North American Spine Society Journal (NASSJ) 8 (2021) 100083

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Systematic Reviews /Meta-analyses

The effect of instrumentation staging on patient outcomes in pyogenic vertebral osteomyelitis: A systematic review

Milo Sanda[a], Amy Singleton[a,*], Jae Yim[a], Roman Rahmani[a], Erin Sheffels[b], Thomas Andreshak[a]

[a] Department of Orthopedic Surgery, Mercy Health-St. Vincent Medical Center, 2409 Cherry St, Suite #10, OH 43608
[b] Superior Medical Experts, 1425 Minnehaha Ave E, St. Paul, MN 55106

ARTICLE INFO

Keywords:
Vertebral osteomyelitis
Spinal instrumentation
Procedure staging
Debridement
Acute instrumentation
Delayed instrumentation

ABSTRACT

Background: Pyogenic vertebral osteomyelitis is a bacterial infection of the vertebral body that is often treatable with antibiotics, but some cases require additional surgical debridement of the infected tissue. Instrumentation is often utilized for stabilization of the spine as part of the surgical treatment, but controversy remains over the relative risks and benefits of acute instrumentation performed simultaneously with debridement versus delayed instrumentation performed days or weeks after debridement. The purpose of this review was to investigate the relative effects of acute and delayed instrumentation in treatment for pyogenic vertebral osteomyelitis on patient outcomes.

Methods: A PRISMA-compliant systematic literature review was conducted to identify studies published between January 1, 1997 and July 23, 2021. Studies were screened for pre-defined inclusion and exclusion criteria. The primary outcome of interest was reinfection. Other outcomes of interest included neurological status, pain, progression of kyphosis, fusion, hardware failure, length of hospitalization, and mortality at two years. Due to the limited multi-armed studies available that distinguish between patients with acute and delayed instrumentation, inferential statistics were not performed, and data are expressed as descriptive statistics.

Results: A total of 9 studies met our inclusion criteria, comprising 299 patients, including 113 (37.8%) with surgical treatment without fixation, 138 (46.2%) with acute instrumentation, and 48 (16.1%) with delayed instrumentation. Reinfection rates were 60.0% (15/25) for surgical treatment without fixation, 28.6% (2/7) for the acute instrumentation, and 14.3% (1/7) for the delayed instrumentation group. Pain was present after surgery in 52.0% (13/25) of the surgical treatment without fixation group, 14.3% (1/7) of the acute instrumentation group, and 0% (0/7) of the delayed instrumentation group.

Conclusions: No major differences in patient outcomes were apparent between acute and delayed instrumentation groups. Further research is needed to determine whether instrumentation staging has a significant impact on patient outcomes.

Introduction

Pyogenic vertebral osteomyelitis (PVO) is a bacterial infection of the vertebral body in the spine that can lead to severe consequences, including pain, long-standing neurological deficits, and even death if not diagnosed and treated promptly [1]. PVO most commonly affects the vertebral body in the lumbar spine followed by thoracic, cervical, and sacral regions in decreasing order [4]. The incidence of PVO has been increasing, in part due to increases in risk factors including longer life expectancy and increases in incidence of diabetes mellitus, intravenous drug use, alcoholism, immunosuppression, and rheumatic disease [2,3]. Improved diagnostic ability, particularly advances in magnetic resonance imaging (MRI), has also contributed to the increase in incidence of PVO incidence [2,3].

Up to 75% of PVO cases are treated successfully with medical therapy and immobilization, but surgical treatment is often considered in cases with concomitant spinal instability, spinal deformity, or decline in neurological status [1,4]. Medical therapy alone usually involves intravenous antibiotics chosen after a sensitivity panel has been performed on any relevant cultures. Antibiotic therapy may be limited to a short course or may be lifelong for infection suppression [5]. Surgical treatment for PVO is indicated for spinal cord compression, biomechanical instability and deformity, abscess drainage, and to treat intractable pain. Instrumentation may or may not be utilized. The use of instrumentation

* Corresponding author at: Mercy Health St. Vincent Medical Center, Department of Orthopedic Surgery, 2409 Cherry St, Suite #10, Toledo, OH 43608, USA.
E-mail address: asingleton@mercy.com (A. Singleton).

https://doi.org/10.1016/j.xnsj.2021.100083
Received 2 September 2021; Received in revised form 27 September 2021; Accepted 1 October 2021
Available online 8 October 2021

