rossbach et al. presented the results of a cohort of patients with spondylodiscitis and a subgroup in which the spondylodiscitis was complicated by a spinal epidural abscess [32]. Patients with a neurological deficit caused by an epidural abscess had a statistically significant better prognosis than patients with other causes of neurological deficit [32] (Table 6).

Table 4 Quality of included studies according the GRADE approach

Author and year of publication	Study design	Selection bias	Performance bias	Attrition bias	Detection bias	Quality of evidence	Recommendation
Aagaard 2013 [1]	RCS	No	No	Yes	Yes	Very low	Weak
Bernard 2014 [2]	RCT	No	No	Yes	No	High	Strong
Hadjipavlou 2000 [3]	RCS	No	Yes	Yes	Yes	Very low	Weak
Jensen 1998 [4]	RCS	No	Yes	Yes	Yes	Very low	Weak
Karadimas 2008 [5]	RCS	No	Yes	No	Yes	Very low	Weak
Lee 2014 [6]	RCoS	Yes	Yes	No	Yes	Very low	Weak
Legrand 2011 [7]	RCS	No	Yes	Yes	Yes	Very low	Weak
Lin 2014 [8]	RCoS	No	No	No	Yes	Very low	Weak
Linhardt 2006 [9]	RCT	No	Yes	Yes	Yes	Moderate	Strong
Loibl 2014 [10]	RCS	No	Yes	No	Yes	Very low	Weak
Mulleman 2006 [11]	RCS	No	Yes	No	Yes	Very low	Weak
Nasto 2014 [12]	RCoS	Yes	No	No	Yes	Very low	Weak
Ozturk 2007 [13]	RCoS	Yes	Yes	No	Yes	Very low	Weak
Park 2013 [14]	PCS	No	Yes	No	Yes	Moderate	Strong
Parra 2012 [15]	RCS	No	Yes	No	Yes	Very low	Weak
Rangaraja 2014 [16]	RCoS	No	Yes	No	Yes	Very low	Weak
Roblot 2007 [17]	RCoS	Yes	Yes	Yes	Yes	Very low	Weak
Rossbach 2014 [18]	RCS	No	Yes	Yes	Yes	Very low	Weak
Schomacher 2014 [19]	RCoS	Yes	Yes	Yes	Yes	Very low	Weak
Si 2013 [20]	PCoS	No	No	No	Yes	Moderate	Strong
Sobottke 2009 [21]	RCoS	No	Yes	Yes	Yes	Very low	Weak
Valancius 2013 [22]	RCos	Yes	Yes	No	Yes	Very low	Weak
Vcelak 2014 [23]	RCos	No	No	No	Yes	Very low	Weak
Wang 2012 [24]	PCos	No	Yes	Yes	Yes	Moderate	Strong
Yong 2008 [25]	RCos	No	Yes	No	Yes	Very low	Weak

RCS retrospective case series, *RCT* randomized controlled trail, *RCoS* retrospective comparative study, *PCS* prospective cohort study, *PCoS* prospective comparative study

Systemic antibiotics versus surgical treatment

Three studies retrospectively compared systemic antibiotics alone versus surgical treatment [27, 34, 43]. The indication for surgical treatment in the first two studies was neurologic compromise, extensive bone destruction, epidural abscess formation, failure of nonoperative treatment or intractable back pain. The descriptive study by Karadimas et al. concluded that nonoperative treatment was effective in 90 % of the patients; decompression alone had a high reoperation rate and no differences in clinical outcome were found [27]. Reoperation rate for decompression without stabilization was 42 %, whereas combined stabilization and decompression had a reoperation rate of 16 % [27]. Although this study reported the complication and reoperation rates in detail, no statistical analysis was performed. Similarly, the retrospective comparative study by Valancius et al. described the results of antibiotics alone and surgical treatment in great detail without statistical analysis and also reported that antibiotics therapy alone was safe and effective in spondylodiscitis without complications [34]. In contrast to these studies, Nastro et al. offered the patients to choose between a TLSO for 3–4 months and bridging percutaneous pedicle screw constructs followed by a soft brace for 4 weeks [43]. They analyzed the differences in the clinical outcome between these groups and report a lower VAS, higher SG-36, and higher EQ-5D in the first 3–6 months in the surgical treatment group. However, no statistically significant differences were found after 9 months [43] (Table 7).

