

Primary spinal infections in patients with solid organ transplant: a systematic literature review and illustrative case

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BACKGROUND Primary spinal infections (PSIs) are a group of uncommon but serious infectious diseases considered more prevalent and aggressive among patients with chronic immunocompromised states. Association of PSI and solid organ transplant has not been systematically analyzed. The authors performed a systematic review analyzing clinical presentation and mortality of patients with PSI in the setting of solid organ transplant.

OBSERVATIONS PSIs in patients with immunosuppressive therapy, such as those with solid organ transplant, may behave differently in terms of epidemiology, clinical presentation, and outcomes compared with nonimmunosuppressed patients. Overall PSI in solid organ transplant patients is associated with a high rate of neurological compromise, postoperative complications, and mortality.

LESSONS Accurate diagnosis and appropriate treatment of PSI require a multidisciplinary effort. Localized pain is the most frequently reported symptom associated with PSI. As opposed to PSI in patients without transplant, inflammatory and infectious markers such as white blood cells and C-reactive protein are often not elevated. Furthermore, the causative microorganism profile varies significantly when compared to pyogenic spinal infection in patients without transplant. *Aspergillus* species was responsible for spondylodiscitis in transplant patients in more than 50% of cases, and the incidence of *Aspergillus* infection is projected to rise in the coming years.

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KEYWORDS spondylodiscitis; solid organ transplant; vertebral osteomyelitis; complications

The number of patients who received solid organ transplant during 2021 was higher than in any prior year on record.¹ Improvements in surgical technique and immunosuppressive regimens have led to increased success rates and greater life expectancy for solid organ transplant recipients. In an attempt to prevent transplant rejection, solid organ transplant recipients frequently receive intense immunosuppression. Typical immunosuppressive regimens following organ transplant include glucocorticoids, antimetabolites such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, and monoclonal antibodies.^{2–5} Regimens consisting of one or any combination of these drugs lead to a decrease in both the humoral and cellular immune responses. This global immunosuppression, paired with the at-risk characteristics of patients receiving solid organ transplantation, leads to an increased susceptibility to spinal infection.

Primary spinal infection (PSI), a term that encompasses a range of clinical conditions including spondylitis, discitis, spondylodiscitis, vertebral

osteomyelitis, spinal epidural abscess, and paravertebral abscess, is a group of infections of the intervertebral disc, the bordering vertebra, or the epidural space. In the general population, PSI is a relatively uncommon orthopedic problem reported to range from 1:100,000 to 1:250,000 per year.⁶ However, PSI has been shown to be a major cause of morbidity and mortality in individuals with comorbidities, leading to altered immune status such as pharmacological immunosuppression following solid organ transplant.^{6,7} The incidence of PSI appears to be on the rise. The observation is likely secondary to the increasing prevalence of immunocompromised persons, increasing numbers of invasive spinal procedures, intravenous drug abuse, increasing life expectancy for patients with chronic debilitating diseases, emergence of drug-resistant microorganisms, and development of complex comorbidities. Higher diagnostic awareness and yield have likely played an important role in the increased incidence of PSI.^{8,9}

ABBREVIATIONS CRP = C-reactive protein; IFI = invasive fungal infection; PSI = primary spinal infection; WBC = white blood cell.

