



Clinical Utility of Diffusion-Weighted Imaging in Spinal Infections

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Abstract

Purpose Both laboratory markers and radiographic findings in the setting of spinal infections can be nonspecific in determining the presence or absence of active infection, and can lag behind both clinical symptoms and antibiotic response. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) has been shown to be helpful in evaluating brain abscesses but has not been commonly used in evaluating spinal infections. We aimed to correlate findings on DWI of the spine to results of microbiological sampling in patients with suspected spinal infections.

Methods Patients who underwent MRI with DWI for suspicion of spinal infections and microbiological sampling from 2002 to 2010 were identified and reviewed retrospectively in this institutional review board approved study. In addition to DWI, scans included sagittal and axial T1, fast-spin echo (FSE) T2, and post-gadolinium T1 with fat saturation. Regions of interest were drawn on apparent diffusion coefficient (ADC) maps in the area of suspected infections, and ADC values were correlated with microbiological sampling.

Results Of 38 patients with suspected spinal infections, 29 (76%) had positive microbiological sampling, and 9 (24%) had negative results. The median ADC value was $740 \times 10^{-6} \text{mm}^2/\text{s}$ for patients with positive microbiological sampling and $1980 \times 10^{-6} \text{mm}^2/\text{s}$ for patients with negative microbiological sampling ($p < 0.001$). Using an ADC value of $1250 \times 10^{-6} \text{mm}^2/\text{s}$ or less as the cut-off value for a positive result for spinal infection, sensitivity was 66%, specificity was 88%, positive predictive value was 95%, negative predictive value was 41% and accuracy was 70%.

Conclusion In patients with suspected spine infection, ADC values on DWI are significantly reduced in those patients with positive microbiological sampling compared to patients with negative microbiological sampling. The DWI of the spine correlates well with the presence or absence of spinal infection and may complement conventional magnetic resonance imaging (MRI).

Keywords Vertebral Discitis-Osteomyelitis · Diffusion weighted imaging · MRI · Radiology-pathology correlation · Bacterial infection

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Introduction

Spinal infections often present a diagnostic challenge due to non-specific symptoms such as fever, malaise, and back or neck pain [1]. Magnetic resonance imaging (MRI) is the most sensitive imaging tool to detect early infection; however, MRI findings of discitis/osteomyelitis often lag behind the clinical symptoms and also lag behind in the healing phase with persistent abnormalities [2, 3]. Findings on MRI suggestive of infection can be non-specific, especially in the postoperative spine where abscesses, hematomas, and seromas can have a similar appearance [4–6]. Diffusion-weighted imaging (DWI) has been useful in the diagnosis of cerebral infections where abscesses have been shown to have low apparent diffusion coefficient (ADC) values

[7–11], but is currently not commonly clinically used for the evaluation of spinal infections.

Previous studies have investigated the role of DWI in differentiating infectious vertebral body changes from malignant or degenerative changes [12–14], and one case report demonstrated a spinal abscess with qualitatively reduced diffusion [15]. Additionally, DWI has been used to guide patient management in the setting of spinal infections, such as in site selection for biopsy or decision-making of surgical drainage [16]; however, to our knowledge, no study has quantitatively validated the utility of DWI as a diagnostic test for spinal infections outside of the vertebral body, and no standards have been developed for ADC values representative of spinal infections. In this study, we correlated findings on DWI of the spine to results of microbiological or pathological sampling in patients with suspected spinal infections. The goals of this study were to assess the sensitivity and specificity of DWI in diagnosing spinal infections, and to identify an ADC threshold value that makes the diagnosis of infection more likely. We hypothesize that DWI in this context will complement conventional MRI in challenging cases to help identify or exclude active infections.

