Journal of Visualized Experiments

Diagnosis and surgical treatment of human Brucellar spondylodiscitis

--Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE61840R2
Full Title:	Diagnosis and surgical treatment of human Brucellar spondylodiscitis
Corresponding Author:	Liang Gao, M.D., Ph.D. Saarland University Medical Center Homburg, Saarland GERMANY
Corresponding Author's Institution:	Saarland University Medical Center
Corresponding Author E-Mail:	lianggao@web.de
Order of Authors:	Yakefu Abulizi
	Xiaoyu Cai
	Tao Xu
	Chuanhui Xun
	Weibin Sheng
	Stephen L. Gao, M.D., Ph.D.
	Maierdan Maimaiti
Additional Information:	
Question	**Response**
Please indicate whether this article will be Standard Access or Open Access.	Standard Access (US$2,400)
Please indicate the **city, state/province, and country** where this article will be **filmed**. Please do not use abbreviations.	Homburg/Saar, Germany
Please confirm that you have read and agree to the terms and conditions of the author license agreement that applies below:	I agree to the Author License Agreement
Please specify the section of the submitted manuscript.	Medicine
Please provide any comments to the journal here.	

TITLE:

Diagnosis and Surgical Treatment of Human Brucellar Spondylodiscitis

AUTHORS AND AFFILIATIONS:

Yakefu Abulizi[1], Xiaoyu Cai[1,2,3], Tao Xu[1], Chuanhui Xun[1], Weibin Sheng[1], Liang Gao[2,3,*], Maierdan Maimaiti[1,*]

[1]Department of Spine Surgery, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

[2]Center of Experimental Orthopaedics, Saarland University Medical Center, Homburg/Saar, Germany

[3]Sino Euro Orthopaedics Network (SEON), Homburg/Saar, Germany

These authors contributed equally: Yakefu Abulizi and Xiaoyu Cai

Email Addresses of Co-authors:

Yakefu Abulizi (yakup0213@126.com)
Xiaoyu Cai (xiaoyucai0418@gmail.com)
Tao Xu (xt0005@sina.com)
Chuanhui Xun (842910290@qq.com)
Weibin Sheng (wbsheng@vip.sina.com)

Corresponding Authors:

Liang Gao, M.D., Ph.D.
lianggao@web.de
Tel: +49-06841-1624569

Maierdan Maimaiti, M.D.
mardanmmtmx@163.com
Tel: +86-0991-4365316

KEYWORDS:

Brucellosis; Brucellar spondylodiscitis; surgical treatment; transforaminal decompression; debridement; interbody fusion; internal fixation

SUMMARY:

We describe a clinical algorithm, based on decades of front-line experience of diagnosis and surgical treatment of human Brucellar spondylodiscitis in the largest medical center of the

China's Xinjiang Pastoral Area.

ABSTRACT:

Brucellar spondylodiscitis (BS) is the most prevalent and significant osteoarticular presentation of human Brucellosis, which is commonly manifested in pastoral communities. It is difficult to differentially diagnose and usually leads to irreversible neurologic deficits and spinal deformities. The initial diagnosis of BS is based on clinical findings and radiographic assessments, and the confirmed diagnosis should be established by the isolation of *Brucella* species from the blood and/or the standard tube agglutination test. Differential diagnosis of multifocal BS from either degenerative disc diseases or tuberculosis is especially highlighted. The surgical approach, either endoscopic or open, is demonstrated in detail, accompanied by radiographic evidence of structural compression or severe instability. Further, the crucial surgical steps, including single-stage transforaminal decompression, debridement, interbody fusion, and internal fixation, are explained. Moreover, perioperative care and postoperative rehabilitation are also addressed. Taken together, this clinical algorithm presents a practical guide that has yielded substantially satisfactory outcomes in the past decades, which can also be introduced for large-scale application to manage human BS, especially in endemic regions.