Microorganism-specific treatment

Five studies focused on microorganism-specific antibiotic treatment [28, 36, 44–46]. Jensen, Loible, and Mulleman

Table 5 Antibiotic treatment

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required	Relapse/failure	Mortality (infection related)	Main conclusion of the article
Aagaard 2013 [1]	Antibiotic treatment 6 wks IV 6 wk oral, $N = 100$	90	91 days	41 %	Relapse 4 % Failure 0 %	8 % (5 %)	Studies evaluating the duration of antibiotic treatment are required
Bernard 2014 [2]	Antibiotic treatment 6 wk $N = 176$	100	6 wk (6–6.6)	ND	Relapse 2.3 % Failure 9.1 %	8 % (6 %)	6 weeks of antibiotic treatment is not inferior to 12 weeks of antibiotic treatment
	Antibiotic treatment 12 wk $N = 175$		12 wk (12–13)	ND	Relapse 0 % Failure 9.1 %	7 % (2 %)	
Hadjipavlou 2000 [3]	Antibiotic treatment 6 wk IV and 6 wk oral $N = 101$	75.5	12 wks	54.4 %	Relapse 2 % Failure 0 %	1 % (ND)	Surgery was preferable to nonsurgical treatment for improving back pain
Legrand 2011 [7]	Variable antibiotic protocols, mainly IV therapy followed by oral antibiotics, $N = 110$	72.8	Antibiotics 103 days (42–285)	ND	ND	1 % (ND)	Wide differences were noted across centers regarding intravenous treatment duration, hospital stay duration, and total treatment duration
	TLSO in 89.1 %		TLSO 81.5 days (SD 63)				
Parra 2012 [15]	Antibiotic therapy, $N = 108$	69.4	IV: 5.2 wk (SD 1.43), oral ND	25 %	Relapse ND Failure ND	10 % (ND)	Prolonged antimicrobial therapy and the judicious application of timely surgical intervention are essential for an optimal outcome
Roblot 2007 [17]	Antibiotic therapy <6wk $N = 36$	100	IV 20 days (SD 16), oral 22 days (ND)	5.5 %	Relapse 0 % Failure ND	8 % (3 %)	Antibiotic therapy can be safely shortened to 6 weeks without enhancing the risk of relapse
	Antibiotic therapy >6wk $N = 84$		IV 35 days (SD 30), oral 63 days (ND)	4.8 %	Relapse 7.1 % Failure ND	12 % (0 %)	

IV Intravenous, *WK* weeks, *ND* not described, *TLSO* thoracolumboscral orthosis, *SD* standard deviation

