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Presentation and management of infection in total disc replacement: A review

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ABSTRACT

Background: Total disc replacement (TDR) is widely used in the treatment of cervical and lumbar spine pathologies. Although TDR infection, particularly delayed infection, is uncommon, the results can be devastating, and consensus on clinical management remains elusive. In this review of the literature, we asked: (1) What are the reported rates of TDR infection; (2) What are the clinical characteristics of TDR infection; and (3) How has infection been managed for TDR patients?

Methods: We performed a search of the literature using PubMed and Embase to identify studies that reported TDR infection rates, the identification and management of TDR infection, or TDR failures with positive cultures.

FDA device/drug status: Approved for this indication (FDA approved cervical disc replacements: M6-C, Prestige LP, ProDisc-C, Mobi-C).

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Twenty database studies (17 focusing on the cervical spine and 3 on the lumbar spine) and 10 case reports representing 15 patients were reviewed along with device Summary of Safety and Effectiveness Data reports.
Results: We found a lack of clarity regarding how infection was diagnosed, indicating a variation in clinical approach and highlighting the need for a standard definition of TDR infection. Furthermore, while reported infection rates were low, the absence of a clear definition prevented robust data analysis and may contribute to underreporting in the literature. We found that treatment strategy and success rely on several factors including patient symptoms and time to onset, microorganism type, and implant positioning/stability.
Conclusions: Although treatment strategies varied throughout the extant literature, common practices in eliminating infection and reconstructing the spine emerged. The results will inform future work on the creation of a more robust definition of TDR infection and as well as recommendations for management.

Background

Total disc replacement (TDR) is widely used in the treatment of cervical and lumbar spine pathologies including degenerative disc disease, radiculopathy, and myelopathy. Introduced as an alternative to fusion, TDRs are designed to mimic the function of a natural intervertebral disc and allow for motion preservation. Since its introduction to the United States in the early 2000s, the procedure has shown positive clinical outcomes in terms of patient outcomes and a reduced risk for adjacent segment degeneration [1–4]. In recent years, TDR utilization has been increasing, especially for the cervical spine [5–7].

Like any orthopedic or spinal procedure, TDR carries the risk of deep infection. This includes both acute infection with virulent organisms (typically occurring within 3 months) and delayed/chronic infections that may present months or years after the TDR procedure [8,9]. Diagnosis of the latter is notably challenging due to the subtlety of common symptoms like pain and implant loosening compared to the more obvious symptoms associated with acute infection (e.g., swelling, fluid accumulation, and fever) [8]. Although TDR infection, particularly delayed infection, is reported to be uncommon relative to large joint arthroplasty, the results can be devastating. Potential infection-related issues like pain and implant loosening often necessitate revision surgery, and, in rare cases, complications can be life-threatening [9,10].

Although management of periprosthetic joint infection is well-summarized in the literature for large joint arthroplasty [11–13], treatment guidance for infection is far less established for cervical and lumbar TDR, motivating the current systematic review. In this study, we asked: (1) What are the reported rates of TDR infection; (2) What are the clinical characteristics of TDR infection; and (3) How has infection been managed for TDR patients?

Methods

Literature search

We performed a systematic search of the literature using PubMed and Embase and used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [14]. Searches were performed on July 20, 2023, using the following search terms: (spine or cervical or thoracic or lumbar) and (disc or disk) and (replacement or arthroplasty or CDA or TDR or CDR) and (infection or bacteria or *Staphylococcus* or *Propionibacterium* or *Cutibacterium* or acnes or MRSA). Duplicates, conference abstracts without full papers, and non-English publications were excluded. The remaining studies were screened according to the inclusion/exclusion criteria (Table 1**)**.

Study selection and data extraction

The database searches resulted in 167 studies from PubMed and 280 from Embase, representing 362 unique papers. Thirty-five additional studies were found from source bibliographies, resulting in 397 papers for consideration. Following screening and assessment of full texts according to the inclusion/exclusion criteria by two independent researchers, 30 studies were included in our review (Fig. 1). The collection included 20 database trend analysis studies and 10 case studies. Case studies were included if a diagnosis of infection was reported or if cultures taken during revision surgery showed positive results for infectious bacteria; we recorded whether the treating clinicians of each case classified the case as an “infection” and if so, how this was defined. Although some clinical cohort studies also reported cases of infection, the information regarding infection treatment provided was highly limited and insufficient for inclusion in the present study.

In addition to our review of the literature, we reviewed Summary of Safety and Effectiveness Data (SSED) reports from cervical and TDRs currently approved for the United States market. SSEDs report the findings from investigational device studies which, per FDA requirements for spinal devices, must have a follow-up of at least 2 years. These reports can thus serve as a thorough dataset for establishing TDR infection rates. In our review of SSEDs, we collected data including the device, number of patients used in infection rate determination, definition of infection, and the rate of infection. We excluded cases of urinary tract infection, but otherwise recorded all events denoted as an “infection” whether or not it was determined to be device specific.

Following study selection, basic details including patient number, follow-up time, and database information were recorded along with procedure characteristics (i.e., TDR device design, surgical levels) and clinical outcomes (i.e., complications, patient symptoms, preoperative and histological work-up, treatment details).

Results

Summary data from the reviewed database studies and case studies are provided in Tables 2 and 3, respectively.

Of the 20 database studies, 17 focused on the cervical spine and 3 focused on the lumbar spine (Table 2). Most of the reviewed database studies (n=13/20) queried the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, which aggregates patient 30-day postoperative outcomes across hundreds of participating hospitals. The PearlDiver Patient Records Database was also queried (n=3/20 studies), along with the Nationwide Inpatient Sample (NIS) database and California Office of Statewide Health Planning and Development (OSHPD) discharge database (n=2/20 each). The number of TDR cases included in each study ranged from 293 to 3976. Follow-up for infection-related complications ranged from time until discharge to 1 year, and one study also tracked instances of reoperations with a follow-up of 5 years. Most studies reported the incidence of superficial, deep, and organ/space infection separately while others reported surgical site infection (SSI) generally, making a summary of the rates challenging. The maximum infection rate reported for cervical procedures was 1.38% (SSI rate for a cohort of 507 at 1 year) [23], and for lumbar procedures it was 3.0% (SSI rate for an outpatient cohort of 101 at 30 days) [33].

