Systematic Review

Infections Following Interventional Spine Procedures: A Systematic Review

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Background: Interventional spine procedures, such as discography, epidural steroid injections (ESIs), facet joint procedures, and intradiscal therapies, are commonly used to treat pain and improve function in patients with spine conditions. Although infections are known to occur following these procedures, there is a lack of comprehensive studies on this topic in recent years.

Objectives: To assess and characterize infections following interventional spine procedures.

Study Design: Systematic review.

Methods: Studies that were published from January 2010 to January 2020 and provided information on infections or infection rates following discography, ESIs, facet joint procedures, and intradiscal therapies were included. PubMed (Medline), EMBASE, and Cochrane Library databases were searched, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Infection data were extracted from included studies, and infection rates were calculated for each procedure type. Case reports and infection-only articles were not included in infection rate calculations.

Results: Seventy-two studies met the eligibility criteria and were included in the systematic review. The overall incidence of infection across all studies was 0.12% (231/200,588). The majority of studies (n = 51) were linked to ESIs. Infections related to ESIs were more common than those related to discography or facet joint procedures (0.13% [219/174,431] vs. 0% [0/269] or 0.04% [9/25,697], respectively). Intradiscal therapies had the highest calculated rate of infections (1.05%; 2/191). Quality assessments of the included studies ranged widely.

Limitations: There was an abundance of case reports in comparison to other study designs; to minimize skewing of the analysis, case reports and infection-only articles were not included in the infection rate. Studies that reported combined infection data for multiple procedures could not be included. Many cohort studies and case series were of lower quality because of their retrospective nature. Additionally, the true incidence of infections related to these procedures is unknown because the majority of these infections often go unreported, and information on regions of the spine and procedure details are often lacking.

Conclusions: Based on our systematic review, the risk of infections following interventional spine procedures appears to be low overall. More studies focusing on infectious complications with larger sample sizes are needed, particularly for intradiscal therapies, in which the microbiome may be an underlying cause of disc infection. To achieve a true incidence of the risk of infections with these procedures, large prospective registries that collect complication rates are necessary.

Key words: Infectious complications, infection incidence, interventional spine procedure, epidural steroid injection, discography, facet joint procedure, intradiscal therapies, biologics

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Low back pain (LBP) and cervical (neck) pain rank first and fourth in disability worldwide, respectively (1-3). Up to 80% of adults experience LBP at some point in their lives (4), whereas neck pain affects up to 38.7% of adults (5). Conservative treatments for LBP and neck pain include physical

therapy, pharmacologic therapy (i.e., nonsteroidal antiinflammatory drugs), and interventional spine procedures (5,6). Guidelines on these treatments have changed over time and vary depending on the etiology and presentation of symptoms.

Interventional spine procedures include discography, epidural steroid injections (ESIs), zygapophyseal (facet) joint injections and nerve blocks, and intradiscal injections and therapies. These interventional procedures are often performed when first-line treatments (i.e., physical and pharmacologic therapies) fail (6,7). The use of discography has diminished in recent years, as it has been shown to increase disc degeneration and pain severity, and its utility as a diagnostic tool has been widely debated; however, it may still be used in conjunction with other spine procedures (7,8). ESIs and facet joint injections or nerve blocks are commonly performed for LBP, but their use depends on the etiology of LBP (7). They may also be performed for neck pain (5). In recent years, intradiscal therapies, such as intradiscal electrothermal therapy (IDET) and intradiscal orthobiologic injections, have become more widely used in the treatment of LBP owing to intervertebral disc degeneration (9).

Infections are a type of complication that may be related to interventional spine procedures. The reported incidence is estimated to range from 1% to 2% (10), but the actual incidence may be higher because infection complications are not always reported in the literature. Aside from the multistate outbreak of fungal infections among patients who received contaminated steroid injections in 2012 (11), most cases of infections appear to be isolated. There are limited studies on the incidence of infections following interventional spine procedures in recent years. This systematic review aimed to characterize the incidence of bacterial, fungal, and viral infections following discography, ESIs, facet joint injections or nerve blocks, IDET, and intradiscal orthobiologic therapies in the cervical or lumbar spine, over the last 10 years.

Methods

Literature Search

A comprehensive search of PubMed (Medline), Cochrane Library, and EMBASE databases was performed in January 2020, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search terms included "infection," "epidural steroid injection," "facet joint injection," "facet joint procedure," "discography," "intradiscal PRP," and "intradiscal biologic." The complete search string is included in Supplementary Appendix 1. Searches in all databases were carried out on the same day. Potential studies were also identified by manually searching the reference lists of relevant review articles.

Studies that were published from January 2010 to January 2020 and provided information on infections following an earlier mentioned interventional spine procedure were included. Studies were excluded if they (1) did not mention infections, (2) were not published in English, (3) involved animals, or (4) were reviews or meta-analyses. The online software program Covidence (www.covidence.org/) was used during the screening phases. Two authors independently screened studies for inclusion; title and abstract screening was conducted first, followed by full-text screening, and any disagreements were resolved through consensus. Conference abstracts that included adequate information about infections and/or infection rates were also included.

Data Extraction

Study design, sample size information, type of interventional spine procedure, presence of infection, and infection-related data were independently extracted from included articles. Infection-related data included type of infection, tests used to diagnose the infection, treatments, and outcomes. The overall incidence of infection among all interventional spine procedures was calculated, based on the articles included. Additionally, for each interventional spine procedure category, the total incidence of infection was calculated. To minimize skewing our analysis as much as possible, these calculations did not include case reports or articles that only reported on infection cases. Furthermore, articles that only reported combined infection data for multiple interventional spine procedures were excluded from calculations.

Quality Assessment

For cohort and case–control studies, assessment of study quality was performed using the Newcastle-Ottawa Scale (12). A score was given to 3 domains: selection, comparability, and outcome. A modified version of the Newcastle-Ottawa Scale was used for cross-sectional studies (13). For case reports and case report series, assessment of study quality was performed using the Joanna Briggs Institute Case Reports Critical Appraisal Tool (14). A score of 0, 1, or 2 was given to each of the 8

questions, for a total score of 16. Finally, the assessment of study quality for randomized controlled trials was performed using the Cochrane Risk of Bias Tool (15). A score was given to 5 domains: selection, performance, attrition, reporting, and other.

Results

Study Selection and Characteristics

The initial search yielded 907 articles that fit the search criteria. After excluding all duplicates there were 804 articles. An additional 34 articles were identified from manual searches. Title and abstract review identified 658 irrelevant articles, and full-text review identified 108 additional articles that were deemed irrelevant. A total of 72 articles remained for inclusion in the systematic review. A schematic of the process can be found in Fig. 1. Of these 72 articles published, 30 were case reports, 19 were prospective studies (including 7 randomized controlled trials), 22 were retrospective studies, and 1 was a cross-sectional study (Table 1). The overall infection incidence was 0.12% (231/200,588).