Methods

Patients

In this cross-sectional study, the electronic medical records were retrospectively searched to identify all patients who underwent spine MRI with DWI for clinical suspicion of spinal infections and had concurrent microbiological and/or pathological sampling from 2002–2010. Both inpatients and outpatients were included. Exclusion criteria included the presence of metallic implants that rendered DWI uninterpretable due to artifacts or recent postoperative state (6 weeks or less) where the presence of blood products would potentially confound DWI. All patients clinically suspected of having spinal infections who had both MRI with DWI and biopsy results were otherwise included in this study. Patient medical history including prior spinal surgery, pertinent concurrent laboratory tests, e.g. white blood cell count (WBC), elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and concurrent antibiotic therapy was also obtained from the medical records. The study was designed and carried out in accordance with the Standards for Reporting Diagnostic Accuracy Studies (STARD 2015 [17]), and with approval of the institutional review board.

Imaging and Analysis

All MR imaging was performed at UCSF on 1.5T MR units (Signa, GE Medical Systems, Milwaukee, WI, USA; Achieva, Philips, Best, The Netherlands) and consisted of sagittal and axial T1 (TR 500–600 ms, TE 8–16 ms), sagittal and axial FSE T2 (TR 3000–4000 ms, TE 102–108 ms), and axial and sagittal post-gadolinium T1 (gadopentate dimeglumine, [Magnevist, Schering-Plough, Kenilworth, NJ, USA] 0.1 mmol/l per kg body weight) with fat saturation. Sagittal and/or axial DWI was acquired in three directions (single shot echo planar: TR $2 \times$ pulse-pulse interval; TE 15 ms; FOV 22 cm; 256×144 ; 5.0-mm slice thickness with 0.5 mm gap; b-values 0 and 400 s/mm²).

In this study two board-certified neuroradiologists with combined 15 years of experience in spine and diffusion imaging blinded to the clinical data retrospectively evaluated the conventional MR and DW images, in consensus. Regions of interest (ROI; [18]) were drawn on the ADC maps within areas of abnormal T2 signal and/or enhancement suspicious for infection and analyzed for mean ADC values using software available on the scanner. Spinal infections can involve various structures including vertebral marrow, intervertebral discs, joints, epidural compartment, and paraspinal soft tissues. One or more of these spaces were involved in the patients included in this study. If the conventional MRI findings spanned multiple compartments of the spine, the area with the lowest ADC value was chosen for analysis, and an ROI was placed within the center of the abnormality. The ROI size depended on the size of the area involved; however, the mean ROI size was 7 mm² and ranged up to 13 mm².

Biopsy and Specimen Analysis

Infection was defined by the presence of a pathogenic organism in microbiological and/or pathological samples, which were obtained at UCSF by using standard computed tomography (CT)-guided techniques targeting the area of MR imaging abnormality as previously described [19], and targeted the area included in the ROI when possible. Samples were routinely processed for microbiological culture and/or pathology by the UCSF Departments of Pathology and Laboratory Medicine as clinically indicated.

Statistical Analysis

Using the results of microbiological and/or pathological testing as the clinical reference standard, a receiver operating characteristic (ROC) curve was generated to evaluate the ability of DWI to diagnose spinal infections. From this curve, several empirical ADC values were chosen as cut-off values for a positive test. These empirically chosen val-

ues were based on prior studies evaluating the ADC values of brain abscesses, which found that brain abscesses had mean ADC values of $1000 \times 10^{-6} \text{mm}^2/\text{s}$ or less [7, 9–11]. Using these ADC values, the specificity, sensitivity, positive and negative predictive values, and diagnostic accuracy of DWI in diagnosing spinal infections were determined. Additionally, in those patients where pertinent corresponding laboratory values were available, the specificity, sensitivity, positive and negative predictive values, and diagnostic accuracy of abnormal laboratory values in diagnosing spinal infections were determined.

To assess whether ADC values in patients with microbiological and/or pathological sampling positive for infections were significantly different from patients with sampling negative for the presence of infections, the Mann-Whitney U-test was used. A χ^2 -test was used to evaluate whether the presence or absence of concurrent antibiotic therapy correlated to the presence or absence of active infection on microbiological and/or pathological sampling.