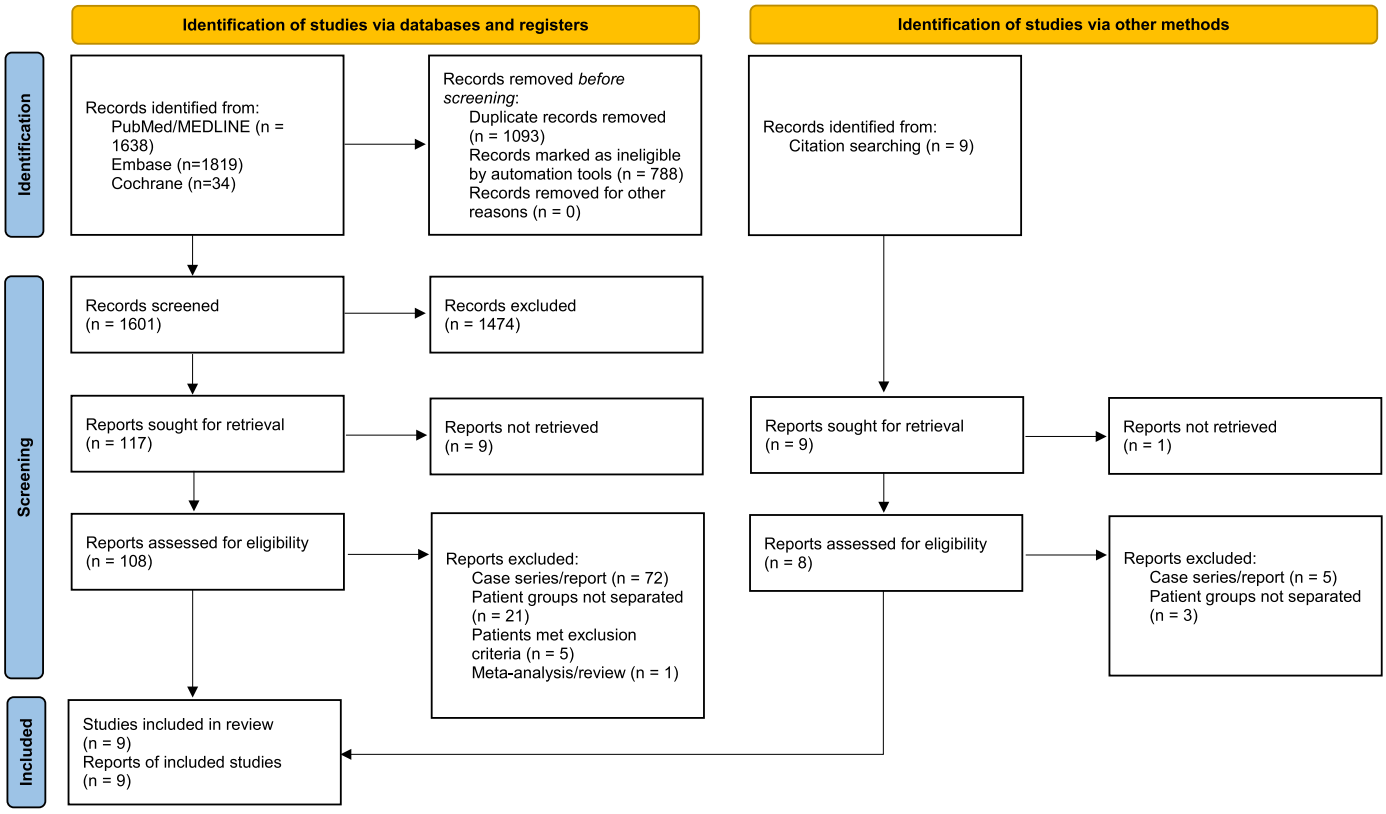

Fig. 1. PRISMA flowchart for study inclusion. (Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.).

to stabilize the spine as part of surgical treatment for PVO has become more common, in part due to the development of minimally invasive techniques that reduce exposure risk, but controversy remains over the relative risks and benefits of acute instrumentation performed simultaneously with debridement versus delayed instrumentation performed days or weeks after debridement [6]. Overall, acute instrumentation is used more frequently than delayed instrumentation, likely due to the desire to limit the number of surgical procedures patients undergo and achieve rapid stabilization of the spine. Potential benefits of acute instrumentation include early spine stabilization and minimizing length of hospitalization and number of surgeries [4,7-9], while delayed instrumentation has been proposed to reduce the risk of the infectious agent growing on the instrumentation by clearing the infection and allow for recovery time before instrumentation is applied [9–11]. Here, we performed a systematic review of the literature to assess the impact of acute versus delayed instrumentation versus surgery without fixation on clinical outcomes of patients undergoing surgical treatment for PVO.

Methods

We performed a systematic review of PVO cases treated with surgical debridement and/or instrumentation within the PubMed/MEDLINE, Cochrane, and Embase databases. The following search terms were used: 1) "vertebral pyogenic osteomyelitis" OR "pyogenic osteomyelitis"; 2) "pyogenic osteomyelitis" AND (surgery OR surgical); 3) (vertebral pyogenic osteomyelitis OR “spinal infection”) AND instrumentation; 4) osteomyelitis AND (vertebral OR cervical OR lumbar) AND (titanium OR fixation OR instrumentation); 5) spondylodiscitis AND (fixation OR fusion OR instrumentation OR titanium) (PubMed and Cochrane); and 6) intervertebral disk degeneration’ AND (’fixation’ OR ’devices’ OR ’titanium’) (Embase). The review was not registered. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Fig. 1**) [12].

Studies published between January 1, 1997 and July 23, 2021 were considered. Articles without English translations available were excluded. We considered all cases of instrumented treatments of PVO included in multi-armed studies. Studies were screened and data was extracted by one author (ES) using the Auto Lit software (Nested Knowledge, nested-knowledge.com). Exclusion criteria consisted of: 1) patient under 18 years old, 2) tuberculosis or fungal causative organism 3) history of cancer 4) unrelated studies, 5) meta-analyses or review articles, 6) pre-clinical studies, 7) case series or reports (relative to the interventions of interest), 8) data for the patient groups of interest were not separated, and 9) studies whose definition of delayed instrumentation included bone grafting or instrumentation during the first surgery.

The Newcastle-Ottawa Scale (NOS) was used to assess risk of bias of the included studies [13]. Using this risk-of-bias tool, two independent contributors assessed each study on the basis of eight criteria under three main categories: selection of study groups, comparability of study groups, and ascertainment of the outcome. One author (ES) verified their determinations and adjudicated disagreements between the assessors. The risk of bias was classified as low, moderate, or high.

Due to the limited multi-armed studies available that distinguished between patients with acute and delayed instrumentation, inferential statistics were not performed, and data are expressed as descriptive statistics only. In some studies, continuous data (e.g., age) were reported as means and standard deviations (SDs); however, only medians and quantiles were reported in some of the other studies considered for inclusion. In order to compute pooled summary statistics from quantile data, we used methods described by Luo et al. [14] and Wan et al. [15] to estimate means and SDs, respectively. Subsequently, simple weighted means and SDs were computed using a homogenous set of summary

measures. Unless otherwise specified, continuous data are reported as mean ± SD.