Table 6 Surgical treatment

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required	Relapse/failure	Mortality (infection related)	Main conclusion of the article
Lee 2014 [6]	Transpedicular curettage and drainage and posterior stabilization $N = 10$	42	91.9 days	0 %	Relapse 10 % Failure 0 %	0 % (ND)	Transpedicular curettage and drainage proved to be a useful technique for treating pyogenic spondylodiscitis in patients who were in poor heath
	Combined anterior and posterior surgery $N = 26$		65 days	6 %	Relapse 0 % Failure 0 %	0 % (ND)	
Lin 2014 [8]	Combined anterior and open posterior $N = 25$	84	28–83 days	0 %	Relapse 8 % Failure 0 %	0 % (ND)	Anterior debridement and interbody fusion with bone grafting followed by minimally invasive percutaneous posterior instrumentation is an alternative treatment for pyogenic spondylodiscitis
	Combined anterior and percutaneous posterior $N = 20$		28–83 days	0 %	Relapse 5 % Failure 0 %	0 % (ND)	
Linhardt 2006 [9]	Ventro-dorsal spondylodesis $N = 12$	ND	23.8 wk (3–52)	0 %	Relapse 8 % Failure 0 %	25 % (8 %)	Patients with an isolated ventral spondylodesis feel significantly better and experience significantly less pain in the area of spinal fusion than patients with ventro-dorsal fusion
	Ventral spondylodesis $N = 10$		24.1 wk (12–52)	0 %	Relapse 0 % Failure 0 %	10 % (0 %)	
Ozturk 2007 [13]	Sequential anterior and posterior surgery $N = 29$	100	6 wk IV, 3 months oral, TBC 9 months	ND	Relapse ND Failure 0 %	ND (ND)	Simultaneous anterior and posterior surgery is a good alternative procedure. It appears to result in less blood loss, a shorter operative time and fewer complications
	Simultaneous anterior and posterior surgery $N = 27$			ND	Relapse ND Failure 0 %	ND (ND)	
Rossbach 2014 [18]	Antibiotic and surgical therapy, $N = 125$, additional TLSO 46 %	59	ND	55.6 %	Relapse ND Failure ND	ND (ND)	Patients with spondylodiscitis and neurological deficits caused by spinal epidural abces might derive considerable benefit from surgery because their neurological deficits are likely to significantly improve
Schomacher 2014 [19]	Antibiotic therapy and PEEK cage $N = 21$	70.3	2–4 wk IV, 8–10 wk oral	4.8 %	ND	ND (ND)	The application of TTN- or PEEK-cages does not appear to influence the radiological outcome or risk of reinfection, neither does the extent of removal of the infected disk in this clinical subset
	Antibiotic therapy and TTN cage $N = 16$		2–4 wk IV, 8–10 wk oral	0 %	ND	ND (ND)	
Si 2013 [20]	Dorsal spondylodesis and anterior debridement $N = 11$	ND	ND	0 %	Relapse 8 % Failure 0 %	ND (ND)	Both procedures are safe. Patients with anterior fixation may achieve better postoperative results, such as better well being and less pain
	Anterior debridement and spondylodesis $N = 12$		ND	0 %	Relapse 0 % Failure 0 %		

Table 6 continued

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required	Relapse/failure	Mortality (infection related)	Main conclusion of the article
Vcelak 2014 [23]	Dorsal transmuscular surgery N = 23	100	ND	8.7 %	Relapse 8.7 % Failure 4.3 %	4.3 (0 %)	Greater loss of sagittal balance without clinical correlation after a dorsal transmuscular approach
	Two-stage posteroanterior surgery *N* = 8		ND	12.5 %	Relapse 0 % Failure 0 %	0 % (0 %)	
Yong 2008 [25]	Anterior cage followed by pedicle screw fixation *N* = 37	50	IV min 6 WK, oral min 6 WK	8.1 %	Relapse ND Failure ND	ND (ND)	Single-stage anterior debridement and cage fusion followed by posterior pedicle screw fixation can be effective in the treatment of pyogenic spondylodiscitis
	Anterior strut followed by pedicle screw fixation *N* = 23		IV min 6 WK, oral min 6 WK	4.3 %	Relapse ND Failure ND	ND (ND)	

IV Intravenous, *WK* weeks, *ND* not described, *TLSO* thoracolumboscral orthosis, *SD* standard deviation, *MIN* minimally, *PEEK* polyetheretherketone, *TTN* titanium, *SEA* spinal epidural abscess

et al. described retrospective cohorts of spondylodiscitis patients and report a higher complication rate in *S. aureus* infections and a higher risk of concomitant endocarditis in enterococcal spondylodiscitis [28, 36, 44]. As a result, Jensen et al. advised a minimum of 8 weeks of antibiotic treatment for *S. aureus* spondylodiscitis. The prospective study by Park et al. compared methicillin-resistant *S. aureus* (MRSA) with methicillin-susceptible *S. aureus* (MSSA) [45]. A higher relapse rate was found in the MRSA patients and again a longer antibiotic treatment was suggested [45]. Rangaraj et al. retrospectively analyzed the efficiency of vancomycin and Daptomycin in the treatment of MRSA spondylodiscitis [46]. The relapse rate in the Daptomycin groups was 3 %, whereas 30 % relapse was found in the vancomycin group [46] (Table 8).