All statistical analyses were performed using GraphPad Prism (version 7.0 for Mac; GraphPad Software; available at: <http://www.graphpad.com>) and two-sided p values of <0.01 were considered statistically significant.

Results

In this study 38 patients with clinically suspected spinal infections underwent MRI with DWI and microbiological sampling and/or pathological sampling between April 2002 and December 2010 (Table 1). All 38 patients had findings on standard MRI concerning for infection (areas of T1 hypointense and T2 hyperintense signal abnormality and/or enhancement in disc, vertebrae, and/or paraspinal soft tissue), and were read as suspicious for infection in the final MRI report.

Of the patients six had findings suspicious for osteomyelitis-discitis, six patients had epidural fluid collections, two patients had sacroiliac joint involvement, and nine patients had paraspinal fluid collections. Additionally, 15 patients had involvement of multiple spinal compartments, which was most commonly osteomyelitis-discitis plus involvement of the epidural space and/or the paraspinal soft tissues.

Of the patients 29 (76%) had positive results on microbiological sampling, and 9 patients (24%) had negative results. Among the 29 patients with positive microbiological results, 27 (93%) had pyogenic infections (17 *Staphylococcus aureus*, 4 *Streptococcus spp.*, 1 *Staphylococcus epidermidis*, 1 *Escherichia coli*, 1 *Enterococcus*, 1 *Pseudomonas*, 1 gram-positive rod, 1 gram-positive cocci), 1 (4%) had an infection with *Mycobacterium tuberculosis* and 1 (4%) had an infection with *Mucor*. In the patients from whom *Staphy-*

Table 1 Patient characteristics

Characteristic		All patients (n=38)
<i>Gender</i>	Females	15 (39.5%)
	Males	23 (60.5%)
<i>Age (years)</i>	Median	58.5
	Range	27–87
<i>Antibiotics^a</i>	Yes	27 (71%)
	No	11 (29%)
<i>Abnormal laboratory parameters^b</i>	Yes	22 (59%)
	No	15 (41%)
<i>Prior spinal surgery</i>	Yes	12 (32%)
	No	26 (68%)
<i>Immunocompromised</i>	Organ transplant	13 (34%)
	Chronic steroid use	5 (13%)
	Diabetes	5 (13%)
	Neutropenia	1 (3%)
<i>Additional risk factors</i>	IV drug abuse	1 (3%)
	Malignancy	6 (16%)
	Renal failure	3 (8%)
	Lyme disease	1 (3%)

^aAt time of magnetic resonance imaging

^bElevated ESR (erythrocyte sedimentation rate), CRP (C-reactive protein) and/or WBC (white blood cells)

lococcus epidermidis, gram-positive cocci, and gram-positive rods were cultured, pathologic evaluation yielded osteomyelitis in each case.

Of the 9 patients with negative microbiological results, 5 (56%) were on antibiotics at the time of MRI and tissue sampling, and 4 were treated by a standard antibiotic regimen despite negative cultures. Of these nine patients, eight had concurrent pathology performed in addition to microbiology, and none revealed pathologic evidence of infection in addition to negative microbiological results. None of the nine patients experienced worsening of clinical symptoms or radiographic findings.

Figs. 1 and 2 show examples of DWI in patients with positive and negative microbiological sampling, respectively. The median ADC value was $740 \times 10^{-6} \text{mm}^2/\text{s}$ for patients with positive microbiological sampling and $1980 \times 10^{-6} \text{mm}^2/\text{s}$ for patients with negative microbiological sampling; the distributions in the two groups differed with high statistical significance (Mann-Whitney U-test=32, $n_1=29$, $n_2=9$, two-tailed $p<0.001$). Fig. 3 shows the distribution of ADC values in both patient groups. In the 29 patients with positive microbiological sampling, the locations of imaging abnormalities can be broken down as follows: 13 (45%) patients had transcompartmental abnormalities involving the vertebral body and intervertebral disc as well as the epidural and/or paraspinal soft tissues, 6 (21%) patients had infections confined to