The 10 case studies represented 15 TDR patients (10 cervical and 5 lumbar, Table 3). All of the lumbar TDRs were classified, per the case report authors, as clinical infections. Four of these occurred more than 6 months postoperatively. Four of the ten cervical TDR cases

Table 1
Inclusion/exclusion criteria for study screening.

Inclusion criteria	Exclusion criteria
• Studies detailing findings of infection and/or positive bacterial cultures for TDR patients • Studies reporting on the rate of infection occurring for TDR patients	• Review articles • Non-English articles • Meeting abstracts without full papers • TDR studies with no cases of infection • Studies that reported combined infection rates for categorical procedures (e.g., "anterior lumbar surgery") and do not specify infection just for TDR • Studies published before the year 2000 • Studies that report outcomes for special patient populations only

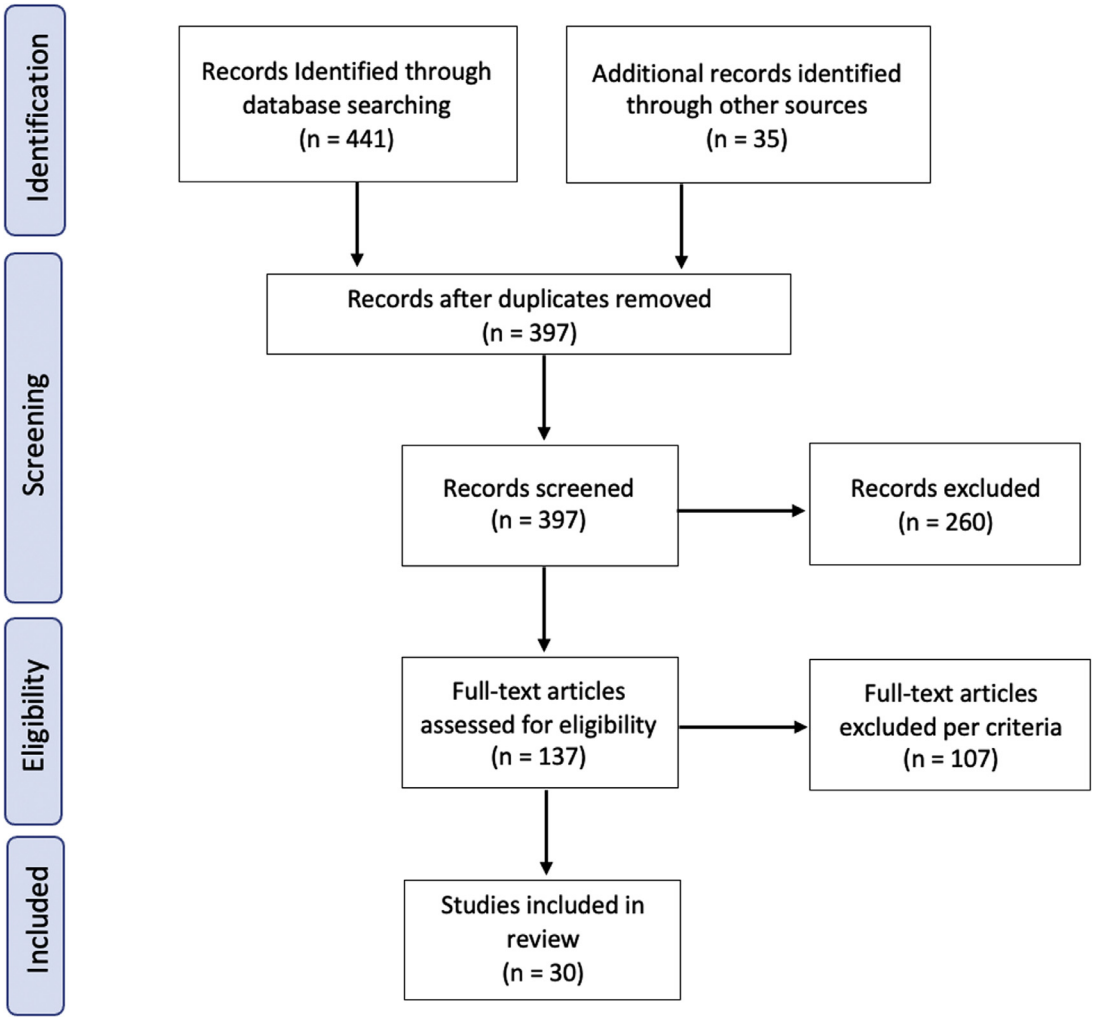

Fig. 1. PRISMA flow diagram for review of the literature.

had definitive infections (though one was somewhat unclear as it involved concurrent implant failure) [10,37–39], four were probable but may have involved hypersensitivity reactions [36], and two had positive tissue cultures but were not classified as infection [34,35]. Two of the four definitive infection cases occurred more than 6 months postoperatively.

How "infection" was specifically defined by the treating clinicians was not reported in any case study. Patients primarily presented with dysphagia (cervical) or severe pain (lumbar). Preoperative imaging with CT or MRI was reported in each case and often elucidated a periprosthetic tissue mass and/or fluid collection. The TDR device was removed in 10 cases but left *in situ* in the others (both cervical and lumbar) due to access difficulty and perceived removal risks. Empirical and targeted antibiotic treatment varied, and *Cutibacterium* (formerly *Propionibacterium) acnes* was the most common organism found (positive cultures in n=8/15 patients, all cervical).

SSEDs were reviewed for 12 cervical and 3 lumbar devices (the Charité disc SSED was excluding due to the device being removed from the U.S. market). The data extracted is presented in Table 4. Rates of infection are provided here as they were reported in the SSEDs, that is, with varying specificity. For any non-zero rate of infection that was definitively device-related, the timing of the cases was also recorded and were generally short-term. The variability in reporting precluded our ability to summarize an overall infection rate. However, we found superficial infections of the surgical site had rates up to 3.4% for cervical and 3.6% for lumbar. Only 5 SSEDs (all cervical) reported "deep" infections, which were 0.0% in all but one report, which included deep wound infection rate of 0.7%.