Results

Of 2,388 total articles identified from the literature search, 9 studies with publications ranging from 1997 to 2020 met our inclusion criteria [5,7,16-22]. A PRISMA diagram detailing our search strategy is shown in **Fig. 1**. Six studies had low risk of bias [7,16,18,20-22] and three studies had moderate risk of bias [5,17,19] **(Supplemental Table 1)**. A total of 299 patients who had undergone surgical treatment for PVO were identified. Of these, 37.8% (113/299) of patients had surgical treatment without fixation, 46.2% (138/299) had acute instrumentation, and 16.1% (48/299) had delayed instrumentation. A full list of studies from our literature review with the surgical treatments and patient background characteristics is provided in **Table 1**, with individual patient data in **Table 2** when available. Patient outcomes are provided in **Table 3**, with individual patient outcomes in **Table 4** when available.

Patient baseline characteristics

Demographics

The mean age of the patient population with available age data by group (n=144) was 60.1±13.8 years. The surgical treatment without fixation group (n=110) had a mean age of 63.2±11.9 years, the acute instrumentation group (n=29) had a mean age of 50.1±14.7 years, and the delayed instrumentation group (n=5) had a mean age of 50.8±19.5 years.

Causative organisms

Of the patients with causative organism(s) reported, Staphylococcus aureus was identified as the causative organism in 36.8% (14/38) of patients overall, including 33.3% (3/9) of the surgical treatment without fixation group, 39.1% (9/23) of the acute instrumentation group, and 33.3% (2/6) of the delayed instrumentation group. Gram-negative rod bacteria were identified as the causative organisms in 42.1% (16/38) of patients overall, including 55.6% (5/9) of the surgical treatment without fixation group, 34.8% (8/23) of the acute instrumentation group, and 50.0% (3/6) of the delayed instrumentation group. Coagulase-negative staphylococci were identified as the causative organisms in 10.5% (4/38) of patients overall, including 0.0% (0/9) of the surgical treatment without fixation group, 17.4% (4/23) of the acute instrumentation group, and 0.0% (0/6) of the delayed instrumentation group. Group B streptococci were identified as the causative organisms in 2.6% (1/38) of patients overall, in a patient with delayed instrumentation. The causative organism was not able to be identified in 10.5% (4/38) of patients who were tested overall, including 11.1% (1/9) of the surgical treatment without fixation group, 13.0% (3/23) of the acute instrumentation group, and 0.0% (0/6) of the delayed instrumentation group. Of the patients with previous spinal surgery status documented, 65.4% (17/26) overall had previous spinal surgery, including 66.7% (6/9) of the surgical treatment without fixation group, 64.3% (9/14) of the acute instrumentation group, and 66.7% (2/3) of the delayed instrumentation group.

Operative details

Operative spine region information was available for 142 patients. The cervical spine was involved in 9.2% (13/142) of cases overall, including 9.1% (10/110) of the surgical treatment without fixation group, 7.7% (2/26) of the acute instrumentation group, and 16.7% (1/6) of the delayed instrumentation group. The thoracic spine was involved in 23.2% (33/142) of cases overall, including 20.9% (23/110) of the surgical treatment without fixation group, 34.6% (9/26) of the acute instrumentation group, and 16.7% (1/6) of the delayed instrumentation group. The lumbosacral spine was involved in 76.1% (108/142) of cases overall, including 76.4% (84/110) of the surgical treatment without fixation group, 73.1% (19/26) of the acute instrumentation group, and 83.3% (5/6) of the delayed instrumentation group. The side of instrumentation was specified for 17.8 % of patients with instrumentation (33/186).

Anterior only instrumentation was performed in 18.2% (6/33) patients overall, including 22.2% (6/27) of the acute instrumentation group, and 0.0% (0/6) of the delayed instrumentation group. Posterior only instrumentation was performed in 51.5% (17/33) patients overall, including 55.6% (15/27) of the acute instrumentation group, and 33.3% (2/6) of the delayed instrumentation group. Combined instrumentation was performed in 30.3% (10/33) patients overall, including 22.2% (6/27) of the acute instrumentation group, and 66.7% (4/6) of the delayed instrumentation group.

Neurological status and pain

Baseline neurological status was available for 43.5% (130/299) of patients overall. Of these patients, 33.1% (43/130) had neurological deficits at diagnosis, including 32.7% (36/110) of the surgical treatment without fixation group, 35.3% (6/17) of the acute instrumentation group, and 33.3% (1/3) of the delayed instrumentation group. Baseline pain status was available for 42.5% (127/299) of patients overall. Of these patients, 91.3% (116/127) had pain at diagnosis, including 90.8% (99/109) of the surgical treatment without fixation group, 100.0% (15/15) of the acute instrumentation group, and 66.7% (2/3) of the delayed instrumentation group. Baseline Visual Analog Scale (VAS) scores were given by one study [16]. Two patients with surgical treatment without fixation had VAS scores of 3 and 6, and six patients with acute instrumentation had a mean VAS score of 4.8 (SD: +/- 1.8).

Patient outcomes

Follow-up ranged from four weeks [5] to 60 months [7]. One patient had a recorded follow-up of two weeks due to death, but the other patients in the study had a minimum follow-up of 12 months [7]. Follow-up information for each study is given in **Tables 3 and 4**. Patient outcomes were gathered regardless of follow-up time, except mortality, where only patients with at least two years of follow-up were considered as negative results.

Reinfection status was available for 85.3% (255/299) of patients, with a follow-up range of four weeks to 60 months. Reinfection occurred in 11.8% (30/255) of patients overall, including 4.4% (4/90) of the surgical treatment without fixation group, 15.7% (19/121) of the acute instrumentation group, and 15.9% (7/44) of the delayed instrumentation group.

Neurological status at follow-up was available for 6.7% (20/299) of patients overall, which included no patients in the delayed instrumentation group. Neurological status follow-up ranged from two weeks to 12 months. Neurological deficit was present in 30.0% (6/20) of patients at follow-up, including 4.4% (4/11) of the surgical treatment without fixation group and 15.7% (2/9) of the acute instrumentation group.