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The accurate diagnosis and appropriate treatment of PSI requires a multidisciplinary effort consisting of laboratory studies, imaging, and nonoperative and operative approaches. Because of the inconsistency in presenting signs of PSI, clinician attentiveness with sensible use of diagnostic tests and radiographic studies provides the most generative means of diagnosing a spinal infection.¹⁰ It is important to note that PSI has historically been diagnosed late in the disease course as a result of its association with nonspecific symptoms such as generalized back pain. This clinical characteristic enables infectious spread, with neurological complications and even death.¹¹ The previous point is particularly true in chronically immunocompromised patients having received solid organ transplant. With regards to the association between solid organ transplant and PSI, invasive fungal infections (IFIs) are aggressive and associated with high mortality rates.^{12,13} *Candida* and *Aspergillus* account for most IFIs status after solid organ transplant. In the last decade, epidemiological data have shown a reduction in infections with *Candida* as the causative organism but a rise in infectious sequelae attributable to *Aspergillus*.¹⁴ Overall, *Candida* and *Aspergillus* account for more than 80% of IFIs in solid organ transplantation.¹² The type of solid organ transplant is also implicated in the likelihood of mycosis: among all types of transplant recipients, small bowel is most susceptible to IFIs, with an incidence of 40%–59%, of which 90% are attributable to *Candida*. This is followed by lung and heart/lung transplantation, with an IFI incidence of 10%–44%, of which *Candida* accounts for 43%–72% and *Aspergillus* accounts for 25%–50%. Liver and heart transplantation are also susceptible to IFI, with incidence rates of 4%–42% and 3%–21%, respectively, with causative microorganisms of 35%–91% *Candida* and 70%–90% *Aspergillus*, respectively.¹⁴ Our review found 62.5% of PSIs (n = 25) to be attributable to fungal infections, with 52.5% (n = 21) due to *Aspergillus* species.

To our knowledge, no comprehensive systematic review concerning the overall incidence, characteristics, prognosis, and estimated mortality in patients with spinal infection secondary to solid organ transplant has been performed. Therefore, the objective of

this study is to analyze, through a systematic literature review, the baseline characteristics, clinical presentation, and mortality of patients with spinal infection in the setting of solid organ transplant.

Illustrative Case

A 68-year-old man with a medical history of liver transplant performed 3 years earlier because of systemic amyloidosis diagnosed 12 years earlier presented for low back pain of 35 days' duration. The patient was on a two-postliver-transplant immunosuppressant medication regimen that included cyclosporin and azathioprine. He did not report any apparent trauma or event that incited his low back pain. The patient rated his pain as 8 on a scale of 10 and denied fever, leg pain, or weakness. Imaging studies showed T12–L1 disc unit erosion (Figs. 1 and 2) resembling spondylodiscitis. Blood cultures were negative, and white blood cell (WBC) count was 12,100 mm³ with C-reactive protein (CRP) of 89 mg/dL at the time of admission. Because of intense low back pain indicative of possible spondylodiscitis, broad-spectrum antibiotics were started, and surgery was indicated. The patient received T11–L2 posterior instrumented fusion plus interbody irrigation and debridement (Fig. 3). Operative duration was 220 minutes, and estimated blood loss was 240 mL. Immediate postoperative follow-up showed back pain improvement. Cultures grew *Aspergillus fumigatus* species, and antibiotics were switched to cover this fungus. However, on postoperative day 7, the patient developed fever and disorientation. His WBC was 14,000 and CRP was 55 mg/dL. The patient's condition deteriorated rapidly as he developed hypotension, and septic shock was diagnosed. Ultimately, the patient died because of septic shock.

Discussion

Observations

PSIs in patients with immunosuppressive therapy, such as those with solid organ transplant, may behave differently in terms of