INTRODUCTION:

With more than half a million new cases annually, human Brucellosis has become a public health concern and remains an enormous burden worldwide[1-4]. BS, as the most common and severe osteoarticular manifestation of human Brucellosis, involves multiple structures including vertebral bodies, intervertebral disc, and paraspinal structures[5,6]. It occurs frequently in the lumbosacral zone and needs to be differentiated from other infectious diseases because of its nonspecific clinical characteristics[7,8]. Despite the significant advances in research over the past decades, accurate and timely diagnosis of BS is still a challenge for clinicians due to its late-onset radiological findings, slow growth rate in blood cultures, and the complexity of its serodiagnosis[9]. Therefore, human BS remains clinically underdiagnosed and underreported. Although the past decades have seen increasingly rapid advances in the introduction and popularization of several therapeutic guidelines, there is still no consensus for an optimal management modality[10]. Frequent relapses, treatment failure, and sequelae are reported constantly[11].

Of note, BS can be severely debilitating and disabling even if it is rarely fatal. If it is not treated appropriately, possible serious sequelae might be induced including persistent back pain, neurological deficiency, and even kyphotic deformity[12,13]. Antibiotic therapy is the core in the treatment of BS and yields generally promising outcomes[9]. However, certain patients may require surgical treatment if neurological dysfunction, spinal instability, abscess formation, intractable pain, or a previous unsatisfactory response to conservative treatments are observed. Surgical intervention remains controversial. Different surgical procedures for debridement and fusion have been described for infectious diseases of the lumbar spine including anterior-only,

posterior-only, and combined approaches[14-16]. Here, diagnostic guidelines have been presented for human BS and for the single-stage surgical treatment with transforaminal decompression, debridement, interbody fusion, and internal fixation via a posterior-only approach. A detailed protocol of this method is given below.

PROTOCOL:

The study was approved by the ethical committee of the First Affiliated Hospital of Xinjiang Medical University, China[17].

1. Informed Consent

1.1. Obtain the patient's informed consent after explaining the details of the surgical procedure, postoperative prognosis, and possible complications (infection, epidural hematoma, spinal cord injury, failure of internal fixation, and cerebrospinal fluid leakage).

1.2. Explain the other risks generally associated with using an implant (e.g., internal fixation system) such as allergic or immune system responses to the implanted materials.

1.3. Rule out any contraindications of the patients.

2. Patient selection

2.1. Diagnosis of BS

2.1.1. Base the initial diagnosis of BS on the clinical manifestations and radiographic assessments[8].

2.1.1.1. Look for clinical manifestations and symptoms such as back pain, undulant fever, malaise, profuse night sweating, weight loss, polyarthralgia, and generalized myalgias[8,18].

2.1.1.2. In plain radiographs, look for osteophytes, sclerosis, osteoporosis of the vertebral body, and narrowing of the intervertebral disc space, with posterior elements being mostly preserved.

NOTE: Central necrosis is mostly not present, and the vertebral body is mostly morphologically intact (**Figure 1**)[18].

2.1.1.3. In computed tomography (CT), look for small bone destruction lesions at vertebral edges that occur in multiple areas, and for hyperplastic and sclerotic lesions that are more prominent and often admixed (**Figure 1**)[18].

NOTE: CT features are divided into those of vertebral osteolysis and vertebral hyperplastic sclerosis stages[19].

2.1.1.4. As magnetic resonance imaging (MRI) is the best imaging tool for BS diagnosis (**Figure 1**)[20-22], look for characteristic MRI findings that can be classified into five subsets: discitis, spondylitis, paraspinal/psoas abscess, appendicitis, and compound (**Table 1**).

2.1.2. Confirm the diagnosis according to the presence of the following three criteria[23]:

2.1.2.1. Ensure that the clinical picture is compatible with that of BS.

2.1.2.2. Confirm the absence of any etiology other than Brucellosis that can explain spinal involvement.

2.1.2.3. Confirm that the results of the standard tube agglutination test reveal a titer of antibodies to Brucella of ≥ 1/160[24].

2.2. Indications for surgery[23]

2.2.1. Look for persistent pain due to spinal instability, which is caused by severe disc or/and vertebral destruction.

2.2.2. Confirm severe or progressive neurologic dysfunction that can be attributed to nerve root compression by inflammatory granuloma or epidural abscesses.

2.2.3. Confirm that there is no response to oral antibiotic therapy (e.g., doxycycline, rifampicin, streptomycin).

3. Preoperative procedure

3.1. Administer a chemotherapy regimen (oral doxycycline 200 mg/day plus oral rifampicin 600–900 mg/day)[25] to all patients.