Pain status at follow-up was available for 30.4% (91/299) of patients, with a follow-up range of 4 months to 45 months. Pain was present in 11.8% (27/91) of patients overall at follow-up, including 27.3% (21/77) of the surgical treatment without fixation group, 50.0% (6/12) of the acute instrumentation group, and 0.0% (0/2) of the delayed instrumentation group. In the study that provided VAS scores [16], the surgical treatment without fixation group had VAS scores of 1 and 3 (change from baseline -2 and -3, respectively) and the acute instrumentation group (six patients) had a mean VAS score of 3 (change from baseline -1.8 +/- 1.0).

Mortality at two years was available for 36.5% (109/299) of patients. Mortality occurred in 12.8% (14/109) of patients overall, including 13.1% (13/99) of the surgical treatment without fixation group, 0.0% (0/9) of the acute instrumentation group, and 100.0% (1/1) of the delayed instrumentation group.

Table 1
Aggregate patient baseline characteristics from a literature review of acute and delayed instrumentation in vertebral osteomyelitis.

Study	Intervention	Sample size (N)	Age (mean ± SD, years)	Causative organism: % (n/N)	Side of instrumentation: % (n/N)	Previous spinal surgery: % (n/N)	Spine region involved: % (n/N)	Baseline neurological deficit: % (n/N)	Baseline pain: % (n/N)
Ahn 2012 [1]	Surgical treatment-no fixation	2	50.0 ± 21.2	Gram-negative rod: 100.0% (2/2)	Not applicable	100.0% (2/2)	Lumbosacral: 100.0% (2/2)	0.0% (0/2)	100.0% (2/2)
	Acute instrumentation	6	41.5 ± 14.6	Gram-negative rod: 66.7% (4/6) Coagulase negative staphylococci: 33.3% (2/6)	Posterior: 100.0% (6/6)	100.0% (6/6)	Lumbosacral: 100.0% (6/6)	16.7% (1/6)	100.0% (6/6)
Arnold P. 1997 [2]	Surgical treatment-no fixation	7	48.6 ± 17.2	–	Not applicable	–	Thoracic: 42.9% (3/7) Lumbosacral: 71.4% (5/7)	85.7% (6/7)	100.0% (7/7)
	Acute instrumentation	3	45.0 ± 10.4	–	Posterior: 100.0% (3/3)	–	Lumbosacral: 100.0% (3/3)	0.0% (0/3)	100.0% (3/3)
Arnold R. 2014 [3]	Acute instrumentation	87	–	–	–	–	–	–	–
	Delayed instrumentation	7	–	–	–	–	–	–	–
Choi 2010 [4]	Surgical treatment-no fixation	3	43.7 ± 13.3	Gram-negative rod: 66.7% (2/3) Not able to identify: 33.3% (1/3)	Not applicable	100.0% (3/3)	Lumbosacral: 100.0% (3/3)	0.0% (0/3)	100.0% (3/3)
	Acute instrumentation	2	36.0 ± 1.4	Gram-negative rod: 50.0% (1/2) Coagulase negative staphylococci: 50.0% (1/2)	Posterior: 100.0% (2/2)	100.0% (2/2)	Lumbosacral: 100.0% (2/2)	0.0% (0/2)	100.0% (2/2)
	Delayed instrumentation	2	47.0 ± 19.8	Gram-negative rod: 100.0% (2/2)	Posterior: 100.0% (2/2)	100.0% (2/2)	Lumbosacral: 100.0% (2/2)	0.0% (0/2)	100.0% (2/2)
Lee 2007 [5]	Surgical treatment-no fixation	3	Range: 51-75	–	Not applicable	–	–	–	–
	Acute instrumentation	6	60.3 ± 10.2	S. aureus: 20.0% (1/5) Coagulase negative staphylococci: 20.0% (1/5) Not able to identify: 60.0% (3/5)	Anterior: 66.7% (4/6) Posterior: 33.3% (2/6)	–	Thoracic: 40.0% (2/5) Lumbosacral: 80.0% (4/5)	–	–
Mavrogenis 2016 [6]	Surgical treatment-no fixation	1	73	Gram-negative rod: 100.0% (1/1)	Not applicable	100.0% (1/1)	Lumbosacral: 100.0% (1/1)	100.0% (1/1)	–
	Acute instrumentation	2	70.5 ± 4.9	S. aureus: 100.0% (2/2)	Anterior: 50.0% (1/2) Combined: 50.0% (1/2)	50.0% (1/2)	Thoracic: 100.0% (2/2) Lumbosacral: 50.0% (1/2)	100.0% (2/2)	–

(*continued on next page*)

Table 1 (*continued*)

Study	Intervention	Sample size (N)	Age (mean ± SD, years)	Causative organism: % (n/N)	Side of instrumentation: % (n/N)	Previous spinal surgery: % (n/N)	Spine region involved: % (n/N)	Baseline neurological deficit: % (n/N)	Baseline pain: % (n/N)
Oktenoglu 2011 [7]	Surgical treatment-no fixation	3	53.7 ± 10.4	S. aureus: 100.0% (3/3)	Not applicable	0.0% (0/3)	Thoracic: 33.3% (1/3) Lumbosacral: 66.7%(2/3)	100.0% (3/3)	100.0% (3/3)
	Acute instrumentation	4	51.0 ± 6.7	S. aureus: 100.0% (4/4)	Anterior: 25.0% (1/4) Posterior: 25.0% (1/4) Combined: 50.0% (2/4)	0.0% (0/4)	Cervical: 50.0% (2/4) Thoracic: 50.0% (2/4)	75.0% (3/4)	100.0% (4/4)
	Delayed instrumentation	1	75	S. aureus: 100.0% (1/1)	Combined: 100.0% (1/1)	0.0% (0/1)	Cervical: 100.0% (1/1)	100.0% (1/1)	0.0% (0/1)
Park 2015 [8]	Surgical treatment-no fixation	94	Median: 65 (Q1-Q3: 59-72)	–	Not applicable	–	Cervical: 10.6% (10/94) Thoracic: 20.2% (19/94) Lumbosacral: 75.5% (71/94)	27.7% (26/94)	89.4% (84/94)
	All instrumentation	59	Median: 67 (Q1-Q3: 59-71)	–	–	–	Cervical: 10.2% (6/59) Thoracic: 35.6% (21/59) Lumbosacral: 71.2% (42/59)	16.9% (10/59)	89.8% (53/59)
	Acute instrumentation	24	–	–	–	–	–	–	–
	Delayed instrumentation	35	–	–	–	–	–	–	–
Verla 2020 [9]	Acute instrumentation	4	51.3 ± 22.0	S. aureus: 50.0% (2/4) Gram-negative rod: 75.0% (3/4)	Posterior: 25.0% (1/4) Combined: 75.0% (3/4)	–	Thoracic: 75.0% (3/4) Lumbosacral: 75.0% (3/4)	–	–
	Delayed instrumentation	3	45.3 ± 20.0	S. aureus: 33.3% (1/3) Gram-negative rod: 33.3% (1/3) Group B streptococci: 33.3% (1/3)	Combined: 100.0% (3/3)	–	Thoracic: 33.3% (1/3) Lumbosacral: 100.0% (3/3)	–	–