Fig. 1 Magnetic resonance imaging with diffusion-weighted imaging of the cervical spine in a 30-year-old female with a history of i.v. drug use who presented with neck pain and fever. Sagittal T2 and post-gadolinium T1-weighted MR images (**a**, **b**) demonstrate diffuse inflammatory changes of the posterior paraspinal muscles with a focal rim enhancing fluid collection (*circles*) at the level of C7. The DWI (**c**) demonstrates high intensity within the collection (*circle*) with corresponding low apparent diffusion coefficient (ADC) (**d**, *circle*) suspicious for an abscess. The ADC value within the fluid collection measures $800 \times 10^{-6} \text{ mm}^2/\text{s}$. Pathological examination of the fluid collection was consistent with abscess, and microbiology yielded *Staphylococcus aureus*

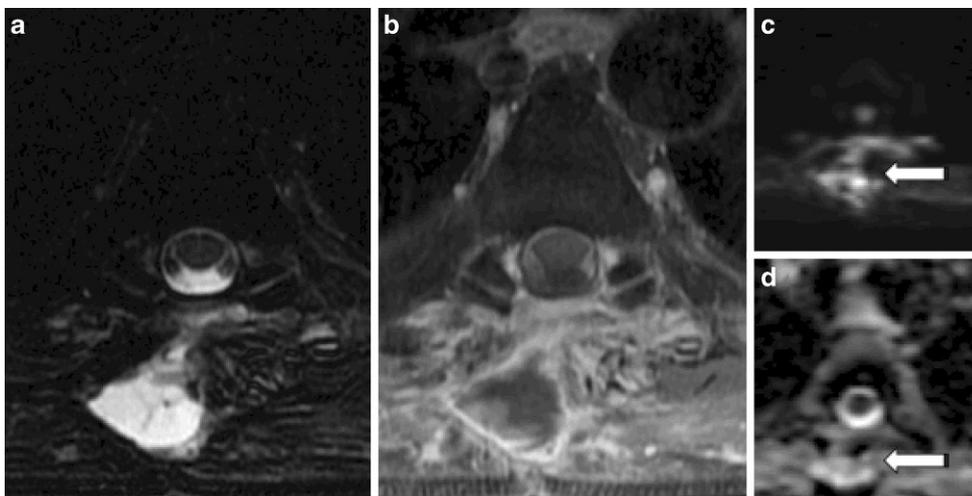


Fig. 2 Magnetic resonance imaging with diffusion-weighted imaging of the thoracic spine in a 65-year-old male with history of liver and renal transplant who presented with back pain after removal of thoracic masses. Axial T2 and post-gadolinium T1-weighted MR images (**a**, **b**) demonstrate a rim enhancing fluid collection in the paraspinal tissues at T5. The DWI (**c**) demonstrates high intensity within the paraspinal collection (*arrow*) with corresponding high apparent diffusion coefficient (ADC) (**d**, *arrow*). The ADC value measures $3268 \times 10^{-6} \text{ mm}^2/\text{s}$. Microbiology of the fluid collection was negative

Table 2 Performance of DWI for diagnosing spinal infection using different maximum ADC (apparent diffusion coefficient; mm^2/s) values as cut-offs for a positive test

ADC	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV ^a (%)	NPV ^b (%)
1000	62	100	70	100	42
1250	66	88	70	95	41
1600	86	63	81	89	56
2130	93	38	81	84	60
2460	97	13	78	80	50