Table 2
Summary of data from reviewed database studies.

Study	# of patients included (TDR only)	Primary or revision	Levels	Database queried	Years queried	Follow up	Infection rates
Cervical							
Bhashyam 2017 [15]	487	Primary	Single	ACS-NSQIP	2013–2014	30 days	Causes of readmission: Deep incisional SSI: 0 Organ space SSI: 1 (0.2%) Unspecified SSI: 0 Superficial SSI: 0 Causes of reoperation: SSI: 0
Boddapati 2021 [16]	390	Not reported	2- and 3-level hybrid	ACS-NSQIP	2011–2018	30 days	SSI: 0.77%
Doan 2021 [17]	Outpatient: 403 Inpatient: 408	Primary	2-level	ACS-NSQIP	2015–2018	30 days	SSI: 0 Deep SSI: 0 Organ/space SSI: 0
Gupta 2022 [18]	3179	Not reported	Single	ACS-NSQIP	2015–2020	30 days	Superficial SSI: 8 (0.25%) Deep incisional SSI: 2 (0.6%) Organ/Space SSI: 1 (0.3%)
Ifarraguerri 2022 [19]	Single level: Outpatient: 506 Inpatient: 1788 Multi-level: Outpatient: 49 Inpatient: 187	Primary	Single & Multi	PearlDiver Patient Records Database	2010–2019	90 days	SSI: Outpatient single level: 3 (0.6%) Inpatient single level: 14 (0.8%) Outpatient multi-level: 0 (0%) Inpatient multi-level: 1 (0.5%)
Jain 2020 [5]	293	Primary	Single & Multi	PearlDiver Patient Records Database	2007–2015	3 months (other outcomes reported for 1 year)	Infection: <11 (<3.7%)
Kelly 2018 [20]	1469	Primary	Single	California Office of Statewide Health Planning and Development discharge database	2003–2010	90 days	Wound infection: 2 (0.14%)
Nandyala 2014 [21]	Primary: 3330 Revision: 256	Primary & Revision	Single, 2-level	Nationwide Inpatient Sample (NIS) database	2002–2011	Perioperative	Infection: Primary (incidence rate): 1.8/1000 Revision (incidence rate): 13.6/1000
Nandyala 2014 (2) [22]	1830	Not reported	Single	Nationwide Inpatient Sample (NIS) database	2002–2009	Perioperative	Infection: 2.2/1000 (0.22%)
Nayak 2023 [23]	507	Primary	Single, 2-level	PearlDiver Patient Records Database	2007–2016	Minimum 1 year	SSI: 30 days: 0.59% 3 months: 0.79% 6 months: 0.99% 12 months: 1.38%

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Table 2 (*continued*)

Study	# of patients included (TDR only)	Primary or revision	Levels	Database queried	Years queried	Follow up	Infection rates
Ng 2022 [24]	1748	Not reported	Multi (>1 level)	ACS-NSQIP	2012–2019	30 days	Superficial infection: 4 (0.2%) Deep infection: 1 (0.1%) Organ/Space infection: 0
Ng 2023 [25]	1731	Not reported	Single	ACS-NSQIP	2012–2019	30 days	Superficial infection: 4 (0.2%) Deep infection: 1 (0.1%) Organ/Space infection: 0
Samuel 2019 [26]	Nonmyelopathy: 2612 Myelopathy: 411	Not reported	Single, 2-level	ACS-NSQIP	2015–2016	30 days	SSI: Nonmyelopathy cohort: 10 (0.4%) Myelopathy cohort: 1 (0.2%)
Segal 2019 [27]	1506	Primary	Single	ACS-NSQIP	2006–2015	30 days	Organ/space infection: 1 (0.0%) Superficial incision infection: 4 (0.3%)
Shillingford 2017 [28]	653	Primary	Single	ACS-NSQIP	2010–2014	30 days	Deep incisional SSI: 0 Organ/space infection: 0 Superficial incisional infection: 2 (0.3%)
Watts 2023 [29]	3976	Primary	Single, 2-level	ACS-NSQIP	2014–2019	30 days	Superficial infection: 11 (0.3%) Deep infection: 2 (0.1%) Organ/Space infection: 0
Zeidan 2021 [30]	3221	Not reported	Single	ACS-NSQIP	2012–2017	30 days	Superficial SSI or disruption of wound: 4 (0.12%) Deep SSI (deep): 1 (0.03%)
Lumbar							
Ansari 2021 [31]	630	Primary	Single	ACS-NSQIP	2011–2019	30 days	SSI: 12 (1.9%) (1 of which was revised)
Eliasberg 2016 [32]	2415	Primary	Single	California Office of Statewide Health Planning and Development discharge database	2004–2010	90 days	Wound infection: 0.25% Periprosthetic joint infection: 0.04%
Katz 2021 [33]	Outpatient:101 Inpatient: 650	Primary	Single	ACS-NSQIP	2005–2018	30 days	SSI: Outpatient: 3 (3.0%) Inpatient: 7 (1.1%) Deep wound infection: Outpatient: 0 Inpatient: 1 (0.2%) Organ space infection: Outpatient: 0 Inpatient: 1 (0.2%)

SSI: surgical site infection.

Table 3
Summary of data from reviewed case reports.