S. aureus=Staphylococcus aureus, SD=standard deviation.

Table 2
Individual patient baseline characteristics from a literature review of acute and delayed instrumentation in vertebral osteomyelitis.

Study	Intervention	Age (years)	Causative organism	Side of instrumentation	Previous spinal surgery	Spine region involved	Baseline neurological deficit	Baseline pain
Ahn 2012 [1]	Surgical treatment-no fixation	35	Gram-negative rod	Not applicable	Yes	Lumbosacral	No	Yes
		65	Gram-negative rod	Not applicable	Yes	Lumbosacral	No	Yes
	Acute instrumentation	29	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		31	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		36	Coagulase negative staphylococci	Posterior	Yes	Lumbosacral	No	Yes
		65	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		34	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		54	Coagulase negative staphylococci	Posterior	Yes	Lumbosacral	Yes	Yes
Arnold P. 1997 [2]	Surgical treatment-no fixation	30	–	Not applicable	–	Thoracic	No	Yes
		67	–	Not applicable	–	Lumbosacral	Yes	Yes
		45	–	Not applicable	–	Lumbosacral	Yes	Yes
		73	–	Not applicable	–	Lumbosacral	Yes	Yes
		43	–	Not applicable	–	Thoracic, Lumbosacral	Yes	Yes
		28	–	Not applicable	–	Thoracic	Yes	Yes
		54	–	Not applicable	–	Lumbosacral	Yes	Yes
	Acute instrumentation	38	–	Posterior	–	Lumbosacral	No	Yes
		40	–	Posterior	–	Lumbosacral	No	Yes
		57	–	Posterior	–	Lumbosacral	No	Yes
Choi 2010 [3]	Surgical treatment-no fixation	55	Not able to identify	Not applicable	Yes	Lumbosacral	No	Yes
		29	Gram-negative rod	Not applicable	Yes	Lumbosacral	No	Yes
		47	Gram-negative rod	Not applicable	Yes	Lumbosacral	No	Yes
	Acute instrumentation	35	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		37	Coagulase negative staphylococci	Posterior	Yes	Lumbosacral	No	Yes
	Delayed instrumentation	33	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
		61	Gram-negative rod	Posterior	Yes	Lumbosacral	No	Yes
Lee 2007 [4]	Surgical treatment-no fixation*	Range: 51-75	–	Not applicable	–	–	–	–
	Acute instrumentation	46	Coagulase negative staphylococci	Anterior	–	Lumbosacral	–	–
		63	Not able to identify	Anterior	–	Thoracic, Lumbosacral	–	–
		63	Not able to identify	Anterior	–	Lumbosacral	–	–
		69	Not able to identify	Anterior	–	Lumbosacral	–	–
		55	S. aureus	Posterior	–	Thoracic	–	–
		Range: 51-75*	–	Posterior	–	–	–	–
Mavrogenis 2016 [5]	Surgical treatment-no fixation	73	Gram-negative rod	Not applicable	Yes	Lumbosacral	Yes	–
	Acute instrumentation	74	S. aureus	Anterior	Yes	Thoracic, Lumbosacral	Yes	–
		67	S. aureus	Combined	No	Thoracic	Yes	–
Oktenoglu 2011 [6]	Surgical treatment-no fixation	57	S. aureus	Not applicable	Yes	Lumbosacral	Yes	Yes
		42	S. aureus	Not applicable	Yes	Thoracic	Yes	Yes
		62	S. aureus	Not applicable	Yes	Lumbosacral	Yes	Yes
	Acute instrumentation	60	S. aureus	Combined	Yes	Thoracic	Yes	Yes
		51	S. aureus	Combined	Yes	Cervical	No	Yes
		49	S. aureus	Anterior	Yes	Thoracic	Yes	Yes
		44	S. aureus	Posterior	Yes	Cervical	Yes	Yes
	Delayed instrumentation	75	S. aureus	Combined	No	Cervical	Yes	No
Verla 2020 [7]	Acute instrumentation	20	S. aureus, Gram-negative rod	Posterior	–	Lumbosacral	–	–
		71	Gram-negative rod	Combined	–	Thoracic, Lumbosacral	–	–
		60	Gram-negative rod	Combined	–	Thoracic, Lumbosacral	–	–
		54	S. aureus	Combined	–	Thoracic	–	–
	Delayed instrumentation	66	Group B streptococci	Combined	–	Lumbosacral	–	–
		26	Gram-negative rod	Combined	–	Thoracic, Lumbosacral	–	–
		44	S. aureus	Combined	–	Lumbosacral	–	–

S. aureus=Staphylococcus aureus.
*Some baseline data did not distinguish between three surgical treatment with no fixation patients and one acute instrumentation patient.

Table 3
Aggregate patient outcomes from a literature review of acute and delayed instrumentation in vertebral osteomyelitis.