3.2. Offer surgical interventions to patients who have surgical indications after two weeks of antibiotic treatment.

4. Operative procedures for single-stage transforaminal decompression, debridement, interbody fusion, and internal fixation via posterior-only approach

4.1. Place the patient on a four-poster frame in the prone position after administration of general anesthesia with endotracheal intubation.

4.2. Disinfect the surgical area with 1% iodophor, and then cover with standard surgical towels (see **Table of Materials**).

4.3. Make a midline longitudinal incision over the spinous process of the infected vertebra.

4.4. Expose the posterior spinal structures including lamina, facet joints, and transverse processes.

4.5. Place the pedicle screws (diameter: 5–7 mm, length: 20–65 mm) into both sides of the affected vertebra with the assistance of C-arm fluoroscopy[26-28] (see **Table of Materials**).

NOTE: To achieve adequate debridement, place the pedicle screws closest to the superior or inferior endplate and away from the infection lesions. Fix the screws to a temporary rod (diameter: 5.5 mm) on the less involved side (see **Table of Materials**).

4.6. Perform the facetectomy at the involved level on the side where neurologic and radiological manifestations are more severe[29].

4.7. Debride the epidural abscess, granulation tissues, infected disc with curettes, and scrape the vertebral endplates. Meanwhile, protect the nerve root with a nerve retractor (see **Table of Materials**).

NOTE: Perform a blunt dissention to adequately drain the psoas abscess from the posterolateral as thoroughly as possible. Analyze the tissues and abscess histopathologically[30,31]. Noncaseating granulomatous inflammation with predominant lymphocyte and monocytes infiltration is the typical histopathologic finding of BS[32]. If the result of decompression and debridement is not satisfactory after a unilateral facetectomy, perform the same procedure on the opposite side.

4.8. After adequately removing the lesions and decompressing the neural elements, use 1000–2000 mL of 0.9% sodium chloride solution for surgical area irrigation to clear the residual Brucellar lesion (see **Table of Materials**).

4.9. Saturate an absorbable gelatin sponge (60 mm x 20 mm x 5 mm) with 0.75–1.5 g of streptomycin, and use it for both hemostasis and local antibiotic treatment within the surgical area (see **Table of Materials**).

4.10. Implant the locally harvested autogenous bone into the defected space for interbody fusion with a bone graft funnel and bone pusher (see **Table of Materials**).

4.11. Fix pedicle screws (diameter: 5–7 mm, length: 20–65 mm) on both sides to the pre-contoured rods (diameter: 5.5 mm) under a slight compression[33,34] (see **Table of Materials**).

4.12. Drain and close the lesion[35] (see **Table of Materials**).

5. Postoperative management

5.1. Administer intravenous antibiotic (cefuroxime sodium, 1.5 g, q12h) for 1–3 days postoperatively.

5.2. Remove the drainage tube when the drainage volume is less than 30 mL per day.

5.3. Administer the aforementioned antibiotic therapies with doxycycline (200 mg/day) and rifampicin (600–900 mg/day) for at least 3 months (range 3–12 months) after surgery.

5.4. Ensure the patient remains in bed for 3–5 days postoperatively, and allow for mobilization by providing effective support with a lumbosacral brace.

5.5. Perform plain radiography before the patient's discharge to evaluate the location of the graft and instrumentation.

5.6. Ensure at least 2–3 months of brace protection.

6. Follow-up evaluation

6.1. Follow up with the patients at 1, 3, and 6 months postoperatively and then annually.

6.2. Monitor the infection by measuring erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

6.3. Evaluate interbody fusion by radiography at the last follow-up.

NOTE: Assess graft fusion with the radiologic criteria of Bridwell[36]. Perform CT scans if there is any uncertainty regarding plain radiographs.

6.4. Utilize the visual analogue scale (VAS) to assess back pain.

6.5. Evaluate pain-related dysfunction with the Oswestry Disability Index (ODI).

6.6. Use the Japanese Orthopedic Association (JOA) scale to evaluate the functional outcomes.

REPRESENTATIVE RESULTS:

This paper describes a prospective, non-randomized, controlled study of 32 consecutive BS patients who were treated by a single-stage transforaminal decompression, debridement, interbody fusion, and internal fixation via a posterior-only approach in the Department of Spine Surgery, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China. **Figure 1** shows a typical case in this study.