Author/year	TDR level (device)	Symptoms and time to presentation	Inflammatory markers	Pre-op imaging workup	Treatment	Histopathology	Outcome
Cervical							
Clark 2020 [34]*	C4–C5 and C5–C6 (M6–C)	Recurrent paresthesia in the left upper extremity, decreased bilateral fine motor dexterity 6.5 y	Normal	X-ray: segmental kyphosis and subsidence of C4–5 device CT: osteolysis at C5 and C6 MRI: stenosis from C3–4 disc to C6–7 disc and signal changes within the cord	Device removed, C5 corpectomy, C3–4 and C6–7 fused using bone grafting and carbon fiber corpectomy cage with anterior plate from C3–7 Antibiotics: (post-op) IV ceftriaxone for 6 weeks then oral cefadroxil for 1 year	Tissue cultures positive for ***C. acnes;*** Ultrasonication cultures negative No evidence of active inflammation	Complete resolution of symptoms, solid fusion at 16 months FU
Clohisy 2023 [35]*	C5–C6 (M6–C)	Severe pain 2.5 y	Normal	X-rays: collapse of the C5–C6 TDR, C2–C3 facet arthrosis CT: osteolysis around device	Device removed, converted to fusion with PEEK cage and auto/allograft Antibiotics: (post-op) 6 weeks IV ceftriaxone then oral amoxicillin and clavulanate for 3 mos.	Tissue cultures positive for broth-only ***C. acnes***	Complete resolution of symptoms at 4 months FU
Harris 2019 [36]	C4–C5 (M6–C)	Dysphagia 4.7 years	Normal	CT: soft tissue mass with fluid collection MRI: no Modic changes	Device removed, no iliac bone graft or plate used in order to maximize infection clearance Antibiotics: (post-op) 6 weeks of IV antibiotics - 5 days of teicoplanin then amoxicillin and rifampicin	Disc space cultures positive for ***C. acnes*** Observed mixed inflammatory infiltrates with abundant neutrophils and fibrin deposits. Numerous macrophages with scanty giant cells, no granuloma formation	Radiographs at 6 weeks FU showed bony destruction of the endplates, minor loss of intervertebral height but well-preserved alignment
	C4–C5 (M6–C)	Paresthesia, itchy throat, rapid dysphagia progression at 7 years	Normal	CT: progressive osteolysis near device, widening of soft tissues secondary to collection, Modic type 3 changes MRI: prevertebral fluid collection spanning C4–5	Device removed, C4–6 fused anteriorly with autologous bone graft; soft-tissue mass partially removed Antibiotics: (post-op) 2 days of prophylactic cefuroxime	Cultures negative Moderate chronic active inflammation, with foreign body–type granulomas and fibrosis within connective tissue	Resolution of symptoms, stable fixation
	C5–C6 and C6–C7 (M6–C)	Dysphagia, coughing, neck pain, respiratory compromise 5 years	Normal	MRI: large retropharyngeal collection compressing esophagus and other structures	Device left in place, abscess drained Antibiotics: (post-op) IV amoxicillin and linezolid for 1 week, then IV ceftriaxone for 6 weeks with oral linezolid for 4 weeks, then oral doxycycline and rifampicin for 1 year	Areas of granulation tissue with foamy histiocytes, hemosiderin, and foreign body material within multi-nucleated giant cells ***C. acnes*** isolated on 16S rRNA molecular sequencing from pus	Resolution of symptoms, residual collection present post-operatively; No infection recurrence, no evidence of fusion or bone loss at 20 mos. FU
	C5–C6 and C6–C7 (M6–C)	Sore throat, dysphagia, neck swelling, sinus formation with pus drainage from surgical scar 2.5 years	Normal	CT: lucency at TDR endplates MRI: superficial collection with enhancing surgical tracks, osteomyelitis with extensive inflammatory changes, and extradural, subligamentous high signal posterior to vertebrae Video fluoroscopy: no fistulous connection between pharynx and spine	Device left in place, fluid drained Antibiotics: (post-op) IV benzylpenicillin, clindamycin, and ceftriaxone with oral ciprofloxacin, rationalized to IV ceftriaxone with oral clindamycin for 6 mos., then oral clindamycin and rifampicin, then clindamycin only for 6 mos.	Tissue culture and 16S rRNA molecular sequencing positive for ***C. acnes***	Resolution of symptoms, stable fusion at 32 mos. FU
Hur 2012 [10]	C6–7 (Prodisc-C)	Sudden neck pain 2 weeks Post-op: pus leakage from wound, fever	Elevated CRP and ESR	(before first revision) X-ray: device displacement and subsidence (before second revision) MRI: aggravation extending from C7 to C2	(first revision) Device removed, C6 corpectomy with autograft and anterior fixation; (second revision) C2–C6 corpectomy, wound unclosed for daily irrigation until infection under control; (third revision) C2–T2 posterior fusion with polyaxial screw-rod system Antibiotics: (post-op) Empirical vancomycin, changed to teicoplanin at one week; (following second surgery): maintenance of teicoplanin	***MRSA*** isolated from pus (first surgery) and cultured specimens (second surgery)	Altered mentality, rising inflammatory markers, and unstable vital signs following second revision; patient treated for bacterial meningitis and septic condition with eventual resolution of symptoms

(*continued on next page*)

Table 3 (*continued*)