Study	Intervention	Sample size (N)	Follow-up (months)*	Reinfection: % (n/N)	Neurological deficit: % (n/N)	Pain: % (n/N)	Mortality at 2 years: % (n/N)
Ahn 2012 [1]	Surgical treatment-no fixation	2	36.0 ± 0.0	–	–	50.0% (1/2)	0.0% (0/2)
	Acute instrumentation	6	27.3 ± 5.9	–	–	100.0% (6/6)	0.0% (0/5)
Arnold P. 1997 [2]	Surgical treatment-no fixation	7	Minimum = 12	–	14.3% (1/7)	0.0% (0/1)	–
	Acute instrumentation	3	Minimum = 12	–	0.0% (0/3)	0.0% (0/3)	–
Arnold R. 2014 [3]	Acute instrumentation	87	Minimum = 1	20.7% (18/87)	–	–	–
	Delayed instrumentation	7	Minimum = 1	57.1% (4/7)	–	–	–
Choi 2010 [4]	Surgical treatment-no fixation	3	Minimum = 4	0.0% (0/3)	–	0.0% (0/3)	–
	Acute instrumentation	2	Minimum = 4	0.0% (0/2)	–	0.0% (0/2)	–
	Delayed instrumentation	2	Minimum = 4	0.0% (0/2)	–	0.0% (0/2)	–
Lee 2007 [5]	Surgical treatment-no fixation	3	Minimum = 10	0.0% (0/3)	–	–	–
	Acute instrumentation	6	Minimum = 10	0.0% (0/6)	–	–	–
Mavrogenis 2016 [6]	Surgical treatment-no fixation	1	Exact = 0.5	–	0.0% (0/1)	–	100.0% (1/1)
	Acute instrumentation	2	Range = 12-60	0.0% (0/2)	0.0% (0/2)	–	0.0% (0/1)
Oktenoglu 2011 [7]	Surgical treatment-no fixation	3	28.0 ± 8.0	–	100.0% (3/3)	–	0.0% (0/2)
	Acute instrumentation	4	30.5 ± 7.0	–	50.0% (2/4)	–	0.0% (0/3)
	Delayed instrumentation	1	Exact = 16	–	–	–	100.0% (1/1)
Park 2015 [8]	Surgical treatment-no fixation	94	Mean = 39	4.8% (4/84)	–	28.2% (20/71)	12.8% (12/94)
	All instrumentation	59	Mean = 45	6.8% (4/59)	–	34.5% (19/55)	0.0% (0/59)
	Acute instrumentation	24	–	4.2% (1/24)	–	–	–
	Delayed instrumentation	35	–	8.6% (3/35)	–	–	–
Verla 2020 [9]	Acute instrumentation	4	Minimum = 6	–	–	–	–
	Delayed instrumentation	3	Minimum = 6	–	–	–	–

Data are expressed as mean ± standard deviation unless otherwise noted.
*To enable data analysis using a uniform metric, follow-up periods were converted to months when reported in alternative timescale metrics.

Table 4
Individual patient outcomes from a literature review of acute and delayed instrumentation in vertebral osteomyelitis.

Study	Intervention	Age (years)	Follow-up (months)*	Reinfection	Neurological deficit	Pain	Mortality at 2 years
Ahn 2012 [1]	Surgical treatment-no fixation	35	36	–	–	No	No
		65	36	–	–	Yes	No
	Acute instrumentation	29	36	–	–	Yes	No
		31	24	–	–	Yes	No
		36	32	–	–	Yes	No
		65	28	–	–	Yes	No
		34	24	–	–	Yes	No
		54	20	–	–	Yes	–
Arnold P. 1997 [2]	Surgical treatment-no fixation	30	Minimum = 12	–	No	No	–
		67	Minimum = 12	–	No	–	–
		45	Minimum = 12	–	No	–	–
		73	Minimum = 12	–	No	–	–
		43	Minimum = 12	–	No	–	–
		28	Minimum = 12	–	No	–	–
		54	Minimum = 12	–	Yes	–	–
	Acute instrumentation	38	Minimum = 12	–	No	No	–
		40	Minimum = 12	–	No	No	–
		57	Minimum = 12	–	No	No	–
Choi 2010 [3]	Surgical treatment-no fixation	55	Minimum = 4	No	–	No	–
		29	Minimum = 4	No	–	No	–
		47	Minimum = 4	No	–	No	–
	Acute instrumentation	35	Minimum = 4	No	–	No	–
		37	Minimum = 4	No	–	No	–
	Delayed instrumentation	33	Minimum = 4	No	–	No	–
		61	Minimum = 4	No	–	No	–
Lee 2007 [4]	Surgical treatment-no fixation	Range: 51-75**	Minimum = 10	No	–	–	–
	Acute instrumentation	46	Minimum = 10	No	–	–	–
		63	Minimum = 10	No	–	–	–
		63	Minimum = 10	No	–	–	–
		69	Minimum = 10	No	–	–	–
		55	Minimum = 10	No	–	–	–
		Range: 51-75**	Minimum = 10	No	–	–	–
Mavrogenis 2016 [5]	Surgical treatment-no fixation	73	0.5	–	No	–	Yes
	Acute instrumentation	74	60	No	No	–	No
		67	12	No	No	–	–
Oktenoglu 2011 [6]	Surgical treatment-no fixation	57	36	–	Yes	–	No
		42	20	–	Yes	–	–
		62	28	–	Yes	–	No
	Acute instrumentation	60	34	–	No	–	No
		51	28	–	No	–	No
		49	38	–	Yes	–	No
		44	22	–	Yes	–	–
	Delayed instrumentation	75	16	–	–	–	Yes
Verla 2020 [7]	Acute instrumentation	20	Minimum = 6	–	–	–	–
		71	Minimum = 6	–	–	–	–
		60	Minimum = 6	–	–	–	–
		54	Minimum = 6	–	–	–	–
	Delayed instrumentation	66	Minimum = 6	–	–	–	–
		26	Minimum = 6	–	–	–	–
		44	Minimum = 6	–	–	–	–

*To enable data analysis using a uniform metric, follow-up periods were converted to months when reported in alternative timescale metrics.
**Some baseline data did not distinguish between three surgical treatment with no fixation patients and one acute instrumentation patient in this study.