The clinical symptoms are summarized in **Table 2**. Patients generally complained of chronic back pain with signs of neurological impairment. Brucella agglutination level was ≥1/160 in all patients; positive blood culture results were observed in 8 cases (25%). According to the aforementioned

diagnostic criteria, all patients were indicated as candidates for a single-stage surgical treatment. The mean duration of surgery was 133.1 ± 36.6 min, and the mean blood loss was 378.1 ± 187.9 ml (range 120–800 mL). Histopathologic examinations on biopsy samples obtained from the paravertebral tissue indicated noncaseating granulomatous lesions infiltrated by inflammatory cells (lymphocyte and monocytes) with various spatial extents (**Figure 2**). Patients were followed up for over 12 months (24.9 ± 8.2 months). Postoperative complications, including superficial wound infection, was seen in 1 patient at postoperative day 10 and treated successfully with intravenous antibiotics. Deep wound infection and sinus formation were perceived in 2 patients with a history of diabetes and treated by a revision surgery and extended intravenous antibiotics. No clinical or radiological relapses were observed throughout the entire follow-up phase.

Radiating pain were immediately relieved after surgery, and significant decrease in constitutional symptoms was achieved within the first postoperative month. ESR and CRP levels returned to normal levels by the third postoperative month. The preoperative levels of ESR (46.03 ± 12.73) and CRP (41.47 ± 41.74) declined to 8.86 ± 3.05 and 4.56 ± 1.75, respectively, in postoperative month 3. The significant improvement in VAS, ODI, and JOA scores between the preoperative assessment and final follow-up are shown in **Table 3**.

The interbody fusion rate was 93.8% at 12 months postoperatively according to the Bridwell criteria. Grade I and II fusion was seen in 30 (93.75%) and 2 patients (6.25%), respectively. These two patients with grade II fusion were evaluated with lateral flexion/extension radiography and CT examinations; no noticeable movement or gap was detected within the interbody area.

FIGURE AND TABLE LEGENDS:

Figure 1: A 69-year-old male presented with L3–L4 Brucellar spondylodiscitis. (**A**) Anteroposterior view shows hyperplastic changes on the lateral edge of the L3–L4 vertebral body and formation of osteophytes (arrow). (**B**) Lateral view shows disc space narrowing and anterior osteophyte formation (parrot's beak). (**C, D**) Sagittal T1- and T2-weighted MRI shows lesions involved in L3–L4 vertebral bodies and intervertebral disc, accompanied by epidural abscess and inflammatory granuloma formation. (**E, F**) Transverse MRI and CT demonstrate spinal canal stenosis. (**G, H**) Postoperative plain radiograph shows intervertebral bone grafting and instrumentation. (**I**) Twelve-month postoperative X-ray showed a firm fixation and interbody fusion. This figure has been modified from Abulizi et al.[37]. Abbreviations: MRI = magnetic resonance imaging; CT = computed tomography.

Figure 2: Histological analysis of lesion biopsies. Hematoxylin and eosin staining shows lymphocyte and monocyte infiltration in the samples biopsied from affected paravertebral tissue. Yellow arrows indicate lymphocytes, and red arrows indicate monocytes. Scale bar = 50 μm.

DISCUSSION:

The present guideline of diagnosis and surgical treatment of human BS with a detailed protocol and satisfactory clinical evidence from representative cohorts shows clinical efficacy and is proposed for large-scale application to manage human BS, especially in endemic regions. The first critical step in the treatment of BS is to make the correct diagnosis. The diagnosis of BS needs to be differentiated from spinal tuberculosis compared to which BS is relatively less bone-destructive and usually responds effectively to antibiotic treatment[38]. In addition, noticeable neurological deficits, persistent pain, spinal instability, and paravertebral abscesses can be observed in BS patients in the later stages. Surgical treatment should be considered as the last resort for patients who do not respond well to antibiotic therapy[39].

Surgical outcomes of BS are rarely elucidated in the literature, and the role of surgery treatment remains controversial. BS typically occurs in the lumbosacral region, particularly at the L4–L5 and L5–S1 levels[8,20,40]. Surgical debridement, decompression, and fusion via multiple approaches have been proposed[14,16,41]. As the gold standard, the anterior-only approach ensures a direct access with adequate exposure to the spinal lesion. However, anterior instrumentation at L4–L5 and L5–S1 is potentially dangerous and insubstantial due to the complicated regional anatomy[16,41,42]. Furthermore, most patients displayed bilateral nerve root compression, epidural abscess formation, and spinal stenosis. Therefore, it may not be possible to achieve complete decompression of the contralateral nerve root via the anterior approach.