^aPPV positive predictive value

^bNPV negative predictive value

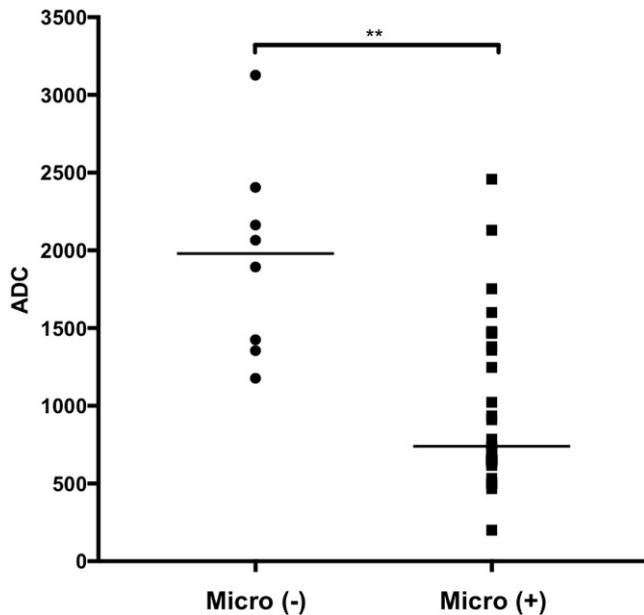


Fig. 3 Distribution of apparent diffusion coefficient (ADC) values in patients with positive microbiological sampling (Micro+) and in patients with negative microbiological sampling (Micro-; two-tailed $p < 0.001$ as indicated by **)

the vertebral body and intervertebral disc, 6 (21%) patients had predominant involvement of the paraspinal soft tissues, and 4 (14%) had predominant involvement of the epidural space.

Using an ADC value of $1250 \times 10^{-6} \text{ mm}^2/\text{s}$ or less as the cut-off value for a positive result for spinal infections, sensitivity was 66%, specificity was 88%, positive predictive value was 95%, negative predictive value was 41% and accuracy was 70%. Table 2 shows the specificity, sensitivity, accuracy, and positive and negative predictive values of DWI in diagnosing spinal infections using different empirically chosen ADC values as cut-off values for a positive test result. The area under the ROC curve was 0.862. In comparison, the calculated sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for having at least one abnormal laboratory value suggestive of infection (elevated WBC, elevated ESR, elevated CRP) in our cohort of patients were 62%, 50%, 82%, 27% and 59%, respectively. There was no correlation between the detection of infection on pathology and/or microbiology and the presence or absence of concurrent antibiotic therapy at the time of sampling (χ^2 -test = 1.377, $p = 0.24061$).

Of the patients with positive microbiological sampling two underwent follow-up spine MRI with DWI after an-