Other outcomes recorded include length of hospitalization, progression of kyphosis, fusion, and hardware failure. Length of hospitalization was given by one study with a minimum follow-up of 6 months [22] with four patients with acute instrumentation. The patients had a mean length of hospitalization of 33.0 days (SD: +/- 19.8), and three patients with delayed instrumentation, who had a mean length of hospitalization of 24.0 days (SD: +/- 17.8).

Kyphosis status was given in one study with a minimum follow-up of 10 months [19] with one patient with surgical treatment without fixation and six patients with acute instrumentation. Progression of kyphosis was not found in any patients and two patients with kyphosis diagnosed at baseline had improvement in kyphosis (-3.6° and -9.4° from baselines of 4.4° and 12.3°, respectively).

Fusion status was reported in one study with a minimum follow-up of four months [18], where fusion was achieved in all patients, including three patients with surgical treatment without fixation, two patients with acute instrumentation, and two patients with delayed instrumentation.. Hardware status was reported in two studies with a follow-up range of 6 months to 60 months [7,22], with no cases of hardware failure, including six patients with acute instrumentation and three patients with delayed instrumentation.

Discussion

We systematically reviewed studies that reported outcomes of patients with PVO treated with acute or delayed instrumentation com-

pared to patients treated with surgery without fixation. We found that among available patients with PVO treated with instrumentation, there was no difference in reinfection rates between acute and delayed instrumentation, although the limited number of studies available makes drawing definite conclusions impossible. Reinfection occurred less frequently in the group treated surgically without fixation compared to either group where instrumentation was used. The percentage of patients with pain decreased after surgery in all three groups. Studies with a moderate risk of bias supported similar conclusions to studies with low risk of bias. Overall, this study suggests that there are no major differences in outcomes between acute and delayed instrumentation for patients with PVO. Further cohort studies and controlled trials directly comparing acute and delayed instrumentation are necessary to confirm this conclusion.

While the use of instrumentation in surgical treatment for PVO is commonly accepted, no consensus exists for the staging of debridement relative to the application of instrumentation. However, our systematic review indicates that acute and delayed instrumentation may not lead to major differences in reinfection rates, in agreement with studies that directly compared acute and delayed instrumentation [5,18,21]. These results suggest that clearing infected tissue before instrumentation may not reduce the risk of regrowth of the infectious agent, or that the infection is not fully cleared between the first surgery and the second. However, delayed instrumentation is sometimes chosen based on concerns for the patient's ability to undergo general anesthesia or recover from the initial surgery due to comorbidities or severe disease [9–11], which may affect comparisons between the groups in non-randomized studies. Additionally, the studies did not report screening for patients with refractory cases of PVO, which would indicate a predisposition to reinfection. Acute and delayed approaches may have advantages in different patient populations and these factors should be considered when choosing the most appropriate technique.

Our results suggest that both the acute and delayed instrumentation groups have higher rates of reinfection than the surgical treatment without fixation group, indicating there may be an increased risk of reinfection due to bacteria growing on the instrumentation. While some studies have reported no increased risk of reinfection [4,23] and suggest that instrumentation should be applied more frequently to prevent progression of kyphosis after treatment for PVO [7–9], our results indicate that the potential increased risk of reinfection should still be considered. Reinfection can lead to increased morbidity and mortality as well as increased hospital costs and long-term complications [24]. Further studies are needed to determine the increase in risk of reinfection from use of instrumentation, including the influence of comorbidities and other patient characteristics on risk of reinfection.

All three surgical treatments reduced pain compared to the baseline data in our review. The acute instrumentation group had higher incidence of pain both before and after treatment than the delayed instrumentation group, but the low number of patients in the delayed instrumentation group limits the validity of the comparison. The individual studies included in the review draw a mix of conclusions about the efficacy of the different treatments in resolving patient pain. Three studies indicated that surgical treatment without fixation and acute or delayed instrumentation are all effective at reducing the incidence of pain compared to baseline [17,18,21]. One study indicated that surgical treatment without fixation decreases the incidence of pain compared to baseline, but that acute instrumentation leads to no change in pain [16]. No studies reported an increase in incidence of pain after surgery. These results are in line with the current treatment guidelines for VO, which include the usage of surgical treatment with or without instrumentation in patients with neurological decline or spinal instability despite the lack of controlled trials to indicate efficacy [4,6].

The limited data available for other outcomes made drawing concrete conclusions about the effect of staging difficult. Neurological status at follow-up was only available for 6.7% of patients, while baseline neurological status was available for 43.5% of patients. Likewise, mortality at two years was only available in one patient in the delayed instrumentation group and nine in the acute instrumentation group. Patient characteristics that may affect outcomes, such as causative organism, spine region, and side of instrumentation, were also sporadically reported. Further work is needed to follow patients with PVO treated with instrumentation long-term and consistently capture relevant patient characteristics and outcomes.

Limitations

A major limitation of this study is the rarity of instrumentation in treatment of PVO, especially delayed instrumentation, so the evidence gathered here came from small, retrospective studies, thus precluding inferential statistics. Our findings are also limited by the low number of studies that distinguish between acute and delayed instrumentation when reporting patient data and the lack of randomized control trials available for instrumentation in the treatment of PVO. The majority of the patients identified come from two of the nine included studies [5,21], which did not provide patient-level data. Selection bias in deciding whether to treat patients with acute or delayed instrumentation due to disease characteristics or comorbidities introduces bias into our results. Additionally, time between debridement and instrumentation was not consistent across patients with delayed instrumentation. Further studies will be needed to directly compare acute and delayed instrumentation across larger numbers of patients.

Conclusion

Currently, the available evidence does not reveal differences in the relative effects of acute or delayed instrumentation on patient outcomes. Use of instrumentation in surgery for PVO, either acute or delayed, may lead to an increase in reinfection rates. Further research is needed to understand the relative benefits and disadvantages of acute and delayed instrumentation in the treatment of PVO.