Author/year	TDR level (device)	Symptoms and time to presentation	Inflammatory markers	Pre-op imaging workup	Treatment	Histopathology	Outcome
Nigh 2023 [37]	C5–C6 (Prestige LP)	Radiculopathy 3 mos.	Normal	CT: no evidence of infection or implant complication MRI: progression of C4–C5 disc degeneration with lateral recesses involvement SPECT-CT: increased metabolic activity of C5/C6 endplates near device	(first revision) Device revised to M6-C disc, C4–C5 TDR with Simplify disc; (second revision) C4–C6 fusion Antibiotics: IV ceftriaxone for 4 weeks, then oral doxycycline for 12 weeks	Cultures from endplates and explanted device positive for ***C. acnes***	(following first revision) worsening neck/shoulder pain, increased metabolic activity in C6 vertebral body and implant endplates (following second revision) resolution of symptoms at 8 mos. FU
Rosselló 2019 [38]	C4–C5 and C5–C6 (M6–C)	Fluctuant and tight cervical mass 2 years	Normal	CT: hypodense mass with peripheral iodine contrast enhancement MRI: T1WI hypointense and T2WI and STIR hyper-intense mass; barium swallow showed no pass of contrast into cavity	Device removed, filled with iliac crest bone graft Antibiotics: IV rifampicin, vancomycin and meropenem changed to amoxicillin-clavulanate for 6 weeks	Bacterial culture and PCR positive for ***C. acnes*** Beta-2-transferrine test positive for pseudo meningocele but later assumed to be false positive	Asymptomatic at 6 mos. FU
Xia 2019 [39]	C6–7 (M6–C)	Dysphagia and neck mass 3 years	Normal	CT and MRI: prevertebral collection near device	Device removed, conversion to fusion with cage/allograft Antibiotics: (post-op) IV benzylpenicillin and moxifloxacin for 6 weeks with ongoing amoxicillin	Aspirate culture negative Intraoperative cultures positive for ***C. acnes*** sensitive to penicillin and moxifloxacin	Solid bony union, no recurrence of the collection at 29 mos. FU
Lumbar							
Flouzat-Lachaniette 2013 [40]	L4–L5 (MobiDisc)	Low back and abdominal pain, fever, nausea 1 month	Elevated CRP and normal WBC	CT: abscess	Device left in place due to difficulty accessing it Antibiotics (post-op) IV cephotaxime and fosfomycin, switched to oral doxycycline after organism identified	Fluid aspiration and abscess cultures positive for ***mycoplasma hominis***	Infection parameter normalized at 2 mos. FU; well-functioning device, no osteolysis or residual collection at 1.5 years FU
Hoffmann 2020 [41]	L4–L5 (M6–C)	Cutaneous fistulas in abdomen, lumbar tenderness, significant pain Case 1: 9 mos. Case 2: 21 mos. Case 3: 72 mos.	Elevated CRP	X-rays: device loosening of the TDA device and malfunction for all cases MRI: the extent of paraspinal abscess; no epidural empyema in any case CT: bony erosion of adjacent vertebrae in case 2; Contrast media used in cases 1 and 2 to delineate fistula tract PET-CT scan: splitting of the tract into two ducts connecting with the two affected disc levels for case 2	Two stages: debridement of abscess, device removed via partial corpectomy, AB spacer inserted, fistula and cutaneous abdominal wound excised/debrided central, posterior stabilization; placement of expandable cage with autograft 12 days later Antibiotics: (post-op) AB sensitive to *S. aureus*	Cultures positive for ***S. aureus***	Successful fusion at 60 mos. FU
	L4–L5 and L5–S1 (M6–C)		Normal		Devices removed via partial corpectomy, excision of fistula, placement of cages/posterior stabilization with autograft only posteriorly owing to infection	Cultures positive for ***S. aureus***	Successful fusion at 12 mos. FU
	L4–L5 and L5–S1 (M6–C)		Elevated CRP			No growth	Successful fusion at 16 mos. FU
Spivak 2010 [42]	L4–L5 and L5–S1 (Prodisc-L)	Severe back, abdominal, and thigh pain, fever, nausea, vomiting, constipation 8 mos.	Elevated CRP and ESR	CT: psoas-based retroperitoneal abscess; contrast injection showed communication between abscess cavity and one of the devices	(non-surgical treatment) Abscess percutaneously drained and catheter left in situ for 2 days; (revision) Devices removed, L4–S1 fusion with allograft and posterior fixation Antibiotics: (first treatment) IV antibiotics for 6 weeks followed by oral suppressive antibiotics for 4–6 months	Blood cultures positive for ***S. aureus***, abscess culture positive for ***S. intermedius*** Intraoperative cultures negative at both levels	(following non-surgical treatment): 85% relief of symptoms, inflammatory markers normalized (following revision) No sign of infection, successful fusion at 4 years FU; retrograde ejaculation and low back pain persisted

FU: follow-up; IV: intravenous; CT: computed tomography; MRI: magnetic resonance imaging.

* Indicates cases in which infection was not suspected despite positive bacterial culture.

Table 4
Summary of SSEDs.

SSED	# of Patients (incl. in infection rate)	Definition of infection	Rate of infection at 24 mos Number of patients (% of total)	Time to device-related infection
		Cervical		
Prestige One level July 2007	276	NR	All AEs in study Infection: 27 (9.8) AEs classified as related to device/procedure Infection: 0 (0)	–
Prodisc One level Dec. 2007	103	NR	All Severe AEs in study Infection - non-wound: 2 (1.9) Infection - superficial wound: 0 (0) Implant related AE Infection - superficial wound: 0 (0)	–
Bryan One level May 2009	242	NR	All AEs in study Superficial infection: 7 (2.9) Deep wound: 0 (0) Other non-wound related: 10 (4.1) AEs classified as related to device/procedure Infection not specifically reported	–
Secure-C One level Sept. 2012	236	Infection - Superficial Wound: An infection near the surface of the surgical incision Infection - Other: An infection in an area other than the surgical incision	All AEs in study Infection - other: 3 (1.3) Infection - superficial wound: 0 (0) AEs classified as related to device/procedure Infection - superficial wound: 0 (0)	–
PCM One level Oct. 2012	289	Ailments associated with an infectious agent	All AEs in study Infection: 19 (6.6) AEs classified as related to device/procedure Infection: 1 (0.3)*	* <6 weeks
Mobi-C One level Aug. 2013	179	Superficial Wound: superficial surgical incision or surgical wound related infections (includes only study surgery events) Deep Wound: deep surgical incision or surgical wound related infections (includes only study surgery events) Other Wound: superficial and/or deep wound related events from non-study surgery	All AEs in study Infection - superficial wound - cervical: 6 (3.4)* Infection - deep wound - cervical: 0 (0) Infection - other wound - non study surgery: 1 (0.6) Infection - systemic: 8 (4.5) Infection - local: 20 (11.2)	*all <3 mos
Mobi-C Two level Aug. 2013	234	Systemic: infections include infections such as Hepatitis and Influenza Local: infections include infections isolated to a specific region or organ	All AEs in study Infection - superficial wound - cervical: 8 (3.4)* Infection - deep wound - cervical: 0 (0) Infection - other wound - non study surgery: 3 (1.3) Infection - systemic: 10 (4.3) Infection - local: 47 (20.1)	*all <6 weeks except 1 at 6–12 months
Prestige LP One level July 2014	280	Superficial: An infection near the surface of the surgical incision Deep: An infection below the fascia at the surgical incision Other Wound: Infection occurring in other surgical wound not involving the study Hematoma: Swelling or mass of blood that has become infected CSF Leak: Infection resulting from the leakage of CSF Systemic: Infection pertaining to the whole body Urinary Tract: Infection of any part of the urinary system Other: Any infection not listed above	All AEs in study Infection: 34 (12.1)	–