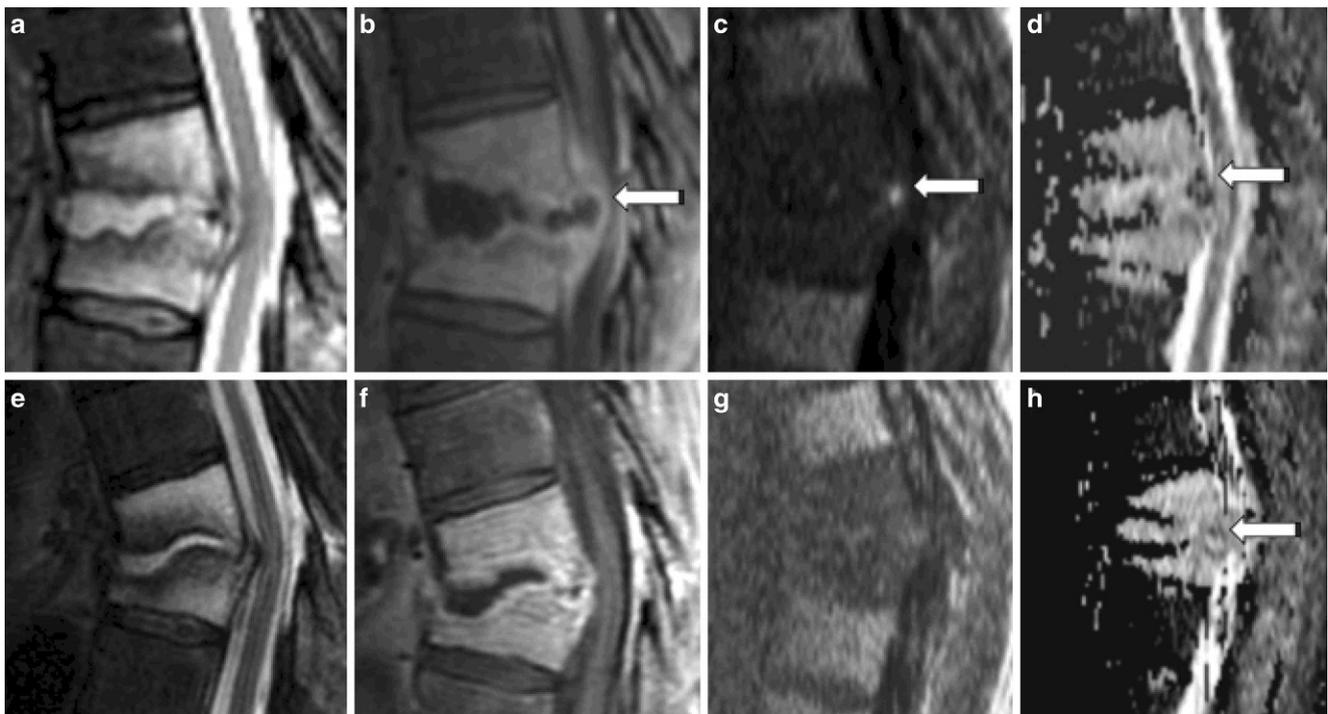


Fig. 4 Magnetic resonance (MR) imaging with diffusion-weighted (DWI) imaging of the thoracic spine in a 64-year-old male with a history of thoracic radiation for esophageal cancer who presented with back pain before (a–d) and after 4 weeks of antibiotic therapy (e–h). Sagittal MR images demonstrate abnormal T2 hyperintensity (a, e) and enhancement (b, f) involving the T9 and T10 vertebral bodies with a rim enhancing fluid collection involving the T9–T10 disc extending into the epidural space (arrow). Before antibiotic therapy, DWI (c) shows focal hyperintensity within the ventral epidural space with associated low apparent diffusion coefficient (ADC) (d) of $200 \times 10^{-6} \text{ mm}^2/\text{s}$. Microbiology of the epidural fluid collection yielded viridans group streptococci. The DWI (g) after 4 weeks of antibiotic therapy shows resolution of the focal hyperintensity, and the ADC (h) is now relatively elevated ($1556 \times 10^{-6} \text{ mm}^2/\text{s}$)

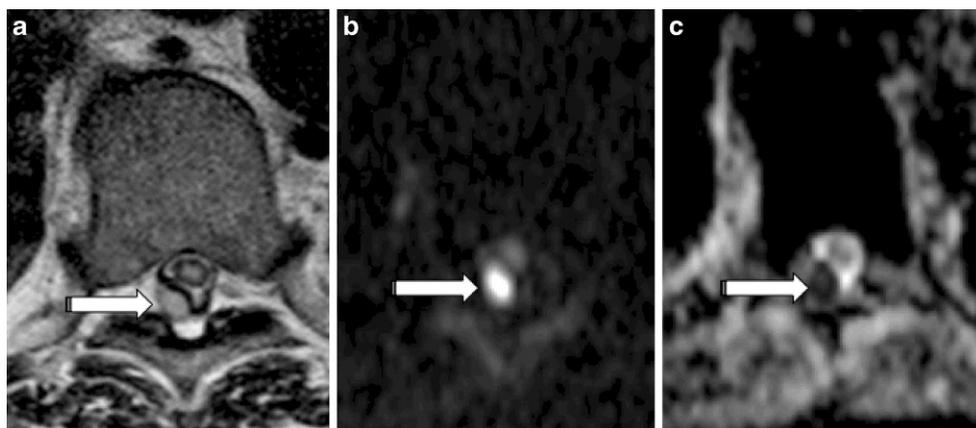


Fig. 5 Magnetic resonance (MR) imaging with diffusion-weighted (DWI) imaging of the thoracic spine in a 57-year-old male with a history of renal failure who presented with back pain and fever. Axial MR images demonstrate a T2 hyperintense (a) posterior epidural fluid collection at T8–T9 (arrow). The patient was unable to receive gadolinium due to renal failure. The DWI (b) demonstrates focal high intensity in the posterior epidural space at T8–T9 (arrow) with corresponding low apparent diffusion coefficient (ADC) (c, arrow) consistent with an epidural abscess. The ADC value in the area of epidural reduced diffusion measured $648 \times 10^{-6} \text{mm}^2/\text{s}$. Microbiology of the epidural fluid collection yielded *S. aureus*