The second critical step is to utilize transforaminal lumbar interbody fusion (TLIF) technology during surgery in the form of a modification of posterior lumbar interbody fusion. This can minimize traction force on the dura and nerve root during surgery and therefore, decrease the risk of postoperative complications[43]. Posterior-only approaches are reported increasingly as alternative surgical therapy for selective spinal tuberculosis[41]. Single-stage transforaminal decompression, debridement, interbody fusion, and internal fixation via posterior-only approach is generally reported in the treatment of spinal tuberculosis. However, obtaining adequate debridement and reconstruction of anterior column defects has been considered insufficient. Furthermore, this strategy is also considered unsuitable for patients with severe vertebral collapse and apparent paravertebral abscess formation[44,45].

Unlike spinal tuberculosis, destruction in BS occurs mainly around and within the intervertebral disc, and vertebral collapse and local kyphosis are less likely to occur. Therefore, debridement and intervertebral bone graft fusion via a posterior approach is an effective and safe procedure for BS[46]. Brucellosis can affect the facets, which may be the reason for severe back pain in these patients. Accordingly, a facetectomy followed by intervertebral debridement and fusion may be more effective than traditional posterior approaches. In this study, no intraoperative complications were observed, and chronic back pain and radiating pain were relieved significantly in the present cohorts after surgery. Besides, no recurrence was reported during the follow-up period. Therefore, this single-stage surgical intervention with transforaminal decompression, debridement, interbody fusion, and internal fixation via the posterior-only approach is clinically effective for surgical candidates of human BS.

The third critical step is to plant the pedicle screw into the affected vertebra to achieve a shorter

segmental fixation. The BS lesion mainly involves the structures within the intervertebral space and causes less bony destruction compared to other infectious diseases that occur in the same region. Therefore, the posterior approach has been suggested to be more convenient and minimally invasive during the process to access the involved structures, allowing for a possibly thorough removal of the lesion and complete decompression of bilateral nerve roots. Posterior bone graft implantation can also be straightforwardly performed via the far-lateral portion of vertebral foramen. As BS-related destruction of vertebral body is commonly not severe, the transpedicular screws can still be implanted in the affected vertebra with a minimal surgical exposure and shorter segmental fixation[47]. In conclusion, application of the aforementioned protocol for timely diagnosis and treatment of BS patients can achieve satisfactory short-term clinical outcomes. Further popularization of this single-stage surgery on a large-scale for surgical candidates, especially in endemic regions, might be helpful to reduce its global burden.

ACKNOWLEDGMENTS:

Dr. Xiaoyu Cai acknowledges the financial support from the China Scholarship Council. This work was funded by the Natural Science Foundation of Xinjiang Province, P. R. China (no. 2016B03047-3).

DISCLOSURES:

The authors have nothing to disclose.

REFERENCES:

1 Rubach, M. P., Halliday, J. E., Cleaveland, S., Crump, J. A. Brucellosis in low-income and middle-income countries. *Current Opinion in Infectious Diseases.* **26** (5), 404–412, (2013).

2 Atluri, V. L., Xavier, M. N., de Jong, M. F., den Hartigh, A. B., Tsolis, R. M. Interactions of the human pathogenic Brucella species with their hosts. *Annual Review of Microbiology.* **65**, 523-541, (2011).

3 Tan, K.-K. et al. Full genome SNP-based phylogenetic analysis reveals the origin and global spread of Brucella melitensis. *BMC Genomics.* **16** (1), 93–93 (2015).

4 Pappas, G., Papadimitriou, P., Akritidis, N., Christou, L., Tsianos, E. V. The new global map of human brucellosis. *The Lancet Infectious Diseases.* **6** (2), 91–99 (2006).

5 Harman, M., Unal, Ö., Onbaşi, K. T., Kıymaz, N., Arslan, H. Brucellar spondylodiscitis: MRI diagnosis. *Clinical Imaging.* **25** (6), 421–427 (2001).