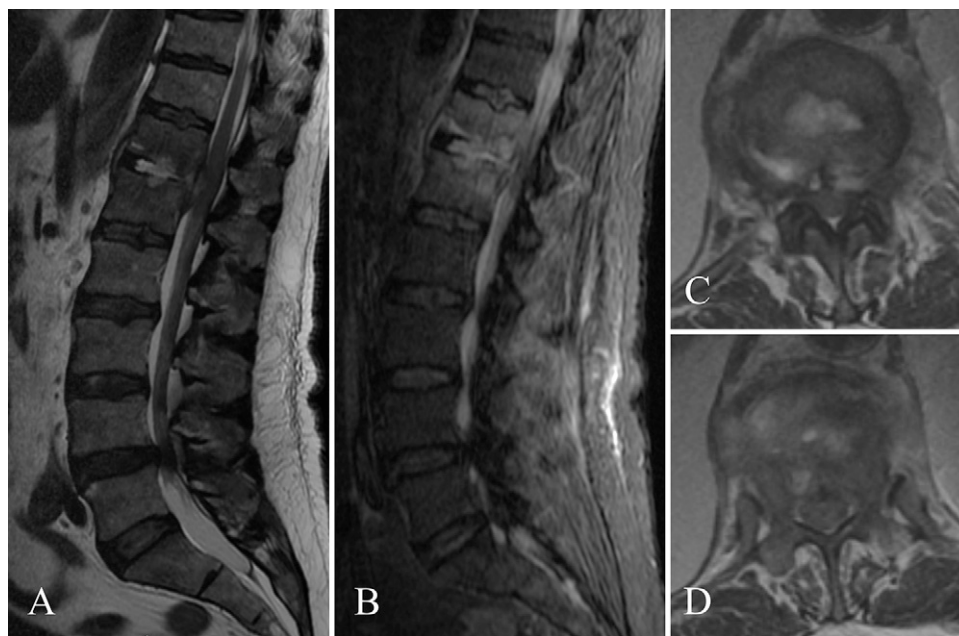


FIG. 1. Sagittal (A and B) and axial (C and D) magnetic resonance images showing T12–L1 compromise with slight spinal canal involvement.

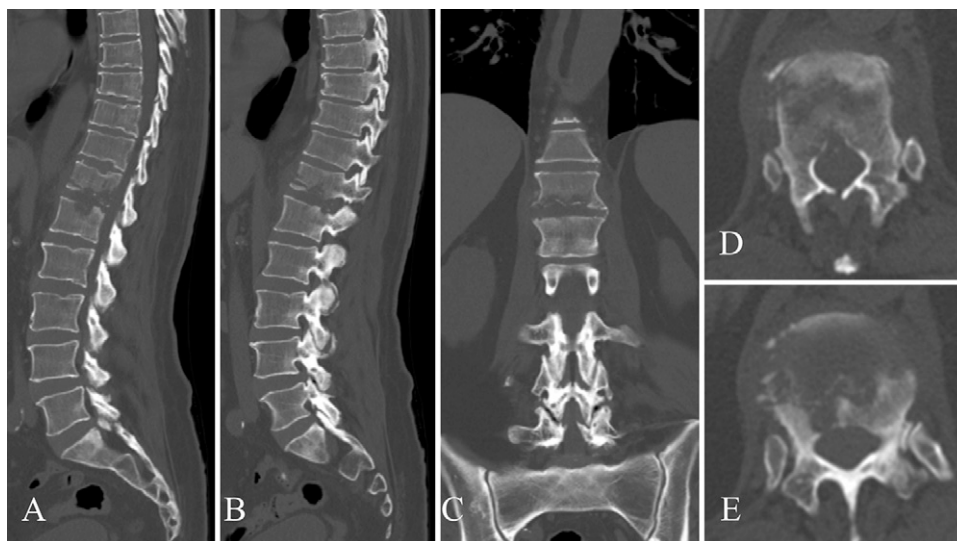


FIG. 2. Sagittal (A and B), coronal (C), and axial (D and E) computed tomography scans showing osseous involvement and bony erosion.

epidemiology, clinical presentation, and outcomes compared with nonimmunosuppressed patients. A systematic literature search was performed in PubMed, Web of Science, and Google Scholar in November 2021 to identify studies reporting the outcome of pyogenic spinal infection in patients with solid organ transplant. The search strategy for PubMed, Web of Science, and Google Scholar is displayed in Appendix A. We performed the literature search with records filtered from January 2000 to November 2021. Records identified through the searches were added to a database, and duplicates were removed. Titles and abstracts from PubMed were screened by one reviewer (G.C.W.), from Web of Science by one reviewer (R.B.), and from Google Scholar by one reviewer (M.H.). The articles were limited to human studies published in English. Editorials, reviews, and letters to the editor were excluded. This systematic review was reported in accordance with the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁵ (Fig. 4). Upon careful review, 13 articles published between 2010 and 2018 met the studies inclusion/exclusion criteria,^{16–28} including 2 case series, 10 case reports, and 1 case-control study (Table 1). These studies featured a total of 67 patients, of whom 40 met inclusion criteria (mean age, 47 years; range, 17 to 80 years; 67.8% males). Lumbar infection was the most common presentation (72.5%), with *Aspergillus fumigatus* (37.5%) as the main causative microorganism. Neurological compromise was present in 22.5% of patients. Surgical intervention occurred in 50% of patients (n = 20), and the average antibiotic duration was 20.75 days (n = 21). Post-operative complication rate was 33.33% (n = 6), with a 30- and 90-day mortality rate of 33.3%.