Discography

We identified 2 studies and 1 case report reporting on infections related to lumbar discography. There

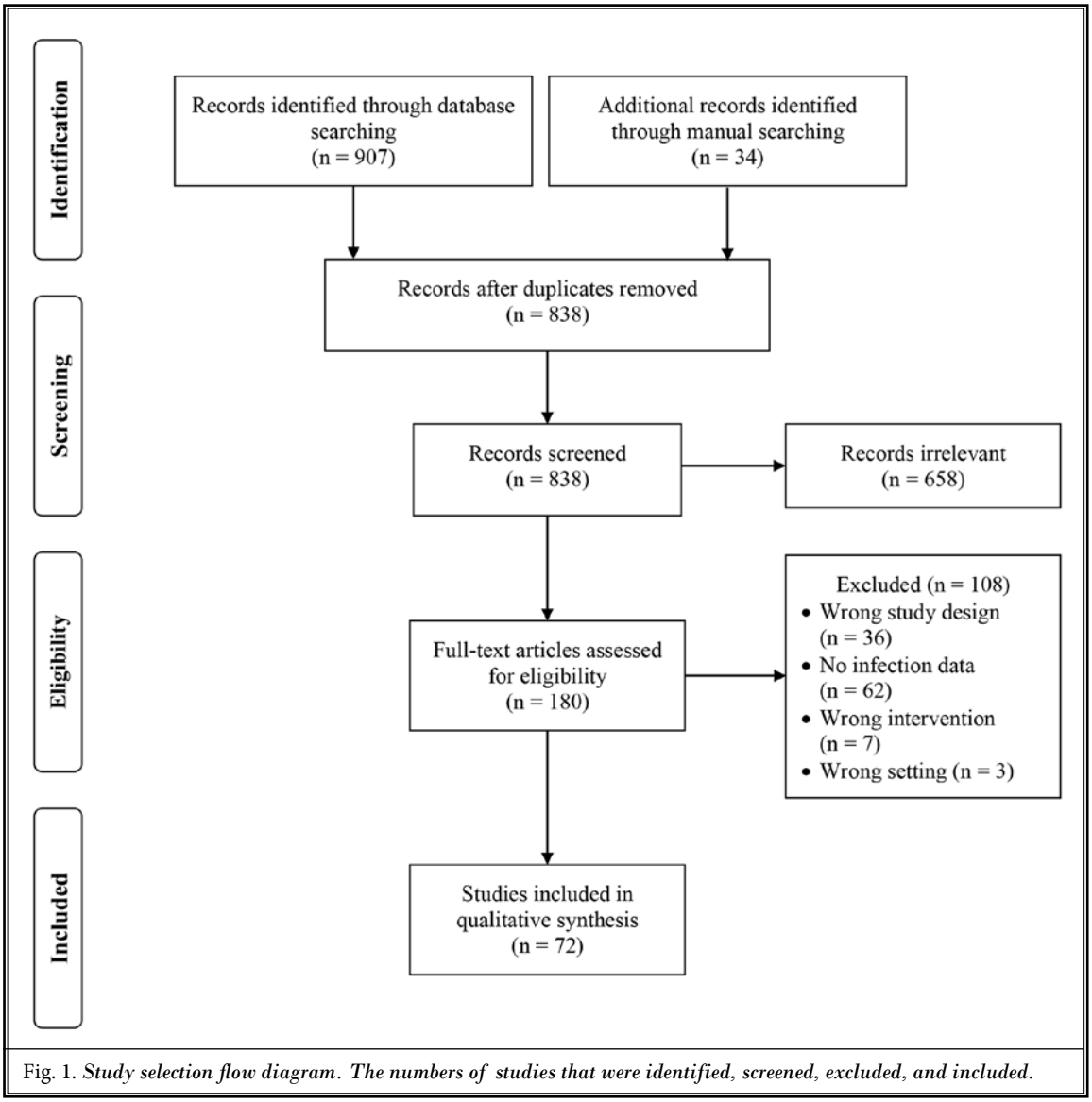

Fig. 1. *Study selection flow diagram. The numbers of studies that were identified, screened, excluded, and included.*

Table 1. *Study characteristics*.

First Author	Year Published	Study Design	Interventional Spine Procedure(s)	Spine Region(s)	Image Guidance Used	Number of Patients or Procedures	Number of Infections
Aronsohn (19)	2010	RCT*	ESI	Lumbar	Not specified	24	0
Beissel (20)	2016	Cross-sectional	ESI	Lumbar	Fluoroscopy	1788	0
Bosnak (80)	2017	Retrospective	IDET	Lumbar	Fluoroscopy	10	10
Brown (21)	2012	RCT	ESI	Lumbar	Fluoroscopy	17	0
Carr (30)	2016	Retrospective	ESI, FJ procedures	Lumbar	Fluoroscopy, CT	16766 (ESI), 6108 (FJ)	0
CDC (11)	2013	Retrospective	ESI, FJI	Lumbar	Not specified	180	180
Centeno (83)	2017	Prospective	Intradiscal MSC	Lumbar	Fluoroscopy	33	0
Chiller (60)	2013	Retrospective	ESI, FJI	Not specified	Not specified	328	328
Cho (67)	2020	Retrospective	ESI	Lumbar	Not specified	49	13
Cohen (31)	2012	RCT*	ESI, intradiscal CB	Lumbar	Fluoroscopy	28 (ESI), 26 (intradiscal CB)	0 (ESI), 1 (intradiscal CB)
Cohen (68)	2015	RCT	ESI	Lumbar	Fluoroscopy	73	2
El-Yahchouchi (22)	2016	Retrospective	ESI	Lumbar	Fluoroscopy, CT	16638	0
Galhom (29)	2013	Prospective	ESI, FJI	Lumbar	Fluoroscopy	37 (ESI), 3 (FJI)	0 (ESI), 1 (FJI)
Huang (78)	2017	Retrospective	Facet cyst rupture	Lumbar	Fluoroscopy, CT	71	1
Jeon (64)	2015	Retrospective	ESI	Lumbar	Fluoroscopy	150	1
Kainer (58)	2012	Retrospective*	ESI, FJI	Not specified	Not specified	137	137
Kainer (57)	2012	Retrospective	ESI, FJI	Not specified	Not specified	66	66
Kang (23)	2011	RCT	ESI	Lumbar	Fluoroscopy	160	0
Kauffman (54)	2015	Retrospective	ESI	Not specified	Not specified	718	718
Kerkering (55)	2013	Prospective	ESI	Lumbar	Not specified	172	172
Kim (70)	2020	Retrospective	FJI	Lumbar	Fluoroscopy	11980	8
Lee (62)	2018	Retrospective	ESI	Cervical, thoracic, lumbar	Fluoroscopy	52935	4
Liu (17)	2018	Prospective	Discography	Lumbar	Fluoroscopy	46	0
Lutz (79)	2018	Prospective	Facet cyst rupture	Lumbar	Fluoroscopy	53	0
Lyons (46)	2013	Prospective*	ESI	Not specified	Not specified	4	4
Manchikanti (24)	2012	Prospective	ESI	Lumbar, thoracic	Fluoroscopy	10261	0
Manchikanti (77)	2012	Prospective	FJ nerve blocks	Cervical, thoracic, lumbar	Fluoroscopy	7482	0
Mcgrath (25)	2011	Retrospective	ESI	Cervical, lumbar	Fluoroscopy	4265	0
Moser (82)	2011	Prospective*	Intradiscal ACS	Lumbar	Not specified	19	0
Moudgal (59)	2014	Retrospective	ESI	Not specified	Not specified	544	153
Park (26)	2015	Retrospective	ESI	Lumbar	Fluoroscopy, Ultrasound	110	0
Pathmanathan (27)	2012	Retrospective	ESI	Not specified	Not specified	47440	0
Plastaras (28)	2010	Retrospective	ESI	Lumbar	Fluoroscopy	8132	0
Radcliffe (65)	2012	Retrospective	ESI	Lumbar	Fluoroscopy (some)	110	8