(*continued on next page*)

Table 4 (*continued*)

SSED	# of Patients (incl. in infection rate)	Definition of infection	Rate of infection at 24 mos Number of patients (% of total)	Time to device-related infection
Prestige LP Two level July 2016	209	Any wound infection that is non-surgical or is not of the surgical site, an infection of any part of the urinary system, or any infection occurring in other surgical would not involving the study	All AEs in study Infection: 35 (16.9) AEs classified as related to device infection not listed AEs classified as related to procedure Infection (other): 1 (0.5)	–
M6–C One level Feb. 2019	160	NR	All AEs in study Infection - local: 4 (2.5) Infection - superficial wound - cervical: 3 (1.9)* Infection - deep wound - cervical: 1 (0.6)^ Infection - systemic: 0 (0) Infection - other wound - non study surgery: 0 (0) AEs classified as device related Infection - deep wound - cervical: 1 (0.6)	*all <3 mos ^ 12–24 mos
Simplify One level Sept. 2020	150	NR	All AEs in randomized group Infection - all other infections NOT at cervical surgical site: 9 (6.0) Infection - localized cervical surgical site: 5 (3.3)* Deep wound infection localized to cervical surgical site: 1 (0.7)^ AEs classified as device or procedure related Infection localized to cervical surgical site: 4 (2.7)^ Deep wound infection localized to cervical surgical site: 1 (0.7)^ Infection - all other infections NOT at cervical surgical site: 0 (0.0)	*all <3 mos ^ <30 days
Simplify Two level Apr. 2021	182	NR	All AEs in randomized group Infection - all other infections NOT at cervical surgical site: 15 (8.2) Infection - localized cervical surgical site: 2 (1.1)* AEs classified as related to device Infection not listed AEs classified as procedure related Infection localized to cervical surgical site: 2 (1.1) Infection - all other infections NOT at cervical surgical site: 3 (1.6)	*all <3 mos
		Lumbar		
Prodisc L One Level Aug. 2006	162	NR	All AEs in study Infection - other non-wound: 5 (3.1) Infection - superficial wound with incision site pain: 0 (0)	–
activL One level June 2015	218	Wound infection: Any wound infection, with the wound identified being the index study procedure wound that gets infected. All other infections get coded within specific body system.	All AEs in study Wound infection: 5 (2.3)*	*all <6 weeks
Prodisc L One or two levels Apr. 2020	165	infection - superficial wound with incision site pain: an infection near the surface of the surgical incision infection - other non-wound related: an infection in an area other than the surgical incision (except urinary tract infections)	All AEs in study Superficial wound with incision site pain: 6 (3.6)* Infection - other non-wound related: 13 (7.9) AEs classified as definitively or probably surgery related Superficial wound with incision site pain: 5 (3.0) Infection - other non-wound related: 1 (0.6)	*all <6 weeks except 2 short term (42–210)

AE: adverse event.

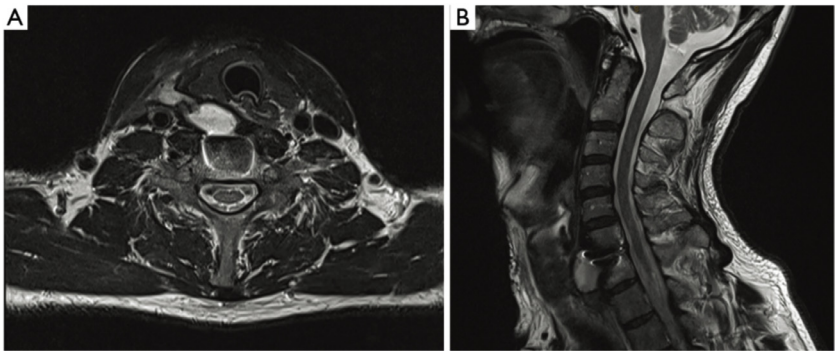

Fig. 2. Pre-operative MRI showing prevertebral fluid collection. (A) Axial T2, (B) sagittal T2. Reproduced from Xia and Winder [39].

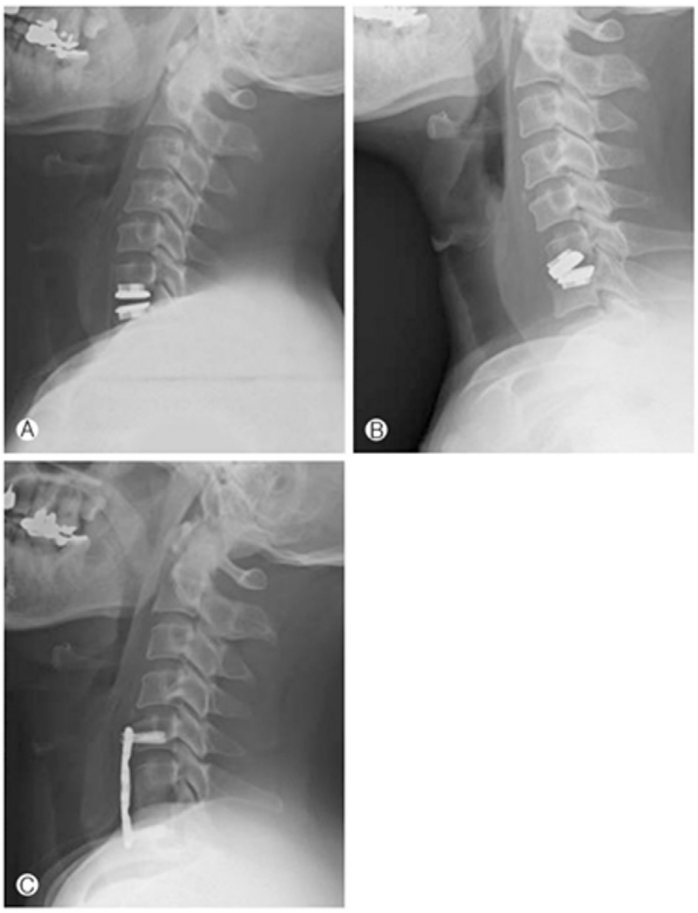

Fig. 3. Well inserted artificial disc noted on postoperative X-ray (A).Follow up X-ray on postoperative day 18 reveals instrument displacement and subsidence (B). Postoperative X-ray after instrument removal, C6 corpectomy and ACDF C5–C7 (C). Reproduced from Hur et al. [10].