Regarding clinical presentation, localized pain was the most frequent symptom (observed in 90%); interestingly, fever was present in only 30% of patients, and neurological compromise was found in 22%. Surprisingly, WBC and CRP levels were elevated in a low percentage of patients (12% and 22%, respectively), and similar findings were observed for fever, present in only 30% of patients. Those findings are opposite to observations in large series in patients without transplant. In 207 patients, Pola et al.²⁹ observed the presence of fever in 64.3%, with CRP level elevated in 92.5% of patients and WBC count elevated in 35.8% of patients.

It is worth mentioning that 17% of patients had multifocal infections at the time of diagnosis. Henkelmann et al.,³⁰ in a retrospective series of 69 patients, found a prevalence of multifocal spondylodiscitis of 13%. Similar prevalence was observed by Stangenberg in 211 patients.³¹ Pola et al.²⁹ found that 53 patients had multifocal involvement (26%). Of note, the prevalence of comorbidities in this study was almost 70%. Moreover, 23% of patients had postsurgical infection.

It is known that some factors increase the risk for spondylodiscitis, such as diabetes or renal insufficiency.³² However, no direct relationship between multifocal involvement and severity has been found in the literature.²⁷ Additionally, in a systematic review of 212 patients, Madhavan et al.³³ only found 0.9% of multifocal

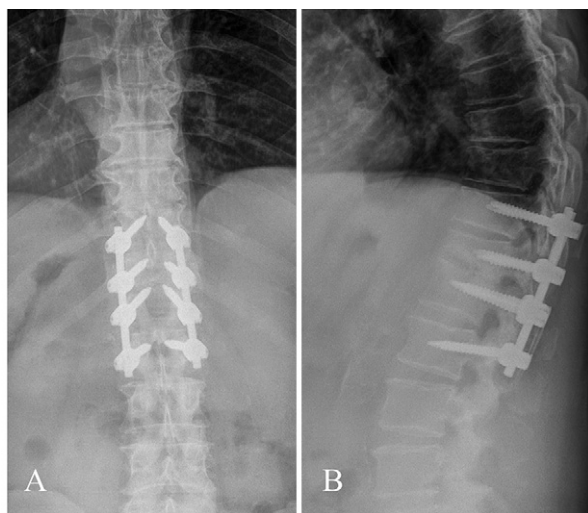


FIG. 3. Postoperative radiographs showing T11–L2 posterior instrumentation and debridement.