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First Author	Year Published	Study Design	Interventional Spine Procedure(s)	Spine Region(s)	Image Guidance Used	Number of Patients or Procedures	Number of Infections
Ritter (56)	2013	Retrospective	ESI, FJI	Not specified	Not specified	40	40
Sainoh (87)	2016	Prospective	Intradiscal CB	Lumbar	Fluoroscopy	31	1
Sainoh (86)	2016	RCT	Intradiscal CB	Lumbar	Fluoroscopy	38	0
Schreiber (69)	2016	Retrospective	ESI	Cervical	Not specified	7	2
Smith (63)	2017	Retrospective	ESI	Cervical, lumbar	Not specified	14247	3
Tuakli-Wosornu (81)	2016	RCT	Intradiscal PRP	Lumbar	Fluoroscopy	44	0
Verrills (16)	2015	Prospective	Discography	Lumbar	Fluoroscopy	223	0
Young (61)	2013	Prospective*	ESI	Not specified	Not specified	650	33
Case Reports							
Bashari (32)	2015	Case report*	ESI	Lumbar	Not specified	1	1
Beatty (85)	2019	Case report	Intradiscal PRP	Lumbar	Fluoroscopy	1	1
Bedoya (33)	2010	Case report	ESI	Lumbar	Not specified	1	1
Bell (34)	2013	Case report	ESI	Cervical	Not specified	1	1
Bunker (35)	2018	Case report*	ESI	Lumbar	Not specified	1	1
Davis (36)	2014	Case report	ESI	Lumbar	Fluoroscopy	1	1
Fayeye (71)	2016	Case report	FJI	Lumbar	Not specified	1	1
Gowda (74)	2018	Case report	FJI	Lumbar	Fluoroscopy	1	1
Haleem (37)	2014	Case report*	ESI	Not specified	Not specified	1	1
Huie (38)	2010	Case report*	ESI	Lumbar	Not specified	1	1
Johnson (39)	2016	Case report	ESI	Lumbar	Not specified	1	1
Kim (66)	2015	Case report*	ESI	Lumbar	Not specified	1	1
Kim (76)	2010	Case report	FJI	Lumbar	Not specified	1	1
Kraeutler (41)	2015	Case report	ESI	Lumbar	Fluoroscopy	1	1
Lam (42)	2017	Case report	ESI	Lumbar	Not specified	1	1
Lee (43)	2015	Case report	ESI	Lumbar	Not specified	1	1
Lobaton (44)	2019	Case report	ESI	Lumbar	Not specified	1	1
Logan (45)	2013	Case report	ESI	Not specified	Not specified	1	1
Martens (75)	2017	Case report*	FJ infiltration	Lumbar	Not specified	1	1
Miner (47)	2013	Case report*	ESI	Lumbar	Not specified	1	1
Noh (48)	2015	Case report	ESI	Lumbar	Not specified	1	1
Rai (72)	2014	Case report*	FJI	Lumbar, cervical	Not specified	2	2
Rein (49)	2015	Case report*	ESI	Lumbar	Not specified	1	1
Schott (50)	2017	Case report*	ESI	Lumbar	Not specified	1	1
Sehu (73)	2014	Case report*	FJI	Lumbar	Not specified	1	1
Spera (51)	2012	Case report*	ESI	Not specified	Not specified	1	1
Subach (84)	2012	Case report	Intradiscal BMA	Lumbar	Fluoroscopy	1	1
Tailor (52)	2012	Case report	ESI	Lumbar	Not specified	1	1
Werner (18)	2011	Case report	Discography	Lumbar	Not specified	1	1
Yuseif (53)	2015	Case report*	ESI	Lumbar	Not specified	1	1

Abbreviations: ACS, autologous conditioned serum; BMA, bone marrow aspirate; CB, cytokine blocker; FJ, facet joint; FJI, facet joint injection; MSC, mesenchymal stem cells; RCT, randomized controlled trial.
*Conference abstract

were no studies reporting on infections related to cervical or thoracic discography. The overall incidence for lumbar discography was 0% (0/269). In a prospective study of 223 patients with chronic LBP who underwent fluoroscopically guided lumbar discography and received intradiscal antibiotics prior to the procedure, no infections were recorded (16). Similarly, in a case series of 46 patients who underwent lumbar discography under fluoroscopic guidance to treat LBP caused by Schmorl nodes, no infections were reported within 1 year postprocedure (17).

Werner et al (18) discussed a case of increasing LBP in an immunocompetent woman who underwent discography 3 weeks prior to admission. After identifying discitis at L3-L4 via magnetic resonance imaging (MRI), the patient underwent a left L3-L4 hemilaminectomy with L3-L4 discectomy. Candida lusitaniae was identified on culture specimens of both the disc and epidural space. The patient was prescribed a 6-month course of fluconazole and remained infection-free at 18 months after completing the course of antibiotics (18).

ESIs

There were 51 reports on infections related to ESIs: 21 case reports, 19 retrospective studies, 10 prospective studies, and 1 cross-sectional survey study. The overall incidence of infections was 0.13% (219/174,431). It is important to note that although no infections were reported among a total of 105,666 ESIs across 13 prospective and retrospective studies (19-31), 915 infections were reported among 21 case reports and 3 observational studies that focused on ESI-related infections (32-55). These 915 infections were not included in the calculation of infection rate.