Discussion

Total disc replacement is a widely used treatment for cervical and lumbar spine degeneration. Like any orthopedic or spinal procedure, TDR carries the risk of infection, both acute and delayed, with potentially severe consequence. Unlike large joint arthroplasty, however, the management of TDR infection is not well-described. In this review of the literature, we asked: (1) What are the reported rates of TDR infection; (2) What are the clinical characteristics of TDR infection; and (3) How has infection been managed for TDR patients?

Our review has some limitations. The included database studies consider only complications occurring within 1 year postoperatively (most within 3 months) and thus do not represent a comprehensive summary of late onset infections, which may be the most devastating. Furthermore, the definition of infection in these databases was heterogeneous, with some sources reporting on SSI, and fewer studies specifying deep infection, which may require revision. However, regardless of the frequency and classification of these infections, their clinical management was fortunately well-reported within the reviewed case studies. We expect that treatment findings and recommendations, and possibly investigations regarding the risk of delayed infection, will increase alongside the growing prevalence of TDR devices. Additionally, the methods and verbiage used in reporting infection varied greatly across the studies, making it difficult to aggregate and compare specific incidence rates. Still, the overall trends were similar between the studies and useful to report.

Finally, the case studies failed to report how the diagnosis of infection was defined, and in many cases, it was undeterminable whether the device failure was septic or aseptic, and whether positive tissue culture findings were coincidental or causal. This is an ongoing clinical challenge given debate about what constitutes an infection for low virulence organisms, as well as the occurrence of false positives (especially for long-held cultures of *C. acnes*). The potential for debris-related inflammatory reactions that mimic deep infection symptoms further muddies the issue [43]. While we reported which cases were definitively classified as infections, the causes of revision were generally nonspecific, and it is not possible for us to draw clear conclusions about how positive cultures relate to patient outcomes.

What are the reported rates of TDR infection?

Across the database studies, infection rates for both cervical and lumbar TDR were low. For 30-day outcomes, which were all reported from the ACS-NSQIP database, SSI rates up to 3.0% for lumbar and 0.77% for cervical were reported. For 90-day follow-up, lumbar TDR wound infection and periprosthetic infection were reportedly up to 0.25% and 0.04%, respectively [32]. For cervical TDR, Kelly et al. reported a 90-day wound infection rate of 0.14% [20] and Ifarraguerri et al. reported SSI rates up to 0.8% [19]. Only one study included longer follow-up for infection outcomes and reported a cervical TDR SSI rate of 0.99% for 6 months and 1.38% at one year [23].

An additional study that queried the Manufacturer and User Facility Device Experience (MAUDE) database was identified but excluded from the data summary since it provides rates of infection specifically among patients with reported complications [44]. Still, the results are notable, with a reported 0.75% (n=10/1347) of cervical TDR complications reported between 2005–2020 being attributed to infection. SSED infection rates were similarly low and generally reported to be superficial.

Multiple studies compared infection rates between TDR and fusion procedures [15–17,20–25,28,29,32]. For cervical procedures, most found no significant difference in infection rate between TDR and anterior cervical discectomy and fusion (ACDF) for both single and multilevel procedures [16,17,20,22,25,28]. Watts and Haapala, however, did report a higher rate of organ space infection for ACDF but did not find a similar association for superficial or deep SSIs [29]. Revision cervical TDR had a higher rate of perioperative wound infection than both revision ACDF as well as primary TDR [21], likely owing to the increased invasiveness of the procedure.

Other studies reported higher superficial and deep infection rates for posterior cervical foraminotomy compared to both TDR and ACDF and highlighted the surgical approach as a potential factor [23–25]. Specifically, cervical foraminotomy requires a posterior approach, which has been associated with greater risk of infection compared to anterior due to limited lymphatic drainage in the posterior spine and decreased vascularization [24,45]. Ng and colleagues thus reinforced the importance of proper surgical preparation and recommended inclusion of powdered antibiotic into the wound site as well as the insertion of a suprafascial drain for patients having an increased risk of infection [24]. Interestingly, lumbar TDR was reportedly associated with fewer acute infections compared to fusion, and it was hypothesized that this may be related to the anterior approach required by TDR [32], unlike what has been reported elsewhere [45,46].

Some database trend studies also explored whether certain factors were associated with TDR infection. No significant difference was found between inpatient and outpatient procedures (for lumbar TDR at 30 days [27,33] and cervical TDR 90 days [19]) or between cervical TDR patients with and without myelopathy [26]. The impacts of infections were also noted; Ansari et al. reported an association between SSI and the likelihood of reoperation, and Zeidan et al. found that wound infection complications were predictors of patient readmission and extended length of stay. Both studies thus recommend “meticulous infection prophylaxis” during surgery, similar to what has been adopted for large joint arthroplasty [47,48].

What are the clinical characteristics of TDR infection?

Thirteen of the reviewed case reports involved definitive or probable infections. For the four cervical TDR infection cases reviewed, patients presented with symptoms including a palpable mass or swelling (Fig. 2) [10,38,39], severe neck pain or dysphagia [10,39], and pus drainage with a fever [10]. The four potential cases of infection presented by Harris et al. each involved delayed presentation of dysphagia and soft tissue masses anterior to the disc, though it was undeterminable whether metal hypersensitivity played a role given similarities in symptoms for each condition [36]. Despite clinical symptoms, preoperative laboratory workup was considered “normal” in all but one case [10].