6 Lee, H. J., Hur, J. W., Lee, J. W., Lee, S. R. Brucellar spondylitis. *Journal of Korean Neurosurgical Society.* **44** (4), 277–279 (2008).

7 Pourbagher, A. et al. Epidemiologic, clinical, and imaging findings in brucellosis patients with osteoarticular involvement. *AJR American Journal of Roentgenology.* **187** (4), 873–880 (2006).

8 Ulu-Kilic, A. et al. Update on treatment options for spinal brucellosis. *Clinical Microbiology and Infection.* **20** (2), O75–82 (2014).
9 Araj, G. F. Update on laboratory diagnosis of human brucellosis. *International Journal of Antimicrobial Agents.* **36** (Supplement 1), S12–17 (2010).
10 Alp, E., Doganay, M. Current therapeutic strategy in spinal brucellosis. *International Journal of Infectious Diseases.* **12** (6), 573–577 (2008).
11 Solís García del Pozo, J., Solera, J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. *PLoS One.* **7** (2), e32090 (2012).
12 Nas, K. et al. Management of spinal brucellosis and outcome of rehabilitation. *Spinal Cord.* **39** (4), 223–227 (2001).
13 Chelli Bouaziz, M., Ladeb, M. F., Chakroun, M., Chaabane, S. Spinal brucellosis: a review. *Skeletal Radiology.* **37** (9), 785–790 (2008).
14 Gregori, F. et al. Treatment algorithm for spontaneous spinal infections: A review of the literature. *Journal of Craniovertebral Junction and Spine.* **10** (1), 3–9 (2019).
15 Lener, S. et al. Management of spinal infection: a review of the literature. *Acta Neurochirurgica.* **160** (3), 487–496 (2018).
16 Sansalone, C. V. et al. Anterior approach to the spine. Role of the general surgeon, techniques and surgical complications. The 10-year experience of the Niguarda Hospitals. *Journal of Neurosurgical Sciences.* **55** (4), 357–363 (2011).
17 Gao, L., Guo, R., Han, Z., Liu, J., Chen, X. Clinical trial reporting. *Lancet.* **396** (10261), 1488–1489 (2020).
18 Tu, L. et al. Imaging-assisted diagnosis and characteristics of suspected spinal Brucellosis: A retrospective study of 72 cases. *Medical Science Monitor.* **24**, 2647–2654 (2018).
19 Zhao, Y. T., Yang, J. S., Liu, T. J., He, L. M., Hao, D. J. Sclerosing vertebra in the spine: typical sign of spinal brucellosis. *Spine Journal.* **15** (3), 550–551 (2015).
20 Yang, X., Zhang, Q., Guo, X. Value of magnetic resonance imaging in brucellar spondylodiscitis. *La Radiologia Medica.* **119** (12), 928–933 (2014).
21 Buzgan, T. et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *International Journal of Infectious Diseases.* **14** (6), e469–478 (2010).
22 Bai, Y., Qiao, P. F., Gao, Y., Niu, G. MRI characteristics of brucellar spondylodiscitis in cervical or thoracic segments. *Biomedical Research-Tokyo.* **28**, 7820–7825 (2017).
23 Katonis, P., Tzermiadianos, M., Gikas, A., Papagelopoulos, P., Hadjipavlou, A. Surgical treatment of spinal brucellosis. *Clinical Orthopaedics and Related Research.* **444**, 66–72 (2006).
24 Yang, B., Hu, H., Chen, J., He, X., Li, H. The evaluation of the clinical, laboratory, and radiological findings of 16 cases of Brucellar spondylitis. *BioMed Research International.* **2016**, 8903635–8903635 (2016).
25 Liang, C., Wei, W., Liang, X., De, E., Zheng, B. Spinal brucellosis in Hulunbuir, China, 2011-2016. *Infection and Drug Resistance.* **12**, 1565–1571 (2019).
26 Merloz, P. et al. Fluoroscopy-based navigation system in spine surgery. *Proceedings of the Institution of Mechanical Engineers, Part H.* **221** (7), 813–820 (2007).
27 Foley, K. T., Simon, D. A., Rampersaud, Y. R. Virtual fluoroscopy. *Operative Techniques in Orthopaedics.* **10**, 77–81 (2000).
28 Foley, K. T., Simon, D. A., Rampersaud, Y. R. Virtual fluoroscopy: computer-assisted