Fungal

Of the 13 studies on fungal infections as a result of ESIs, 12 were related to the outbreak resulting from contaminated methylprednisolone acetate (MPA) injections manufactured by the New England Compounding Center in 2012 (56). Most of these studies did not specify the type of ESI approach and/or image guidance used. As of July 2013, 749 cases and 61 deaths associated with the contaminated MPA lots had been reported (57), with 52% of probable or confirmed spinal or paraspinal infections in Michigan (11). A case series published in 2012 found that 81% of cases were infections of the central nervous system (CNS), and 36% of cases identified Exserohilum rostratum, a dematiaceous fungus that typically infects plants, as the source (56,57). However, 7 other fungal species have been cultured (57), including Aspergillus fumigatus (58). The median symptom onset occurred at 18 days after the last ESI, although those with CNS infections presented earlier than those with localized infections (57). Kainer et al (57) showed that the risk of infection increased when the translaminar approach was utilized. Nearly 75% of patients experienced headaches, and approximately 50% experienced worsening back pain (57). Several case series reported that infected patients presented with epidural abscess, vertebral osteomyelitis, arachnoiditis, neutrophilic meningitis, cauda equine syndrome, and/or circulation stroke (54,55,57). Bell et al (34) reported on histological findings in a patient who had undergone a cervical ESI with contaminated MPA and developed a fatal infection. Logan et al (45) reported on a patient who developed a rare complication, basilar artery stroke, as a result of a fungal infection. The patient was also diagnosed with meningitis. Antifungal treatment was given long-term, but the patient died after her condition deteriorated (45).

Infection was identified via MRI in most cases but was also confirmed by hyphae on culture or in tissues (59). MRI findings included arachnoiditis, osteomyelitis, and hemorrhage (55,59). Many patients presented with severe meningeal inflammation, as confirmed by a high white blood cell (WBC) count in the cerebrospinal fluid (CSF) (60,61). Examination of the brain and spinal cord of a deceased patient with a confirmed Exserohilum rostratum infection revealed inflammation of the meninges with foci of fungal elements, as well as necrosis (34).

Patients with fungal infections were generally treated with voriconazole and/or liposomal amphotericin for at least 2 weeks (46,54,55,59). Adverse events from antifungal treatment were common and included photopsia, nausea, and visual hallucinations. Some patients underwent surgical debridement in addition to antifungal treatment (59).

There was one case report of a fungal infection post-lumbar ESI of triamcinolone that was unrelated to the MPA outbreak. Bunker et al (35) discussed a 73-year-old woman who presented with persistent fever and worsening pain 5 months following an ESI. MRI revealed discitis, and blood cultures were positive for Candida albicans. She was treated with intravenous micafungin, although her response to treatment was not specified (35).

Viral

We identified 5 case reports on viral infections as a complication of ESIs, 4 of which were related to the reactivation of a herpesvirus. Davis et al (36) discussed a woman who developed acute, severe odynophagia as a result of herpes esophagitis shortly after undergoing 3 fluoroscopy-guided lumbar ESIs for LBP; all ESIs were performed with triamcinolone. Laboratory studies revealed anemia and leukocytosis; after unsuccessful treatment with a proton pump inhibitor, an esophagogastroduodenoscopy revealed significant hemorrhagic, necrotic esophagitis. The patient was then treated with intravenous and oral acyclovir, which improved her symptoms (36). The case report by Miner (47) discussed a woman who was admitted 3 weeks after lumbar ESI with nausea, vomiting, headache, and neck stiffness. Despite no genital lesions on admission, no sexual activity in over 20 years, and no history of meningitis or herpes simplex virus (HSV), HSV-2 was detected in the CSF, along with elevated opening pressure and elevated protein levels on spinal tap (47). This patient was similarly treated with intravenous and oral acyclovir (47). Another woman with a history of shingles, chickenpox, and viral meningitis developed clustered vesicles on the buttock 6 weeks after an L4 transforaminal ESI, and viral serologies were positive for varicella zoster virus, HSV-1, and HSV-2 (38). Similarly, Rein et al (49) reported the development of a vesicular rash in the S1 dermatome a few days after a left-sided S1 transforaminal ESI was performed. The patient was treated with gabapentin, and the rash resolved.

A case study by Schott et al (50) discussed a woman who experienced a flare-up of cyclic erythema multiforme as a result of progesterone sensitivity a few weeks after a bilateral L3-L5 ESI. She had previously undergone surgery to treat the progesterone sensitivity. The patient presented with oral and skin lesions, which resolved with oral steroids, followed by prednisone taper. The patient had previously reported autoimmune progesterone dermatitis, which had since resolved. Administration of triamcinolone is thought to have induced the erythema multiforme flare (50).

Bacterial

There were 14 studies that reported on bacterial infections as a complication of ESIs. For prospective and retrospective studies, the infection rates ranged from 0.01% to 7% and averaged 0.03% (15/47,217) (62-65). Patients with bacterial infection most commonly presented with epidural abscess, vertebral osteomyelitis, and meningitis. Treatments varied for each presentation and bacterial strain.

There were 3 case reports of methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE) infections after ESI. Spera et al (51) discussed a man who presented with back pain and difficulty walking 5 months after an ESI. The patient had an elevated WBC count, and blood cultures were positive for MRSA (51). Treatment with vancomycin was pursued, but the patient developed acute renal failure secondary to intravenous contrast medium, after which the vancomycin dose was adjusted, and rifampin was added to improve microbial penetration. Vancomycin was later discontinued and replaced with daptomycin. Although there was clinical improvement after a few days, an MRI revealed several pelvic abscesses, which were then drained (51). Tailor and York (52) reported an immunocompetent female patient who presented with an L3 motor incomplete paraplegic spinal cord injury a couple of weeks after receiving an L3-L4 ESI. On admission, the patient was found to have MRSA-positive epidural abscess, bacteremia, coronary vegetation, and septic emboli in several essential organs, causing multiple system organ failure. Throughout her 2-month hospitalization, the patient received intravenous antibiotics and underwent multiple procedures in an attempt to remove the infection. After discharge, the patient underwent a femoral head ostectomy with antibiotic therapy but later developed a pulmonary embolus and axillary abscesses (52). Similarly, a woman experienced septic shock and quadriparesis after a few lumbar ESIs, with the most recent being 3 weeks prior (48). Imaging revealed epidural abscess, a compressed dura and spinal cord, hydrocephalus, and cerebral meningitis. Surgical debridement and ventriculoperitoneal shunting were performed. Blood culture was positive for MRSE, which is similar to MRSA but is coagulase negative. The infection resolved, but the quadriparesis remained (48).