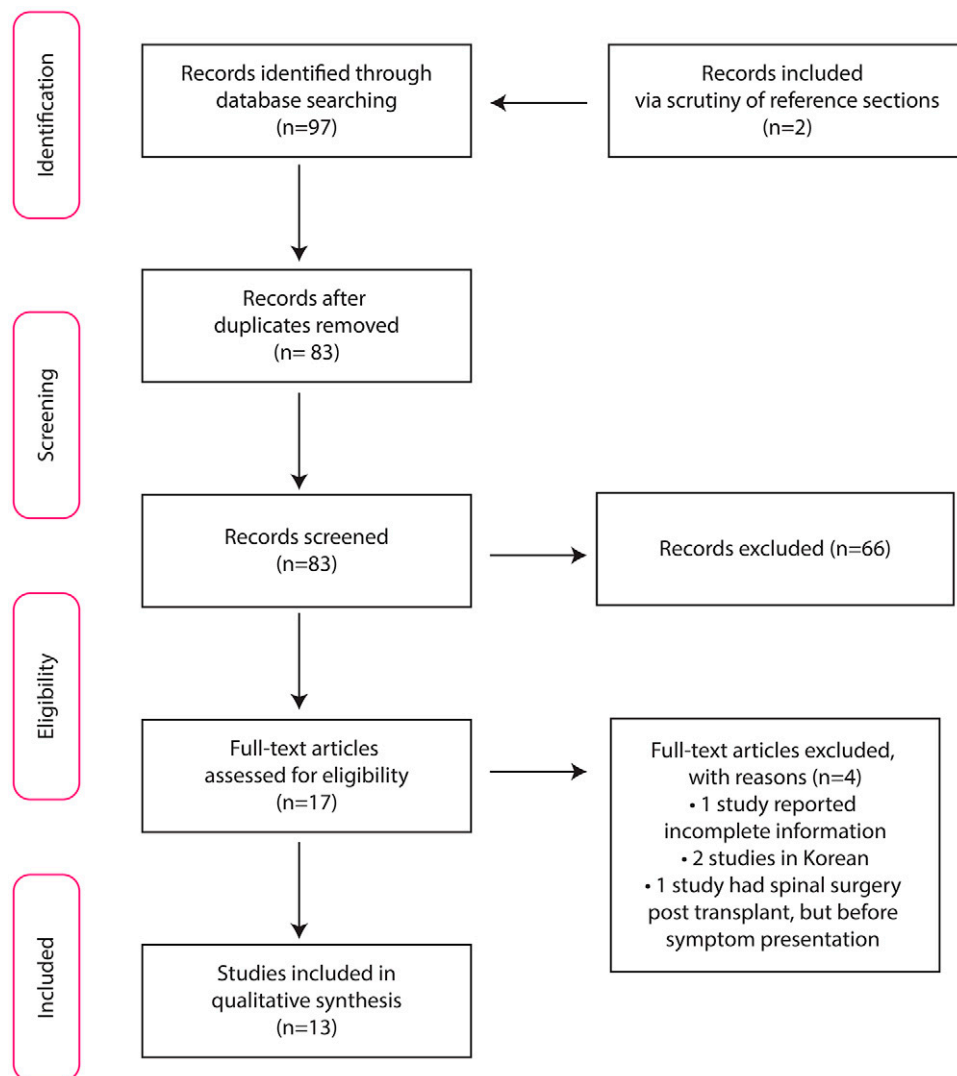


FIG. 4. PRISMA study selection flow diagram. Data added to the PRISMA template (from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6[7]:e1000097) under the terms of the Creative Commons Attribution License.

compromise while mortality was 24%. The highest prevalence of multifocal involvement was reported in a systematic review of 112 patients with vertebral aspergillosis, with the authors reporting a prevalence of 32%.³⁴ Considering that the most frequent causative microorganism in our study was *Aspergillus*, that could explain the relatively higher prevalence of multifocal involvement.

Limitations

Our study has some limitations. First, all data are provided by case series and case reports; therefore, the quality of this study relies on the quality of the included articles. However, considering the relatively rare occurrence of this condition, it is the best and most recent evidence related to spondylodiscitis in solid organ transplant patients. Of the 40 patients who were included in this systematic review, only 7 patients died. However, time of death was only reported for 3 of these 7 patients, thus potentially changing our

measurements of 30-day, 1-year, and 2-year mortality due to the smaller denominator. Because spondylodiscitis and solid organ transplant are both expected to increase over the next few years, this association should be considered, emphasizing the need for early detection and proper treatment.