fluoroscopic navigation. *Spine.* **26**, 347–351 (2001).
29 Kang, K. et al. Partial facetectomy for lumbar foraminal stenosis. *Advances in Orthopedics.* **2014**, 534658 (2014).
30 Bostian, P. A. et al. Novel rat tail discitis model using bioluminescent *Staphylococcus aureus*. *Journal of Orthopaedic Research.* **35** (9), 2075–2081 (2017).
31 Scott, M. A. et al. Brief review of models of ectopic bone formation. *Stem Cells and Development.* **21** (5), 655–667 (2012).
32 Li, T., Liu, T., Jiang, Z., Cui, X., Sun, J. Diagnosing pyogenic, brucella and tuberculous spondylitis using histopathology and MRI: A retrospective study. *Experimental and Therapeutic Medicine.* **12** (4), 2069–2077 (2016).
33 Foley, K. T., Gupta, S. K. Percutaneous pedicle screw fixation of the lumbar spine: preliminary clinical results. *Journal of Neurosurgery.* **97** (1 Suppl), 7–12 (2002).
34 Verma, K., Boniello, A., Rihn, J. Emerging techniques for posterior fixation of the lumbar spine. *Journal of the American Academy of Orthopaedic Surgeons.* **24** (6), 357–364 (2016).
35 Stoker, D. L.; Jain, S. K. Drains in Surgery. in *Basic Surgical Skills and Techniques*. Jain, S.K., Stoker, D. L., Tanwar, R. (Eds) Jaypee Brothers Medical Publishers (P) Ltd., doi: 10.5005/jp/books/18099_10 (2018).
36 Bridwell, K. H., Lenke, L. G., McEnery, K. W., Baldus, C., Blanke, K. Anterior fresh frozen structural allografts in the thoracic and lumbar spine. Do they work if combined with posterior fusion and instrumentation in adult patients with kyphosis or anterior column defects? *Spine.* **20** (12), 1410–1418 (1995).
37 Abulizi, Y., Liang, W.-D., Muheremu, A., Maimaiti, M., Sheng, W.-B. Single-stage transforaminal decompression, debridement, interbody fusion, and posterior instrumentation for lumbosacral brucellosis. *BMC Surgery.* **17** (1), 82 (2017).
38 Ioannou, S. et al. Efficacy of prolonged antimicrobial chemotherapy for brucellar spondylodiscitis. *Clinical Microbiology and Infection.* **17** (5), 756–762 (2011).
39 Herren, C. et al. Spondylodiscitis: diagnosis and treatment options. *Deutsches Arzteblatt International.* **114** (51–52), 875–882 (2017).
40 Erdem, H. et al. Comparison of brucellar and tuberculous spondylodiscitis patients: results of the multicenter "Backbone-1 Study". *Spine Journal.* **15** (12), 2509–2517 (2015).
41 Garg, B., Kandwal, P., Nagaraja, U. B., Goswami, A., Jayaswal, A. Anterior versus posterior procedure for surgical treatment of thoracolumbar tuberculosis: A retrospective analysis. *Indian Journal of Orthopaedics.* **46** (2), 165–170 (2012).
42 Bian, Z., Gui, Y., Feng, F., Shen, H., Lao, L. Comparison of anterior, posterior, and anterior combined with posterior surgical treatment of thoracic and lumbar spinal tuberculosis: a systematic review. *Journal of International Medical Research.* **48** (2), 300060519830827 (2019).
43 Yan, D.-L., Pei, F.-x., Li, J., Soo, C.-l. Comparative study of PILF and TLIF treatment in adult degenerative spondylolisthesis. *European Spine Journal.* **17** (10), 1311–1316 (2008).
44 Schwender, J. D., Holly, L. T., Rouben, D. P., Foley, K. T. Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. *Journal of Spinal Disorders and Techniques.* **18** (Supplement 1), S1–6 (2005).
45 Rouben, D., Casnellie, M., Ferguson, M. Long-term durability of minimal invasive posterior transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. *Journal of Spinal Disorders and Techniques.* **24** (5), 288–296 (2011).

46 Chen, Y. et al. One-stage surgical management for lumbar Brucella spondylitis by posterior debridement, autogenous bone graft and instrumentation: a case series of 24 patients. *Spine.* **42** (19), e1112–e1118 (2017).