Three studies discussed infectious complications related to methicillin-sensitive S. aureus (MSSA) after ESI. In a retrospective case series, Radcliffe et al (65) reported that 7% of patients experienced illness onset within 2 weeks after lumbar ESI. Illness onset was defined as an MSSA-positive culture from a normally sterile site and presentation with at least 2 of the following: tachycardia, leukocytosis, tachypnea, and fever. Two patients were admitted to the intensive care unit (65). Kraeutler et al (41) discussed a man with a spinal subdural empyema positive for MSSA after a series of

fluoroscopically guided lumbar transforaminal ESIs. The patient presented with perianal numbness, radicular pain to the posterior buttocks, right leg weakness, and mild abdominal tenderness and tenderness over the paraspinal muscles. Initial labs were unremarkable, and the patient was discharged. However, he presented 3 days later with exacerbated symptoms and a fever. Repeat MRI revealed extensive subdural fluid from the cervical to sacral regions, with evidence to the basal meninges of the brain. Bloodwork indicated elevated WBC count, erythrocyte sedimentation rate, and C-reactive protein. The patient was given intravenous vancomycin and ceftriaxone and underwent surgical decompression. After discharge, he continued to receive ceftriaxone via a peripherally inserted central catheter for 42 days. His urinary retention, LBP, and right leg weakness resolved afterward (41). Lee et al (43) discussed a 60-year-old man who experienced severe neck and chest pain a couple of hours after a lumbar ESI. Within a few hours of admission, the patient developed a fever, and bloodwork revealed elevated WBC count, C-reactive protein, and plasma glucose. As the blood culture was positive for MSSA, clindamycin and ceftriaxone treatments were initiated. After 3 days, he was switched to vancomycin and Tazocin, owing to extension of weakness to the upper extremity. After 10 days, the patient was afebrile but noted significant weakness in his lower extremities, at which point the cervical spine MRI revealed meningitis. The patient underwent a C1-C2 laminectomy to remove the abscess, but he did not experience any neurologic improvement and was transferred to the rehabilitation department for intensive motor power and sitting balance therapy (43).

Three case reports were identified on infectious complications post-lumbar ESIs because of other Streptococcus species: viridians streptococci, alpha streptococci, and penicillin-sensitive Streptococcus pneumoniae, which are typically indolent bacteria found in the skin flora, oral flora, and nasal cavity, respectively (39,42,44). MRI demonstrated epidural abscess in all 3 cases, as well as discitis, osteomyelitis with severe bone loss (44), spinal stenosis (42), and cauda equina impingement (39). Two patients experienced motor weakness (42,44), and one patient experienced neurologic deficits as a result of the epidural abscesses (39). All 3 patients underwent laminectomy decompression and evacuation of the epidural abscesses, one of whom had an abscess aspirated with computed tomography (CT) guidance prior to surgical intervention (39). After surgery, the patient with viridians streptococci infection was treated with intravenous penicillin for 6 weeks, and his motor strength in his lower extremity improved only on his right side (44). The patient with the Streptococcus pneumoniae infection was treated with ceftriaxone twice daily for 6 weeks, and repeat MRI after antibiotic treatment revealed resolution of bone marrow signaling changes (39). An additional case report by Bedoya and Gentilesco (33) discussed a 65-year-old man who presented with fevers, chills, weakness, and pain 1 week after a lumbar ESI. MRI revealed osteomyelitis and/or discitis, as well as an epidural abscess, and blood cultures were positive for coagulase-negative Staphylococci; the exact species was not specified. Treatment with antibiotics was initiated; however, the patient developed first-degree heart block and acute tubular necrosis and required aortic valve replacement surgery, after which he recovered without issues (33). Furthermore, another report by Yuseif et al (53) discussed a patient who presented with a decline in mentation 2 days after lumbar ESI and was diagnosed with pneumocephalus. The patient was started on vancomycin, cefepime, and voriconazole. Lumbar puncture revealed cloudy CSF that was gram-positive for nutritionally variant streptococci, which is also known as Abiotrophia defectiva. The patient's mental function improved, and she was discharged with a 14-day course of vancomycin and ceftriaxone (53).

Other notable cases of bacterial complications include unspecified bacterial meningitis and sepsis. Smith et al (63) reported 3 infections out of nearly 6,000 cervical and lumbar interlaminar ESIs, which were all related to lumbar injections. One infection was bacterial meningitis, which was treated via intravenous antibiotics. A case report by Kim et al (66) discussed a 19-year-old woman who presented 4 days after a lumbar ESI with fever, headache, and photophobia. Lumbar puncture showed elevated WBC count, 55% of which were neutrophils; this was indicative of bacterial meningitis (66). The patient was treated with vancomycin and cefepime, and the symptoms resolved in 1 day (66). Also of note, a retrospective review by Lee et al (62) identified 3 infections out of 52,935 ESIs performed under fluoroscopic guidance (0.01%): 2 caudal and 1 lumbar interlaminar ESIs. All infections were in patients over the age of 60 (62) years. A 92-year-old man presented with LBP, fever, and an altered mental state 21 days after receiving a lumbar interlaminar ESI. The patient was determined to have infectious spondylitis with sepsis. He was treated with antibiotics but ended up dying as a result of septic shock (62).

Other

Six studies reported infections following ESIs but did not specify the type of infection (e.g., bacterial, viral, fungal) and/or treatments and outcomes (32,37,64,67-69). Two patients described in case reports had vertebral osteomyelitis, which is often bacterial but may also be caused by other types of infections (32,37). Both patients recovered successfully with antibiotics.

Facet Joint Procedures

Seventeen articles reported on infections as a complication of facet joint procedures: 11 were prospective or retrospective studies, and 6 were case reports. The overall incidence of infections was 0.04% (9/25,697); this did not include case reports, studies that combined incidence rates from multiple interventional spine procedures, or studies that focused solely on infections. Five studies were related to the outbreak of contaminated MPA from the New England Compounding Center; these involved both facet joint procedures and ESIs and are covered in the ESI section earlier (11,56-58,60).

Facet Joint Injections

Results from a prospective descriptive study found that 1 out of 3 patients who received fluoroscopically guided lumbar facet joint injections had an infection that required surgical root decompression; the type of infection was not specified (29). Furthermore, in a retrospective review of 11,980 facet joint injections under fluoroscopic guidance, 8 infections were reported. Seven of these infections occurred following lumbar facet joint injections (6 bilaterally), and one occurred following a thoracic facet joint injection. There were no reported infections following facet joint injections in the cervical region (70). Of the 8 infections, there were 7 cases of infectious spondylitis, and 1 systemic fungal infection that spread to the spine (Aspergillus). One patient with infectious spondylitis received antibiotics only and refused surgery; she died of uncontrolled sepsis (70). Additionally, a multi-institutional study reported no infections following 5,841 facet joint injections that were performed under fluoroscopic guidance in all spine regions; exact numbers per spine region were not specified (30). This yielded an infection rate of 0.05% (9/17,824) for facet joint injections.