Lessons

It is important to mention that the causative microorganism profile varies significantly when compared to pyogenic spinal infection in general. Based on large case series, it is known that main microorganisms involved in spondylodiscitis are *Mycobacterium tuberculosis* and *Staphylococcus* species.^{35,36} Interestingly, in our study, *Aspergillus* was the most common agent (52%) followed by *Staphylococcus* species. Vertebral aspergillosis is a relatively rare and often misdiagnosed entity that usually requires long-term antibiotic treatment and surgical treatment. In the previously mentioned

TABLE 1. Summary of studies included

Authors & Year	Study Design	No. of Pts	Age (yrs), Sex	Type of Solid Organ Transplant	Pathology	Level of Manifestation	Main Microorganism	Neurological Deficit		Time Btwn Sxs & Op		Antimicrobial Tx Duration	Last FU
								Op	NA	7 days*	6 mos		
Belvisi et al., 2013 ¹⁶	CR	1	61, F	Liver	L4–5 spondylodiscitis	Lumbar (1)	<i>Streptococcus pneumoniae</i> (1)	1	NA	7 days*	6 wks		1 mo
Buzel� et al., 2015 ¹⁷	1:3 case-control	9	Mean, 52.7; range, 28–61	Liver (9)	Vertebral osteomyelitis (9), epidural abscess (5)	Thoracic (3), lumbar (4), multifocal (2)	<i>Staphylococcus aureus</i> (2), <i>Escherichia coli</i> (1), <i>Aspergillus fumigatus</i> (2), <i>Candida albicans</i> (1), <i>Mycobacterium tuberculosis</i> (1), no growth (2)	3	1	5 wks (range, 1–9 wks)*	Median, 12 wks; range, 6–88 wks		Median, 48 wks; range, 7–150 wks
Ersoy et al., 2011 ¹⁸	CR	1	46, M	Kidney	T8–9 & L2–3 spondylodiscitis	Thoracic (1), lumbar (1), multifocal (1)	<i>A. fumigatus</i> (1)	NA	1	82 days	6 mos		18 mos
Falakassa et al., 2014 ¹⁹	CS	6	Mean, 63; range, 51–80; 4M, 2F	Kidney (2), liver (2), combined liver/kidney (2)	Spondylodiscitis (6), epidural abscess (1)	Thoracic (2), lumbar (4)	<i>S. aureus</i> (1), <i>E. coli</i> (2), <i>Streptococcus gallolyticus</i> (1), <i>Staphylococcus epidermidis</i> (1), <i>Enterococcus faecalis</i> (1)	1	4	NR	7 wks (2), NR (4)		Mean, 20 mos
Freiberg et al., 2019 ²⁰	CR	1	49, M	kidney	L2–5 & S1–2 epidural abscesses	Lumbosacral (1), multifocal (1)	<i>Nocardia cyriacigeorgica</i> (1)	NA	NA	2 wks*	12 mos		12 mos
Li et al., 2010 ²¹	CS	15	Mean, 43.2; range, 18–59; 12M, 3F	Liver (3), kidney (4), heart (7), SPK (1)	Spondylodiscitis (15)	Cervical (1), thoracic (4), lumbar (13), multifocal (3)	<i>A. fumigatus</i> (11), <i>Aspergillus flavus</i> (2), <i>Aspergillus</i> (2)	3	9	NR	NR		NR
Li et al., 2012 ²²	CR	1	44, M	Liver	L4–5, L5–S1 spondylodiscitis	Lumbar (1)	<i>A. flavus</i> (1)	NA	1	4 mos	20 wks		20 wks
Luijk et al., 2011 ²³	CR	1	17, F	Lung	L2–3 spondylodiscitis	Lumbar (1)	<i>Scedosporium apiospermum</i> (1)	NA	NA	2 mos*	3.5 yrs		6 yrs
Navanukroh et al., 2014 ²⁴	CR	1	42, F	Kidney	S1 osteomyelitis, epidural abscess L4–S1	Lumbar (1)	<i>Cunninghamella bertholletiae</i> (1)	1	1	12 days	3 mos		3 mos
Tv et al., 2015 ²⁵	CR	1	34, M	Kidney	Thoracic spondylodiscitis	Thoracic (1)	<i>A. fumigatus</i> (1)	NA	1	2 mos	16 days		16 days