tibiotic treatment. Both patients had epidural abscesses that initially were reduced in diffusion (ADC values of $200 \times 10^{-6} \text{mm}^2/\text{s}$ and $468 \times 10^{-6} \text{mm}^2/\text{s}$). Follow-up DWI after antibiotic treatment demonstrated normalization of diffusion findings (ADC values of $1556 \times 10^{-6} \text{mm}^2/\text{s}$ after 3 weeks of therapy and $4021 \times 10^{-6} \text{mm}^2/\text{s}$ after 6 weeks of therapy, respectively). Fig. 4 demonstrates the change in DWI in one of these patients and three patients were unable to receive gadolinium-based contrast due to renal insufficiency. Fig. 5 demonstrates an example from one of these patients, where an epidural fluid collection with corresponding low ADC values yielded *Staphylococcus Aureus* on percutaneous sampling.

Discussion

The preferred diagnostic modality for detection of spinal infections is MRI; however, MRI findings in pyogenic and atypical infections may be relatively non-specific, especially in the postoperative spine, and can lag behind the clinical symptoms during the initial phase and lag behind during the healing phase [20, 21]. Ill-defined T1 hypointense and T2 hyperintense signal within the vertebral marrow and intervertebral disc space are compatible with inflammatory exudates or edema along with loss of end-plate definition. Loss of disc space height is a characteristic but late finding. Postcontrast sequences show enhancement of the disc and adjacent end-plates. A conclusive diagnosis often requires invasive biopsy and culture [4–6]. Definitive diagnosis is imperative for optimal clinical management, to avoid subjecting patients to unnecessary long-term antibiotics and to avoid contributing to bacterial antibiotic resistance.

The use of DWI has been useful in distinguishing brain abscesses from necrotic neoplasms [7–10], but has not been commonly used in the evaluation of spinal infections due to previous technical limitations of DWI of the spine related to the small size of the spine and involuntary motion from cerebrospinal fluid (CSF) pulsations that require much more optimization of these DWI pulse sequences when compared to DWI of the brain [22]. The DWI is based on the random movement of water molecules within tissues. The calculated ADC relates the average displacement of a molecule over an area to the observation time, with higher values indicating more mobile water. In abscesses, the high cellularity and viscosity of pus cause impeded water mobility and thus low ADC values and reduced diffusion [23]. With an average acquisition time of 3–4 min, the addition of a DWI sequence will not significantly lengthen a standard spine MRI protocol.

Our study correlated the findings on DWI of the spine with the results of microbiological sampling in patients with suspected spinal infections and found a statistically significant difference in ADC values between patients with positive and negative sampling results, with median ADC values lower in the patients with positive sampling across a variety of different pathogenic bacterial and fungal organisms. Prior studies evaluating the ADC values found that brain abscesses had mean ADC values less than $1000 \times 10^{-6} \text{mm}^2/\text{s}$ [7, 9–11]. When applied to this study, an ADC value was highly specific for spinal infections; however, the sensitivity was only 62%. While we do not propose a strict cut-off value for which infections can be entirely ruled in or excluded based on our data, an ADC value of less than $1250 \times 10^{-6} \text{mm}^2/\text{s}$ yielded a positive predictive value of 95% in our cohort with additional parameters that are more reliable than laboratory values alone.