There were 6 case reports discussing 7 cases of bacterial infections following facet joint injections. Most patients responded well to antibiotic therapy. Fayeye et al (71) discussed a 47-year-old woman who developed left L4-5 facet septic arthrosis with subdural empyema and meningitis following a left L4-5 facet joint steroid injection. Blood cultures revealed S. aureus, and the patient was treated successfully with intravenous meropenem and vancomycin, followed by ciprofloxacin and rifampicin, for 6 weeks (71). Rai et al (72) reported 2 patients who presented with worsening pain and were found to be infected with S. aureus; one patient had received a lumbar facet joint injection, and the other patient had received a cervical facet joint injection. Both patients were treated successfully with antibiotics and/or surgical debridement (72). A female patient presented with symptoms of meningitis 24 hours following a lumbar facet joint infection and had elevated WBC levels. Streptococcus salivarius was found in the CSF; the exact treatment was not specified, but the patient recovered well (73). A male patient developed native vertebral discitis and bilateral psoas abscesses with Streptococcus caprae 2 weeks after receiving fluoroscopically guided L3-L5 facet joint injections and was treated initially with renally dosed vancomycin and piperacillin-tazobactam, followed by renally dosed cefazolin for 6 weeks. Fifteen days later, a follow-up MRI showed decreases in the size of fluid collections in the psoas muscles (74). Martens et al (75) reported a 68-year-old man who presented with escalating pain and leukocytosis 4 days after L4-L5 facet joint infiltration; biopsies taken during L5-S1 microdecompression showed Aerococcus urinae growth, and intraspinal epidural abscesses were seen on MRI. The patient was treated with intravenous penicillin and gentamicin for 2 weeks, followed by intravenous ceftriaxone for 2 weeks and oral clindamycin for 3 weeks. At 1 year, the patient presented without functional impairment (75). Negative outcomes were reported in only one case, in which a 50-year-old man presented with severe tenderness in the lumbar spine following a lumbar facet joint injection and was subsequently diagnosed with an epidural and paraspinal abscess, sepsis, and acute renal failure. Although the patient was treated with cephalosporin antibiotics, epidural abscess debridement, and aggressive surgical abscess draining, the sepsis persisted, and he died from multiple organ failure (76).

Facet Joint Medial Branch Blocks

Two articles reported on facet joint medial branch blocks. No infections were reported out of a total of 195 cases. All cases were performed in the lumbar spine with fluoroscopic guidance (29,30).

No infections were reported in a prospective study of 7,482 facet joint nerve blocks (77). These included

facet joint nerve blocks in all regions of the spine. Fluoroscopy was used for all nerve blocks.

Radiofrequency Neurotomy

Only one study by Carr et al (30) discussed radiofrequency neurotomy. There were no infections following 86 cases, all of which were performed in the lumbar spine with fluoroscopic guidance (30).

Facet Joint Cyst Rupture

There were 2 studies involving facet joint cyst ruptures. Of the 79 lumbar facet joint cyst ruptures that were performed in a study by Huang et al (78), there was one case of a bacterial skin infection that resolved with antibiotic therapy. The ruptures were performed under CT or fluoroscopic guidance, although the exact guidance performed in the infection-related case was not specified. Lutz et al (79) reported no infections following 53 lumbar facet joint cyst ruptures that were performed under fluoroscopic guidance.

Intradiscal Procedures

We identified 9 articles related to infections following intradiscal procedures in the spine: 6 prospective studies, 2 case reports, and 1 retrospective review. The overall incidence of infections related to intradiscal procedures was 1.05% (2/191). All but one article involved the intradiscal injection of biologics.

IDET

There was one study involving fluoroscopically guided lumbar IDET that evaluated 10 patients who developed nosocomial spondylodiscitis with Pseudomonas aeruginosa. This was the first report of infection post-IDET in the literature (80). All 10 patients had continuous LBP and high fever and were treated initially with parenteral meropenem for approximately 21 days, followed by oral ciprofloxacin and rifampicin on discharge. Some patients underwent abscess drainage and abscess wall resection (80). As this study included infection patients only, it was not included in the infection rate for intradiscal procedures.

Intradiscal PRP, Autologous Conditioned Serum, or Mesenchymal Stem Cell Injections

No infections were reported among a total of 96 patients who received intradiscal injections of platelet-rich plasma (PRP), autologous conditioned serum, or culture-expanded autologous mesenchymal stem cells in the lumbar spine in retrospective and prospective studies (81-83). Two case reports reported infections following intradiscal PRP or bone marrow aspirate. A 64-year-old man presented with cauda equine syndrome, fever, and back pain 2 weeks after receiving an intradiscal injection of adipose cells, bone marrow aspirate, and plasma in the lumbar spine under fluoroscopic guidance (84). MRI revealed an epidural abscess, which was drained via emergency decompressive surgery. The cultures were positive for MRSE, and the patient received intravenous antibiotics for 3 days, followed by oral antibiotics for 6 months. He recovered within 1 year (84). A 40-year-old woman developed progressive LBP several weeks following a fluoroscopically guided lumbar intradiscal PRP injection and was diagnosed with spondylodiscitis on imaging. Cutibacterium acnes was detected on biopsy cultures. The patient was treated with intravenous antibiotics for 6 weeks via a peripherally inserted central catheter and did not require surgical treatment (85). Intradiscal orthobiologic therapy using autologous PRP, bone marrow concentrate, or a combination of these are becoming increasingly used to treat chronic lumbar discogenic pain. However, the variability between methods, techniques, and actual cell content creates a fertile ground for the rise in the risk for infection. As of this date, there have been only 2 reported cases in the literature, but we suspect that, based on our interactions with our colleagues performing these procedures, most infections often go unreported.

Intradiscal Injections of Cytokine Blockers

There were 3 prospective studies related to the intradiscal injection of cytokine blockers, such as tocilizumab, an interleukin-6 receptor antibody, and etanercept, a tumor necrosis factor inhibitor (31,86,87). All injections were performed in the lumbar spine with fluoroscopic guidance. The infection rate among all 3 studies was 2.11% (2/95). One infection developed following an intradiscal injection of tocilizumab and presented as discitis. The type of infection was not specified, but the patient recovered with antibiotics (87). Another infection occurred 1 month following an intradiscal injection of etanercept; this presented as a vaginal yeast infection and was thought to be related to the injection (31).