CONTINUED ON PAGE 6 »

TABLE 1. Summary of studies included

Authors & Year	Study Design	No. of Pts	Age (yrs), Sex	Type of Solid Organ Transplant	Pathology	Level of Manifestation	Main Microorganism	Neurological Deficit	Op	Time Btwn Sxs & Op	Antimicrobial Tx Duration	Last FU
Silva et al., 2015 ²⁶	CR	1	71, F	Heart	T6 vertebral osteomyelitis	Thoracic (1)	<i>Mycobacterium abscessus</i> (1)	NA	NA	2 mos*	3 mos	11 mos
Thomson et al., 2015 ²⁷	CR	1	19, F	Lung	T12-L3 spondylodiscitis	Thoracic (1), lumbar (1), multifocal (1)	<i>S. apiospermum</i> (1)	NA	1	5 yrs	9.5 mos	3.5 mos
Zhu et al., 2011 ²⁸	CR	1	46, M	Liver	L1-5 spondylodiscitis	Lumbar (1)	<i>A. flavus</i> (1)	NA	1	66 days	15 mos	27 mos

CR = case report; CS = case series; FU = follow-up; NR = not reported; Pts = patients; Sxs = symptoms; Tx = treatment.

* Time between symptoms and diagnosis.

review of patients with vertebral aspergillosis, organ transplant was the most common risk factor, observed in 15 patients (13.5%), followed by acute myeloid leukemia and previous tuberculosis. Those findings support the fact that *Aspergillus* vertebral infection is higher in patients with organ transplant.³⁵ This important association should be emphasized because of the increased number of immunocompromised patients during the last decades.^{37,38} Moreover, considering that *Aspergillus* is the most common infection in solid organ transplant recipients,³⁹⁻⁴¹ it is important to highlight that any new back pain should raise suspicion of vertebral infection in this population. Our review yielded a relatively higher rate of postoperative complications in the 18 patients who received surgical intervention (33.6%; n = 6) and a mortality rate of 17.5% (n = 7). IFIs are particularly challenging to diagnose because of a lack of reliable diagnostic measures.⁴²⁻⁴⁵ In the context of most PSIs in this review being caused by fungal infections (62.5%; n = 25), this highlights the aggressive nature of IFIs and the importance of early identification and treatment interventions status after solid organ transplantation.

Spondylodiscitis in solid organ transplant patients was found to be caused by *Aspergillus* species in more than 50% of cases and is associated with higher rate of multifocal compromise and higher mortality when compared to nontransplant recipients. This association should be considered because both spondylodiscitis and solid organ transplantation are expected to increase over the next few years. This finding is in alignment with current trends in the literature regarding the increased prevalence of *Aspergillus* species IFIs. Specifically, while the prevalence of IFIs status after solid organ transplant has decreased over the past decade as a whole, largely because of improvements in transplant surgical methods, infections related to *Aspergillus* species specifically have been on the rise.¹⁴

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Disclosures

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Author Contributions

Conception and design: Camino-Willhuber, Hatter, Franklin, Brown, Bhatia, Lee. Acquisition of data: Camino-Willhuber, Hatter, Beyer, Franklin, Brown. Analysis and interpretation of data: Hatter, Beyer, Brown, Bhatia, Lee. Drafting the article: Camino-Willhuber, Hatter, Beyer, Franklin, Brown, Bhatia. Critically revising the article: Camino-Willhuber, Hatter, Franklin, Brown, Hashmi, Oh, Bhatia, Lee. Reviewed submitted version of manuscript: Hatter, Beyer, Franklin, Brown, Hashmi, Oh, Bhatia. Approved the final version of the manuscript on

behalf of all authors: Camino-Willhuber. Statistical analysis: Hatter, Beyer. Administrative/technical/material support: Bhatia. Study supervision: Camino-Willhuber, Brown, Bhatia, Lee.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Appendix A. <https://thejns.org/doi/suppl/10.3171/CASE22157>.

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