Treatment of HIV and IVDU patients

Two studies focused on the treatment of specific patient groups [33, 47]. Sobottke et al. retrospectively compared surgical with systemic antibiotics therapy alone in HIV patients and found no statistically increased complication or relapse rate in the surgically treated patients [33]. Wang et al. prospectively compared the outcome of spondylodiscitis in intravenous drug users (IVDUs) and non-IVDUs [47]. A higher percentage of hardware failure and a longer hospital stay was found in de IVDU groups; however, a higher in-hospital mortality was found in the non-IVDU group (Table 9).

Discussion

A total of 25 studies were included in this systematic review of English language literature comprising data from 2407 patients with pyogenic spondylodiscitis. All studies described the outcome of conservatively or surgically treated pyogenic spondylodiscitis. Only two RCTS and three prospective studies were found. The quality of the evidence was high in just one study, moderate in four studies, and very low in the remaining 20 retrospective studies. Based on the finding of the studies focusing on systemic antibiotics treatment of pyogenic spondylodiscitis, treatment of 6 weeks results in a similar mortality, relapse, and failure rate compared to longer treatment duration [4, 30, 31, 35, 37, 38]. The nine articles that described the outcome of surgical treatment strategies show that a large variety of surgical techniques can successfully treat spondylodiscitis, whereas the less elaborate and less invasive approaches appear to have a better functional outcome [16–18, 29, 32, 39–42]. So far, no additional long-term beneficial effect of surgical treatment could be shown in the studies comparing surgical versus conservative treatment [27, 34, 43]. However, we should consider that most of the surgical interventions were performed in cases with complications and/or inadequate response to a conservative approach and the groups are difficult to compare. If surgical intervention is chosen an isolated decompression procedure leads up to 43 % reoperation rates [27]. Concomitant surgical stabilization is

Table 7 Antibiotic versus surgical treatment

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required	Relapse/failure	Mortality (infection related)	Main conclusion of the article
Karadimas 2008 [5]	Antibiotic treatment 4 wk IV 1–6 months oral and TLSO (group A $N = 70$)	59	2–7 months	11 % (group A)	Relapse ND Failure 0 %	11.4 % (ND) (group A)	Nonoperative treatment was effective in nine-tenths of the patients. Decompression alone had high a reoperation rate compared to decompression and internal stabilization
	Decompression without (group B $N = 56$) or with stabilization (group C $N = 37$)		2–7 months	42 % (group B) 16 % (group C)	Relapse ND Failure 0 %	12.5 % (ND) (group B) 13.5 % (ND) (group C)	
Nasto 2014 [12]	Antibiotic therapy and TLSO $N = 15$	100	76 days (SD 23)	0 %	Relapse 0 % Failure 0 %	0 % (ND)	Surgical stabilization was associated with faster recovery, lower pain scores, and improved quality of life compared with TLSO conservative treatment
	Antibiotic therapy and percutaneous posterior stabilization $N = 12$		84 days (SD 19)	0 %	Relapse 0 % Failure 0 %	0 % (ND)	
Valancius 2013 [22]	Conservative treatment $N = 91$, Additional TLSO $N = 83$	72.9	IV min 2 weeks, oral 3–6 months	13.1 %	Relapse 7.6 % Failure 13.1 %	8.7 % (3.3 %)	Conservative measures are safe and effective for carefully selected patients without spondylodiscitic complications. Failure of conservative therapy requires surgery that can guarantee thorough debridement, decompression, restoration of spinal alignment, and correction of instability
	Surgical treatment $N = 105$ TLSO $N = 28$		ND	17.1 %	Relapse 2.9 % Failure 0.0 %	1.9 % (0.0 %)	

IV intravenous, *WK* weeks, *ND* not described, *TLSO* thoracolumboscral orthosis, *SD* standard deviation, *MIN* minimally

associated with less complications and reoperations. The five microorganism-specific studies suggest at least 8 weeks of antibiotic treatment for *S. aureus* spondylodiscitis and Daptomycin for the treatment of MRSA spondylodiscitis [28, 36, 44–46]. The two studies focusing on immunosuppressed patients described that surgical treatment in HIV patients is not associated with more complications, while early hardware failure was more common in surgically treated IVDUs [33, 47].