Quality Assessments

Quality assessments were conducted using the Newcastle-Ottawa Scale, Cochrane Risk of Bias Tool, or the Joanna Briggs Institute Case Report Appraisal Tool, depending on the study design. Prospective and retrospective observational studies ranged widely (2–7 out of a total score of 9). Many studies received low

scores because of the retrospective nature of the studies (Table 2). In addition, many studies were focused on infections and did not involve a comparable group of noninfectious individuals. Of the 7 randomized

Table 2. *Quality assessment: Observational studies (Newcastle-Ottawa Scale).*

Study	Selection†						Comparability	Outcome‡				Score
	A	B	C	D	E	F		A	B	C	D	
Beissel 2016 (20)*	0		1		0	0	0	0			1	2 (out of 8)
Bosnak 2017 (80)	0	0	1	1			0	1	1	1		5
Carr 2016 (30)	1	1	1	1			1	1	0	0		6
Centeno 2017 (83)	0	0	1	1			0	1	1	1		5
CDC 2013 (11)	1	0	1	0			0	1	0	0		3
Chiller 2013 (60)	1	0	1	0			0	1	1	0		4
Cho 2020 (67)	0	0	1	0			0	1	0	0		2
El-Yahchouchi 2016 (22)	1	1	1	0			1	1	1	1		7
Galhom 2013 (29)	1	1	1	1			1	1	1	0		7
Huang 2017 (78)	1	0	1	0			0	1	0	0		3
Jeon 2015 (64)	1	1	1	0			1	1	1	1		7
Kainer 2012 MMWR (58)	1	0	1	0			0	1	0	0		3
Kainer 2012 NEJM (57)	1	0	1	0			0	1	0	0		3
Kauffman 2015 (54)	1	0	1	0			1	1	1	0		5
Kerkering 2013 (55)	1	0	1	1			0	1	1	1		6
Kim 2020 (70)	0	0	1	0			0	1	1	1		4
Lee 2018 (62)	1	1	1	1			1	1	1	0		7
Liu 2018 (17)	1	0	1	1			0	1	1	0		5
Lutz 2018 (79)	1	0	1	1			0	1	1	1		6
Lyons 2013 (46)	0	0	1	0			0	1	1	0		3
Manchikanti 2012 FJ (77)	1	0	1	0			1	1	0	0		4
Manchikanti 2012 ESI (24)	1	0	1	0			1	1	1	0		5
Mcgrath 2011 (25)	1	0	1	1			1	1	0	0		5
Moser 2010 (82)	1	0	1	0			0	1	1	0		4
Moudgal 2014 (59)	1	0	1	0			0	1	1	0		4
Park 2015 (26)	1	1	1	1			1	1	0	0		6
Pathmanathan 2012 (27)	1	0	0	0			0	1	0	0		2
Plastaras 2010 (28)	1	1	1	1			2	1	0	0		7
Radcliffe 2012 (65)	1	1	1	0			1	1	1	0		6
Ritter 2013 (56)	1	0	1	0			0	1	0	0		3
Sainoh 2016 (87)	1	1	1	1			1	1	1	0		7
Schreiber 2016 (69)	1	1	1	0			2	1	1	0		7
Smith 2017 (63)	0	1	1	0			1	1	0	0		4
Verrills 2015 (16)	1	1	1	1			1	1	1	0		7
Young 2013 (61)	1	0	1	0			0	1	0	0		3

*Cross-sectional study.
†Selection: (A) representativeness of the exposed cohort (back pain patients); (B) selection of the nonexposed cohort; (C) ascertainment of exposure; (D) demonstration that outcome of interest (infection) was not present at start of study; (E) sample size (cross-sectional studies only); and (F) nonrespondents (cross-sectional studies only).
‡Outcome criteria: (A) assessment of infection; (B) was follow-up long enough for outcomes to occur; (C) adequacy of follow-up of cohorts; and (D) statistical test (cross-sectional studies only).

controlled trials, 3 were rated as low risk across all 7 domains, and 3 had 2 or more domains that were rated as high risk. Areas of highest bias included allocation concealment and blinding of patients and personnel (Table 3). For case reports, 67% (20/30) had a total score of 12 or higher, out of 16, based on the Joanna Briggs Institute Appraisal Tool (Table 4).

Discussion

Results from this systematic review demonstrate a low rate of reported infections (0.12%) following interventional spine procedures. Infections that were reported in the form of case reports were not included in the rate calculations. However, the high numbers of case reports and studies focusing solely on procedure-related infections suggest that the true incidence may be higher than expected, owing to underreporting. Infection rates seemed to be higher with ESIs compared with discography and facet joint procedures. Most ESI-related infections were fungal or bacterial in nature, and almost all fungal infections were related to the outbreak of contaminated MPA in 2012. Intradiscal therapies had the highest rate of infections, but this was likely because of the inclusion of different types of orthobiologics and their corresponding small sample sizes. Additionally, unlike medications injected into the spine, these orthobiologics are not terminally sterilized so they do pose an increased risk for infection because of this.

The reported incidence of infections following interventional spine procedures ranges from 1% to 2% in the literature (10). The incidence varies more widely depending on the type of procedure and area of the spine (e.g., cervical, lumbar). Discography is a provocative method of determining whether an abnormally appearing disc is the source of a patient's pain. The clinical utility of discography is controversial, but the procedure is generally considered safe (16). However, discography may have serious complications, such as discitis. The rate of discitis after discography has been reported to be 0% to 4%, depending on whether prophylactic antibiotics or double-needle techniques are used to prevent infection (18,88,89). In the current review, no infections were reported in studies on lumbar discography. This could be due to a lack of reporting on discography, recent changes in practice in reducing infections after discography, or the decreased use of discography itself (7,8).

Infections following ESIs are uncommon and are reported to range from 0% to 0.1% (24,25,44,90). The current study found an overall incidence that was close to the reported range. Aside from those related to the outbreak of contaminated MPA, fungal infections were extremely rare. Furthermore, bacterial infections would appear to be much more common because of the plethora of case reports, yet still rare when looking at overall incidence across studies. We also included 5 cases of viral infections in this review; however, rates of viral infection following ESIs have not been reported in the literature.

Facet joint procedures include intraarticular steroid injections, nerve blocks, cyst rupture, and radiofrequency denervation and are the second most commonly performed interventional spine procedure (91,92). Infections following facet joint procedures appear to be either less common or less frequently reported, compared with those following other interventional spine procedures (70). Our calculated incidence of 0.04% was very low. Most cases were discussed either in the form of isolated case reports or were linked to the outbreak of contaminated MPA in 2012.