Previous studies have investigated the role of DWI in differentiating infectious vertebral body bone marrow changes from malignant or degenerative changes [12–14]. For example, Balliu et al. evaluated DWI in 16 patients with osteoporotic compression fracture, 15 patients with neoplastic endplate bone marrow infiltration, and 14 patients with infectious endplate bone marrow infiltration and found high mean ADC values for the acute osteoporotic fractures, and lower mean ADC values for the infectious lesions, but no statistically significant difference in mean ADC values between malignant and infectious lesions [13]. These studies did not evaluate spinal infections outside of the bone marrow.

Eastwood et al. described a case of spinal epidural abscess with qualitatively reduced diffusion [15], and in a review on DWI of the spine, Thurnher and Bammer described an unpublished series of patients with spinal infections in whom all epidural abscesses also demonstrated qualitatively reduced diffusion with corresponding low ADC values [22]. Although these reports support the use of DWI in evaluating spinal infections, particularly epidural abscesses, they have not quantitatively validated the utility of DWI as a diagnostic test for spinal infections, and no standards have been developed for ADC values representative of spinal infections. Our sample size of 38 patients, while limited, is clinically relevant as the largest available study to date evaluating DWI data with pathology sampling as a gold standard in patients with suspected spinal infection. Our study confirmed the utility of DWI in helping to diagnose spinal infections and suggests that an ADC value of less than $1250 \times 10^{-6} \text{ mm}^2/\text{s}$ may be suspicious for spinal infections. In cases where gadolinium-based contrast cannot be administered due to underlying renal insufficiency, DWI may be especially helpful in discriminating between infected and non-infected spinal fluid collections.

In addition, in the two patients who underwent follow-up DWI after long-term antibiotic therapy, we noted improvement and near normalization of DWI changes and ADC values on the follow-up DWI despite persistent changes on the conventional MRI sequences. This may be of greatest clinical utility: the ability to confirm adequacy of medical treatment in the presence of ongoing imaging abnormalities. Additional prospective studies with DWI before, during, and after antibiotic treatment are warranted to further evaluate the role of DWI in following response to antibiotic treatment in spinal infections.

Limitations of this study include small sample size, a heterogeneous patient cohort including a variety of spinal infections, and a skewed population with high positive predictive values. Due to the retrospective nature of the study, the MR imaging protocols were not standardized. In addition, many of the patients were already on antibiotics at the time of MRI and DWI, which may affect the sensitivity of

DWI to infections as the timeline and correlation of ADC values and antibiotic therapy is not established; however, statistical analysis of our population demonstrated that, in spite of antibiotic use, there was no correlation between the detection of infection on pathology and/or microbiology and the presence or absence of concurrent antibiotic therapy at the time of sampling. The use of microbiological sampling as the clinical reference standard also has limitations as sampling errors and indolent infections may yield negative cultures; however, no other reference standard for spinal infection currently exists.

Conclusion

Spinal infections are difficult to diagnose. The MRI findings often lag behind the clinical symptoms and lag behind during the healing phase resulting in uncertainty in initiating treatment as well as knowing when treatment has been adequate and can therefore be stopped. The DWI has been useful in the evaluation of cerebral infections, but is not commonly used in diagnosing spinal infections. The current study, which is the largest available to the best of the authors' knowledge, has quantitatively validated the utility of DWI as a diagnostic test for spinal infections both inside and outside of the vertebral body. Additionally, this study has suggested standards for ADC values representative of spinal infections, which have not been previously documented in the literature. This study found that in patients with suspected spinal infections, ADC values on DWI are significantly lower in patients with positive microbiological sampling than in patients with negative microbiological sampling. An ADC value of less than $1250 \times 10^{-6} \text{ mm}^2/\text{s}$ may be indicative of spinal infections and ADC values can normalize during effective treatment of spinal infections. The DWI of the spine correlates well with the presence or absence of spinal infections by microbiological sampling and may also be a useful marker for response to antibiotic therapy, complementing conventional MRI when the clinical picture is equivocal.

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Conflict of interest R.A. Dumont, N.N. Keen, C.W. Bloomer, B.S. Schwartz, J. Talbott, A.J. Clark, D.M. Wilson and C.T. Chin declare that they have no competing interests.

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