Strength and limitations

This is the first systematic literature review on the outcome of the treatment of pyogenic spondylodiscitis comprising all spinal regions. A literature review regarding the treatment of cervical spondylodiscitis had been published previously [48]. In order to obtain an evidence-based assessment of the literature on this subject, this review was performed in adherence to the PRISMA statement and used the GRADE approach. We limited our search to articles published in English, since our knowledge of other languages was not sufficient to guarantee a valid critical appraisal. This could have introduced a selection bias in our literature review. Moreover, the articles published before 2000 were not systematically searched and were only screened by reference checking of the included articles and recent relevant reviews. This theoretically could introduce a selection bias to our systematic literature review. However, the literature published before 2000 predominantly concerns infections caused by tuberculosis. Therefore, we have chosen a more pragmatic approach as described in the "Method" section. Furthermore, this review focused on clinical decision-making and therefore case reports and small case series were not included. The main focus of our search strategy was on studies that compared different treatment strategies, which might also have introduced selection bias in our search.

Table 8 Microorganism-specific treatment

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required	Relapse/failure	Mortality (infection related)	Main conclusion of the article
Jensen 1998 [4]	Antibiotic therapy for *S. aureus* spondylodiscitis, $N = 133$	100	76 days (9–90) TLSO: 121 (24–1425)	ND	Relapse 10 % Failure 13 %	16 % (ND)	Antibiotic treatment for *S. aureus* spondylodiscitis is recommended for at least 8 weeks
Loibl 2014 [10]	Antibiotic therapy $N = 46$ Surgical and antibiotic therapy $N = 56$	59	ND	30 %	Relapse ND Failure ND	12.4 % (ND)	Infections with *S. aureus* are associated with a higher rate of complications and a trend toward higher mortality
Mulleman 2006 [11]	Antibiotic therapy $N = 124$ Surgical and antibiotic therapy $N = 12$ Additional TLSO 74 %	100	122 days (56–347) TLSO 126 days (SD 45)	SESD 9.3 % SSD 8.0 %	Relapse ND Failure ND	SESD 4.6 % (ND) SSD 4.6 % (ND)	High incidence of infective endocarditis (26 %) during enterococcal spondylodiscitis
Park 2013 [14]	Antibiotic therapy for MSSA $N = 77$ Antibiotic therapy for MRSA $N = 62$	100	IV: 46 days, oral: 12 days IV: 55 days, oral: 17 days	29.9 % 27.4 %	Relapse 4.1 % Failure ND Relapse 16.1 % Failure ND	10.4 % (ND) 8.1 % (ND)	MRSA spondylodiscitis was associated with more frequent persistent bacteremia relapse, and longer hospital stay. Antibiotic therapy for >8 weeks may be benefit patients with MRSA
Rangaraja 2014 [16]	Vancomycin $N = 30$ Daptomycin $N = 31$	70.5	41 days (ND) 45 days (ND)	23 % 29 %	Relapse ND Failure 30 % Relapse ND Failure 3 %	0 % (0 %)	The use of daptomycin resulted in a significantly higher rate of cure in MRSA spondylodiscitis compared with that of vancomycin

IV intravenous, *ND* not described, *TLSO* thoracolumboscral orthosis, *SESD* streptococcus and enterococcus Spondylodiscitis, staphylococcal Spondylodiscitis, *SD* standard deviation, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*

Next to the limitations induced by our search methodology, the characteristics of the included studies also introduce their own specific bias into this review. As a result of our aim to review the outcome of both conservative and surgical treatment of pyogenic spondylodiscitis, we have created a very heterogenic study population. Moreover, this heterogeneity is also seen in the separate study populations of the included articles. Fifteen of the included studies contain a minority of patients that no completely meet our inclusion criteria [4, 16–18, 27–36, 44]. Ten studies include a small number patients with tuberculosis and postoperative infections representing, respectively, 3.1 and 2.2 % of the included patient in this review [16–18, 27–33]. Moreover seven studies included children and adolescents representing 1.3 % of the study population of this review [4, 27, 32, 34–36, 44]. The patients with spondylodiscitis caused by tuberculosis could have negatively influenced the clinical outcome since tuberculosis has been suggested to have higher treatment failure rates, higher risk of deformity, and more often need surgical treatment [49, 50]. On the other hand, childhood and postoperative spondylodiscitis are known to have a more favorable prognosis and could have positively influenced outcome results [2, 51, 52]. Final limitation of our current review is the quality of the available evidence, 80 % of the include studies have a very low level of evidence resulting in a weak level of recommendation.