Table 3. *Quality assessment: Randomized controlled trials (Cochrane Risk of Bias Tool).*

Study	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Sources of Bias	Blinding (patients and personnel)	Blinding (outcome assessment)	Incomplete Outcome Data	Score (low risk total)
Aronsohn 2010 (19)	Unclear	High	Low	Unclear	High	Unclear	Unclear	1
Brown 2012 (21)	Low	Low	Low	Low	Low	Low	Low	7
Cohen 2015 (68)	Low	Low	Low	Low	Low	Low	Low	7
Cohen 2012 (31)	Low	Low	Low	Unclear	Low	Unclear	Low	5
Kang 2011(23)	Low	Low	Low	Low	Low	Low	Low	7
Tuakli-Wosornu 2016 (81)	Low	Low	Low	High	Unclear	Low	High	4
Sainoh 2016 (86)	High	High	High	High	High	High	Low	1

The calculated incidence rate following intradiscal procedures (1.05%) was higher than that following other interventional spine procedures. It is important to note that the denominator used in this calculation was much lower than that of other procedures. Also, this included various types of orthobiologics, each of which may differentially affect infection development. Only a handful of studies have provided information on infections after these intradiscal procedures, and these have all been randomized controlled trials or case series with small sample sizes. In the majority of these trials or cohort studies, no infections following intradiscal therapies were reported. However, a recent study by Rajasekaran et al (93) found that intervertebral discs, which were long considered sterile, not only have a unique microbiome, but also have a microbiome that differs between a healthy disc and a degenerated disc. A healthy disc is largely populated by protective bacteria, whereas degenerated discs are largely populated by human pathogens. This suggests that dysbiosis—a disruption of the symbiotic relationship in a microbiome that has been implicated in many diseases—likely also occurs in disc degeneration (93). As a result, the high rate of infection after intradiscal injection may in part be attributed to subclinical infection as an initiating factor for disc degeneration, long before the intradiscal injection. For this reason, we recommend using a leukocyte-rich PRP formulation to reduce the potential risk of discitis (94).

This systematic review had several limitations. First, the infection rates may be skewed because of presentation bias; as a result, it may be difficult to determine true incidence rates. There was an abundance of case reports in comparison to cohort studies, randomized controlled trials, and case series. To minimize skewing, infection numbers from case reports and infection-only articles were not included in the infection rate calculations. Thus, it is possible that the calculated rates are underestimated. Second, data on spine regions and image guidance were only available for some of the studies. Finally, many observational studies were of lower quality because of their retrospective nature. Therefore, the quality assessment of included studies ranged widely.

Conclusions

The rate of infections following interventional spine procedures based on a systematic review of the literature was low overall. Infections were less common following discography and facet joint thera-

Table 4. *Quality assessment: Case reports (Joanna Briggs Institute Critical Appraisal Tool).*

Study	Criteria								Score
	A	B	C	D	E	F	G	H	
Bashari 2015 (32)	1	1	1	0	1	1	1	2	8
Beatty 2019 (85)	2	1	2	2	2	2	2	2	15
Bedoya 2010 (33)	1	2	2	2	1	1	1	2	12
Bell 2013 (34)	0	1	2	2	1	0	0	1	7
Bunker 2018 (35)	1	2	2	2	2	0	1	2	12
Davis 2014 (36)	2	2	2	2	2	2	1	2	15
Fayeye 2016 (71)	2	2	2	2	2	2	2	2	16
Gowda 2018 (74)	2	2	2	2	2	2	1	2	15
Haleem 2014 (37)	2	2	2	2	1	1	1	2	13
Huie 2010 (38)	2	2	2	1	1	0	0	2	10
Johnson 2016 (39)	2	2	2	2	2	2	1	2	15
Kim 2015 (66)	2	2	2	2	1	2	0	2	13
Kim 2010 (76)	2	1	1	2	1	2	1	2	12
Kraeutler 2015 (41)	2	2	2	2	2	2	1	2	15
Lam 2017 (42)	0	1	1	1	1	1	1	1	7
Lee 2015 (43)	2	2	2	2	2	2	1	2	15
Lobaton 2019 (44)	2	2	2	2	2	2	1	2	15
Logan 2013 (45)	2	1	2	1	1	2	1	2	12
Martens 2017 (75)	2	1	1	2	2	2	0	2	12
Miner 2013 (47)	2	2	2	2	1	1	1	2	13
Noh 2015 (48)	2	2	2	2	2	2	1	2	15
Rai 2014 (72)	2	2	2	1	1	1	0	2	11
Rein 2015 (49)	2	1	1	1	1	1	0	2	9
Schott 2017 (50)	0	1	2	1	1	1	1	2	9
Sehu 2014 (73)	2	2	1	1	0	1	0	2	9
Spera 2012 (51)	2	2	2	1	1	1	2	1	12
Subach 2012 (84)	1	2	2	1	1	1	1	2	11
Tailor 2012 (52)	2	2	1	1	1	1	1	2	11
Werner 2011 (18)	2	2	2	2	2	2	1	2	15
Yuseif 2015 (53)	2	2	2	2	1	1	1	2	13

Criteria:
(A) Were the patient's demographic characteristics clearly described?
(B) Was the patient's history clearly described and presented as a timeline?
(C) Was the current clinical condition of the patient on presentation clearly described?
(D) Were diagnostic tests or assessment methods and the results clearly described?
(E) Was the intervention(s) or treatment procedure(s) clearly described?
(F) Was the postinterventional clinical condition clearly described?
(G) Were adverse events (harms) or unanticipated events identified and described?
(H) Does the case report provide takeaway lessons?
0: no, 1: unclear, 2: yes.

pies. Intradiscal orthobiologics may have a higher incidence of infections, however, the sample sizes of included studies for intradiscal therapies in comparison were very small. This review underscores the need for further studies to investigate the true incidence of infections following interventional spine procedures. These types of studies will require large, prospective, multicenter trials or registries, in which there is systematic collection of procedure data that includes if spine region injection was performed, specific injection technique used, contents of injectate used, whether or not antibiotic prophylaxis was administered, and whether or not image-guidance was employed. In the meantime, clinicians performing these procedures are encouraged to share not only their wins, but also their losses and report complications when they occur. It is through this sharing of knowledge we can hopefully learn to mitigate these complications and ultimately improve clinical outcomes.

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Supplementary Appendix 1

Search strategy:
Infection[tw]
OR infections[tw]
OR infected[tw]
OR abscess[tw]
OR epidural abscesses[tw]
OR Epidural Abscess[MeSH]
OR pathogenicity[MeSH]

AND

epidural steroid injection[tw]
OR epidural injection[tw]
OR epidural injections[tw]
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OR facet injection[tw]
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OR intradiscal electrothermoplasty[tw]
OR intradiscal infection[tw]

AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])
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