For infected lumbar TDRs, significant back and leg pain was the primary symptom present for every patient. Two patients also presented with cutaneous fistulas in the abdomen [41], and two had fever and nausea [40,42]. Preoperative laboratory workup was normal in one case, all others had elevated C-reactive protein levels. In many cases, both lumbar and cervical, preoperative imaging with MRI and/or CT revealed fluid collection or a soft tissue mass near the treated spine segment and led to a diagnosis of infection. The inclusion of contrast in imaging was particularly useful in multi-level constructs for determining which devices were affected by infection: in one case, communication between an abscess and only one device of a multilevel treatment was observed [42], in another, the tract of a fistula was mapped to both devices implanted [41], and in a third, increased metabolic activity near a vertebral endplate raised suspicion of an infection[37]. Patient risk factors were also considered in the diagnosis of infection [38].

Cultures were taken from tissue, fluid aspiration, and blood to determine the presence of infectious organisms. For delayed infections, cultures were most often positive for *Cutibacterium acnes* [34–39]. *Staphylococcus aureus* was reported in 4 patients [10,41,42], one of whom had an acute infection with MRSA and suffered bacterial meningitis and sepsis [10]. *Streptococcus intermedius* was cultured from an abscess in one case [42]. Flouzat-Lachaniette et al. detailed a case of deep wound infection involving *Mycoplasma hominis*, a bacterium of the urogenital tract, for a patient with unreported intrauterine device endometritis [40]. It was suspected that contamination of the TDR occurred via the bloodstream or due to laceration of the peritoneum during surgery. This led the authors to underscore the importance of delaying anterior approach lumbar procedures for patients with suspected endometritis and the recommendation to test specifically for *M. hominis* in patients with a history of gynecological pathology and/or peritoneal breach during surgery [40]. Hypothesized causes of the delayed infection cases included latent, dormant implant contamination, esophageal/tracheal microperforation, and bacteremia [36,38,39]. However, infection etiology is difficult to pin down, and the presence of a device failure further confounds it.

Cases with reported findings of positive bacterial cultures were included in our review regardless of whether infection was otherwise clinically established. We found that these cases were useful for contextualizing the clinical significance and response to bacterial contamination, especially for *C. acnes*. In two cases, tissue cultures taken during revision surgery for non-infection-related reasons were positive for *C. acnes* [34,35]. Despite the absence of any histological evidence of infection, each patient was given 6 weeks of IV antibiotics postoperatively followed by a course of oral antibiotics. It was highlighted alongside these cases that the clinical significance of *C. acnes* for TDR (and for spine procedures in general) is a topic of great interest. Although contamination with *C. acnes*, a skin commensal, is always a possibility during surgery, multiple studies have reported high rates of detection of the bacteria in herniated disc tissue [49,50]. While this is generally no cause for concern of infection, it poses a possible source of contamination for TDR devices [36]. Additionally, although *C. acnes* infection is slow-growing and frequently devoid of related symptoms like fever and elevated inflam-

matory markers, its proinflammatory properties have been theorized to play a role in back pain [51]. Altogether, these characteristics make the clinical significance of *C. acnes* positive cultures in TDR somewhat ambiguous.

How has infection been managed for TDR patients?

Surgical treatment, which was warranted in most cases due to the delayed/chronic nature of the infection, was driven by two main goals: eliminate infection and stabilize the spine. For the former, vigorous debridement and irrigation were standard, as were abscess drainage and soft tissue mass removal where applicable. For the latter, deciding whether to remove or retain the TDR device was essential. Given the presumed presence of biofilm (supported by the involvement of notable biofilm-forming pathogens like *C. acnes*), devices were most often removed. Potential difficulties related to removal, such as vascular lesions or scar tissue complicating the surgical approach, also led to the retention of some devices, though potentially at the expense of infection eradication [36,40].

While device removal was generally unremarkable, one case required a full corpectomy due to an inflammatory reaction in the cervical vertebral body (Fig. 3)[10], and two lumbar cases required partial corpectomy in order to remove the keel-based device [41]. A corpectomy may also be performed following extensive bone loss during implant removal [39]. Extra precautions, such as the removal of the posterior longitudinal ligament to prevent ascending infection, may need to be taken in life-threatening cases like that presented by Hur et al. [10]. Regardless of the surgical approach, the importance of meticulous preoperative planning with input from a multidisciplinary team was emphasized throughout the literature.

Throughout the case reports, fusion was achieved using a mix of instrumentation and bone graft, though the addition of anterior instrumentation near the infected site has been advised against [52]. Both broad spectrum and targeted antibiotics were used postoperatively dependent on identification of the infectious agent, and it was recommended that antibiotics should be continued until serum infection parameters return to normal [41]. Courses of antibiotics up to one year postoperatively were reported. Ultimately, the surgical infection treatments were generally associated with symptom resolution and stable spinal fixation.

One case of infection was successfully treated nonoperatively. As reported by Spivak and Petrizzo, the patient presented with severe symptoms, elevated inflammatory markers, and upon CT with contrast showed a retroperitoneal abscess that communicated with one of two nearby lumbar TDR device [42]. The abscess was drained percutaneously, and the patient received 6 weeks of intravenous antibiotics followed by a course of oral suppressive antibiotics. Inflammatory markers normalized and symptoms subsided through 5 months, at which point the lumbar devices were removed upon the patient's insistence. No evidence of active infection was found upon revision. Interestingly, although infection in this case presented at 8 months postoperatively and may therefore be classified as a delayed, Spivak and Petrizzo considered it acute (due to the specific symptoms and a lack of bony erosion) and treated it as such.

Conclusions

Our review summarizes the reported incidence and state of clinical management for TDR infection, an infrequent but serious complication. We found a lack of clarity regarding how infection was diagnosed, indicating a variation in clinical approach and highlighting the need for a standard definition of TDR infection. Furthermore, while reported infection rates were low, the absence of a clear definition prevented us from pooling the data and may contribute to underreporting in the literature. As for infection management, we found that treatment strategy and success rely on several factors including patient symptoms and time to onset, microorganism type, and implant positioning/stability. While treatment strategies varied throughout the literature, some standard practices in eliminating infection and reconstructing the spine emerged. The results will inform future work on the creation of a standardized definition of TDR infection and an evidence-based algorithm for its identification and management.

Declaration of competing interest

None.

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