Clinical implications

Conservative treatment is indicated for the majority of pyogenic spondylodiscitis patients [3, 27, 34]. One of the most important findings of this review is that 6 weeks of antibiotic treatment appear to have a similar mortality, relapse, and failure rate as 12-week treatment [31, 38]. This was shown by the RCT of Bernard et al. and the

Table 9 Treatment HIV patients and IVDU

Author and year of publication	Treatment	Positive cultures (%)	Duration of antibiotic treatment	Additional surgical treatment required (%)	Relapse/failure	Infection-related mortality	Main conclusion of the article
Sobottke 2009 [21]	Conservative treatment in HIV patients $N = 10$ Additional TLSO $N = 5$	100	ND TLSO = 51 days	20	Relapse 0 % Failure 30 %	0 % (ND)	Operative therapy of spondylodiscitis in HIV positive patients is not associated with an increased surgical complication rate
	Surgical treatment in HIV patients $N = 10$ Additional TLSO $N = 2$		ND TLSO = 51 days	10	Relapse 10 % Failure 0 %	0 % (ND)	
Wang 2012 [24]	Antibiotic and surgical treatment in IVDU $N = 51$, additional halo frame $N = 29$	52	62 days (ND)	4.5	Relapse ND Failure ND	0 % (ND)	Among the IVDUs, surgical management is complex with a high incidence of early hardware failure. SSI is significantly more common among non-IVDU
	Antibiotic and surgical treatment in non-IVDU $N = 51$		45 days (ND)	9.0	Relapse ND Failure ND	7.8 % (ND)	

ND not described, *TLSO* thoracolumboscral orthosis, *IVDU* intravenous drug users, *SSI* surgical site infection

retrospective study of Roblot et al. of which the RCT was evaluated as a strong level of recommendation according the GRADE criteria. Contrastingly, prolonged antibiotic treatment has been suggested by other studies for spondylodiscitis caused by *S. aureus* and MRSA with a weak and strong level of recommendation, respectively [6, 30, 45]. Nevertheless, these studies focusing on *S. aureus* report similar mortality, relapse, and failure rates as Bernard and Roblot et al. [30, 31, 38, 44, 45]. Moreover, *S. aureus* was also the most predominant microorganism in the studies by Bernard and Roblot et al. (41 and 36 % respectively [31, 38]). Since reduction of antibiotic treatment duration in uncomplicated pyogenic spondylodiscitis, defined as spondylodicitis without epidural abscess, deformity or neurological deficit does not lead to an increase in mortality, relapse, and failure rate, treatment duration can safely be reduced to 6 weeks (2 weeks intravenous, followed by 4 weeks oral). Due to the contrasting findings regarding *S. aureus* and MRSA, further research is required to determine the length of antibiotic treatment for these specific microorganisms.

Other conservative treatment options such as bed rest and TLSO have not been investigated in detail. Therefore, we are unable to give a level of recommendation regarding this subject. However, a pragmatic approach with bed rest until pain and infection parameters are decreasing and start of mobilization with a TLSO as tolerated appear to be a generally accepted strategy [3, 10, 11, 33–35, 43, 53].

The indications of surgical treatment have been clearly described in literature: compression of neurological structures, spinal instability, spinal deformity, and failure of conservative treatment [1–3, 10, 11]. This postulation was further underscored by the included articles in this review, although with a low level of recommendation [27, 34, 43]. Moreover, there are also some indications that surgical treatment in uncomplicated spondylodiscitis could result in faster recovery, faster mobilization and a better short-term quality of life when compared to conservative treatment. However, this is only supported by a low level of recommendation without significant clinical differences after 9 months [43, 54].