Funding disclosures

ES is employed by Superior Medical Experts.

Data Availability

All data relevant to the study are included in the manuscript and its tables.

Informed Patient Consent

The authors declare that informed patient consent was taken from all the patients.

Declaration of Interest

The authors report no known conflict of interest or personal relationships that could have appeared to influence the work reported here.

Acknowledgements

The authors acknowledge Superior Medical Experts research and drafting assistance.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2021.100083.

References

[1] Sato K, Yamada K, Yokosuka K, et al. Pyogenic spondylitis: clinical features, diagnosis and treatment. Kurume Med J 2019;65(3):83–9. doi:10.2739/kurumemedj.MS653001.

[2] Kehrer M, Pedersen C, Jensen TG, Lassen AT. Increasing incidence of pyogenic spondylodiscitis: a 14-year population-based study. J Infect 2014;68(4):313–20. doi:10.1016/j.jinf.2013.11.011.

[3] Akiyama T, Chikuda H, Yasunaga H, Horiguchi H, Fushimi K, Saita K. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. BMJ Open 2013;3(3). doi:10.1136/bmjopen-2012-002412.

[4] Waheed G, Soliman MAR, Ali AM, Aly MH. Spontaneous spondylodiscitis: review, incidence, management, and clinical outcome in 44 patients. Neurosurg Focus FOC 2019;46(1):E10. doi:10.3171/2018.10.FOCUS18463.

[5] Arnold R, Rock C, Croft L, Gilliam BL, Morgan DJ. Factors associated with treatment failure in vertebral osteomyelitis requiring spinal instrumentation. Antimicrob Agents Chemother 2014;58(2):880–4. doi:10.1128/aac.01452-13.

[6] Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: an update. Br Med Bull 2016;117(1):121–38. doi:10.1093/bmb/ldw003.

[7] Mavrogenis AF, Igoumenou V, Tsiavos K, et al. When and how to operate on spondylodiscitis: a report of 13 patients. Eur J Orthop Surg Traumatol 2016;26(1):31–40. doi:10.1007/s00590-015-1674-6.

[8] Lin CP, Ma HL, Wang ST, Liu CL, Yu WK, Chang MC. Surgical results of long posterior fixation with short fusion in the treatment of pyogenic spondylodiscitis of the thoracic and lumbar spine: a retrospective study. Spine 2012;37(25):E1572–9. doi:10.1097/BRS.0b013e31827399b8.

[9] Rayes M, Colen CB, Bahgat DA, et al. Safety of instrumentation in patients with spinal infection. J Neurosurg Spine 2010;12(6):647–59. doi:10.3171/2009.12.Spine09428.

[10] Zarghooni K, Röllinghoff M, Sobottke R, Eysel P. Treatment of spondylodiscitis. Int Orthop 2012;36(2):405–11. doi:10.1007/s00264-011-1425-1.

[11] Shiban E, Janssen I, Wostrack M, et al. A retrospective study of 113 consecutive cases of surgically treated spondylodiscitis patients. A single-center experience. Acta Neurochir 2014;156(6):1189–96. doi:10.1007/s00701-014-2058-0.

[12] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med 2021;18(3):e1003583. doi:10.1371/journal.pmed.1003583.

[13] Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. University of Ottawa; 2000. [updated 01/2000; cited 2021 8/15/21]; Available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp .

[14] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27(6):1785–805. doi:10.1177/0962280216669183.

[15] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. doi:10.1186/1471-2288-14-135.

[16] Ahn Y, Lee SH. Postoperative spondylodiscitis following transforaminal percutaneous endoscopic lumbar discectomy: clinical characteristics and preventive strategies. Br J Neurosurg 2012;26(4):482–6. doi:10.3109/02688697.2011.650739.

[17] Arnold PM, Baek PN, Bernardi RJ, Luck EA, Larson SJ. Surgical management of nontuberculous thoracic and lumbar vertebral osteomyelitis: report of 33 cases. Surg Neurol 1997;47(6):551–61. doi:10.1016/s0090-3019(96)00242-x.

[18] Choi KB, Lee CD, Lee SH. Pyogenic spondylodiscitis after percutaneous endoscopic lumbar discectomy. J Korean Neurosurg Soc 2010;48(5):455–60. doi:10.3340/jkns.2010.48.5.455.

[19] Lee DG, Park KB, Kang DH, Hwang SH, Jung JM, Han JW. A clinical analysis of surgical treatment for spontaneous spinal infection. J Korean Neurosurg Soc 2007;42(4):317–25. doi:10.3340/jkns.2007.42.4.317.

[20] Oktenoglu T, Sasani M, Cetin B, et al. Spontaneous pyogenic spinal epidural abscess. Turk Neurosurg 2011;21(1):74–82.

[21] Park KH, Cho OH, Lee YM, et al. Therapeutic outcomes of hematogenous vertebral osteomyelitis with instrumented surgery. Clin Infect Dis 2015;60(9):1330–8. doi:10.1093/cid/civ066.

[22] Verla T, North R, Simpson V, Ropper AE. Osteomyelitis-discitis at the thoracolumbar junction and the development of postinfectious spinal deformity: a surgical case series. Int J Spine Surg 2020;14(4):552–8. doi:10.14444/7073.

[23] Bydon M, De la Garza-Ramos R, Macki M, Naumann M, Sciubba D, Wolinsky J. Spinal instrumentation in patients with primary spinal infections does not lead to greater recurrent infection rates: an analysis of 118 cases. World Neurosurg 2014;82:e807–ee14. doi:10.1016/j.wneu.2014.06.014.

[24] Garcia del Pozo E, Collazos J, Carton JA, Camporro D, Asensi V. Factors predictive of relapse in adult bacterial osteomyelitis of long bones. BMC Infectious Dis 2018;18(1):635. doi:10.1186/s12879-018-3550-6.