Currently, many different surgical treatment strategies are being used for the treatment of pyogenic spondylodiscitis [1–3, 10, 11]. Historically anterior debridement combined with posterior stabilization has been the golden standard in the surgical treatment of spondylodiscitis [2]. However, since this is an elaborate procedure which can be undesirable in critically ill patients, many different less invasive procedures have been developed [16, 17, 29, 39, 40, 55]. Among these less invasive procedures are solely anterior or posterior procedures, combined procedures with percutaneous posterior stabilization, and percutaneous

drainage [16, 17, 29, 39, 40, 55]. The RCT by Lindhardt et al. and the prospective study by Si et al. demonstrated that an isolated anterior approach results in a better clinical outcome (SF36, Oswestry, ODI, and VAS) than a combined anterior–posterior procedure [29, 39]. These two studies were evaluated as a strong level of recommendation according the GRADE criteria. Although prospective and of adequate quality, it must be mentioned that these two studies only comprise a total of 50 patients. Isolated posterior approaches demonstrated to have similar mortality, relapse, and failure rates as the combined procedures; however, level of recommendation of these studies was evaluated as weak [16, 17, 55]. Percutaneous posterior methods have especially been advocated for patients in a poor general condition [16, 56]. Based on the literature in this review, there seems to be a trend to less elaborate procedures with similar mortality, relapse, and failures rates compared to the traditional methods while clinical outcome appears to be better. Solely percutaneous posterior procedures could be a good alternative in patients with multiple morbidities [56, 57]. Surgical treatment of spondylodiscitis could be more complex in specific patient groups, for example, in IVDUs where early hardware failure and surgical site infections were more common [47]. Interestingly surgical treatment in HIV patients is not related with higher complication rates [33]. This might be explained by the fact that outcome of spondylitis in this patient group is much more related to the HIV disease severity than the chosen treatment strategy [58].

As one of the study characteristics we reported, the percentage of positive cultures for each included study. The percentage of positive cultures ranges from 42–100 % in the current review. The assumption that identification of the causative microorganism leads to more effective treatment is well established; however, there are no studies available to support this hypothesis [2, 9, 59]. On the contrary, the recent study by Kim et al. showed a more favorable outcome in empirical treated patient versus patients with microbiologically confirmed spondylodiscitis. Kim et al. suggest that the patients with culture negative spondylodiscitis often have a less severe infection and therefore a more better outcome [59]. In our review, no difference in outcome is seen between the studies with a low percentage of positive cultures versus studies with a high percentage.

Future research

At this moment, there is insufficient high-quality data available to create a complete evidence-based guideline with strong recommendations for the treatment of pyogenic spondylodiscitis. More prospective and preferably randomized studies are required. Besides an increase in data quality, a change in research focus is also desirable. Although only 10–20 % of the patients with pyogenic spondylodiscitis may require a surgical intervention, this is the largest treatment group reported in the current review (9 out of 25 articles). There seems to be a strong publication bias in favor of surgical treatment. This phenomenon was also observed in the 16 abstracts of scientific conferences found in our literature search [8, 54–56, 60–71]. Nine of the 16 abstracts are focusing purely on surgical strategies, whereas only three on the antibiotics treatment were found. Since the vast majority of the spondylodiscitis patients are treated conservatively more high-quality research regarding the conservative treatment of spondylodiscitis is required. Moreover many fundamental aspects of the conservative treatment of spondylodiscitis are still unknown and require further research. For example, a randomized trial regarding bed rest or TLSO treatment could be a major contribution to the treatment of pyogenic spondylodiscitis.

Moreover, the current systematic literature review is limited on the outcome of different treatment strategies, whereas it has been well know that patient characteristic also significantly influence the outcome of spondylodiscitis [58, 72, 73]. A prognostic systematic review regarding the effect of patient characteristic on the outcome of spondylodiscitis could be a valuable addition to the available literature.

Conclusion

The current systematic literature review summarizes the outcome of conservatively and surgically treated pyogenic spondylodiscitis and assesses the quality of the available evidence. Unfortunately the majority of the included studies had a very low level of evidence. However, there is a strong level of recommendation for 6 weeks of systemic antibiotics treatment in uncomplicated pyogenic spondylodiscitis, although this has only been shown by one RCT. If surgical treatment is indicated, a prospective comparative study and a RCT have shown, with a strong level of recommendation, that an isolated anterior approach could result in a better clinical outcome compared to more extensive combined anterior–posterior procedures. Emerging less invasive surgical techniques should be studied more extensively in order to gather more robust data.

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Compliance with ethical standards

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