47 Choma, T., Pfeiffer, F., Vallurupalli, S., Mannering, I., Pak, Y. Segmental stiffness achieved by three types of fixation for unstable lumbar spondylolytic motion segments. *Global Spine Journal.* **2** (2), 79–86 (2012).

Figure 1

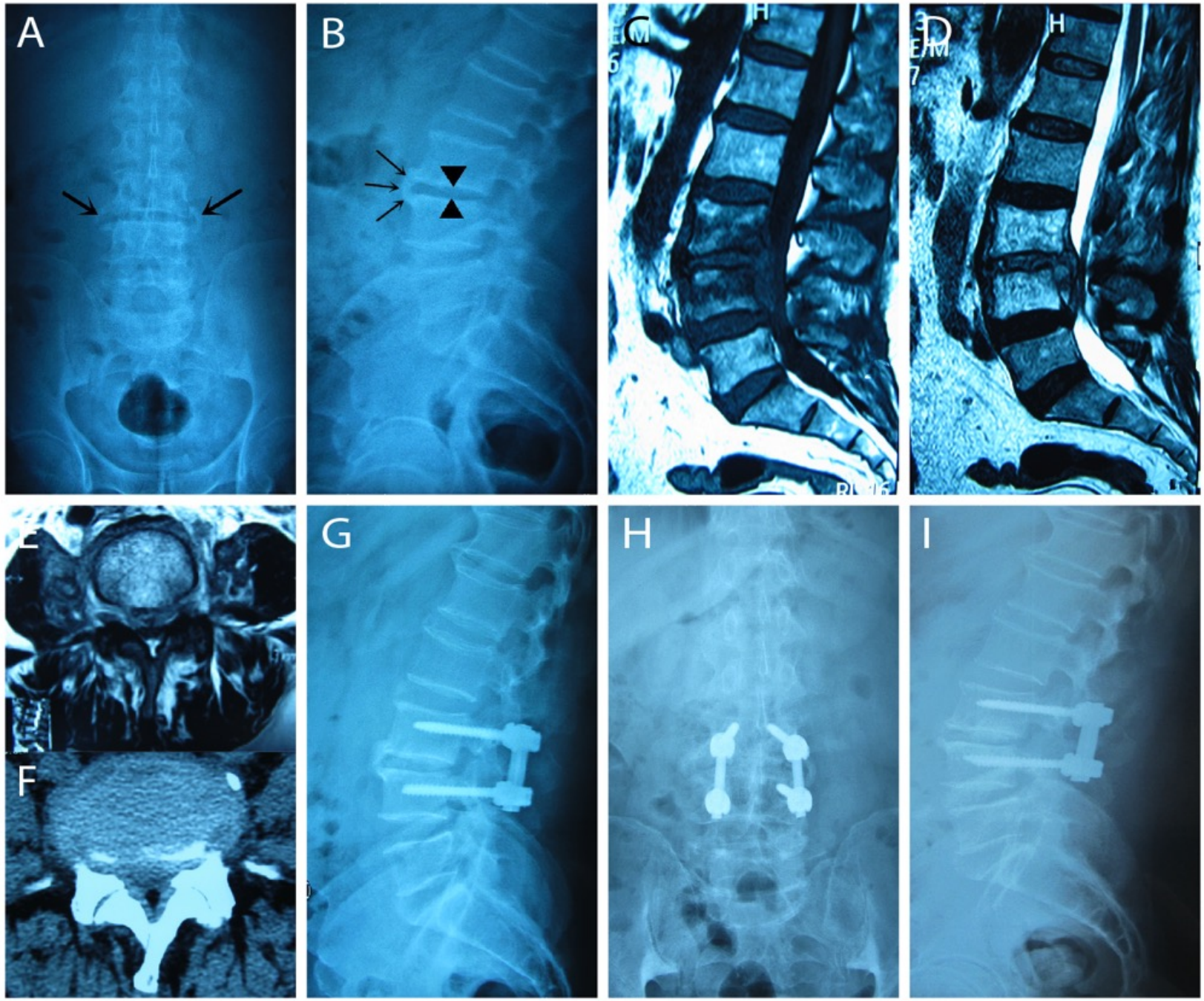

Figure 2

Click here to access/download;Figure;Figure 2.pdf

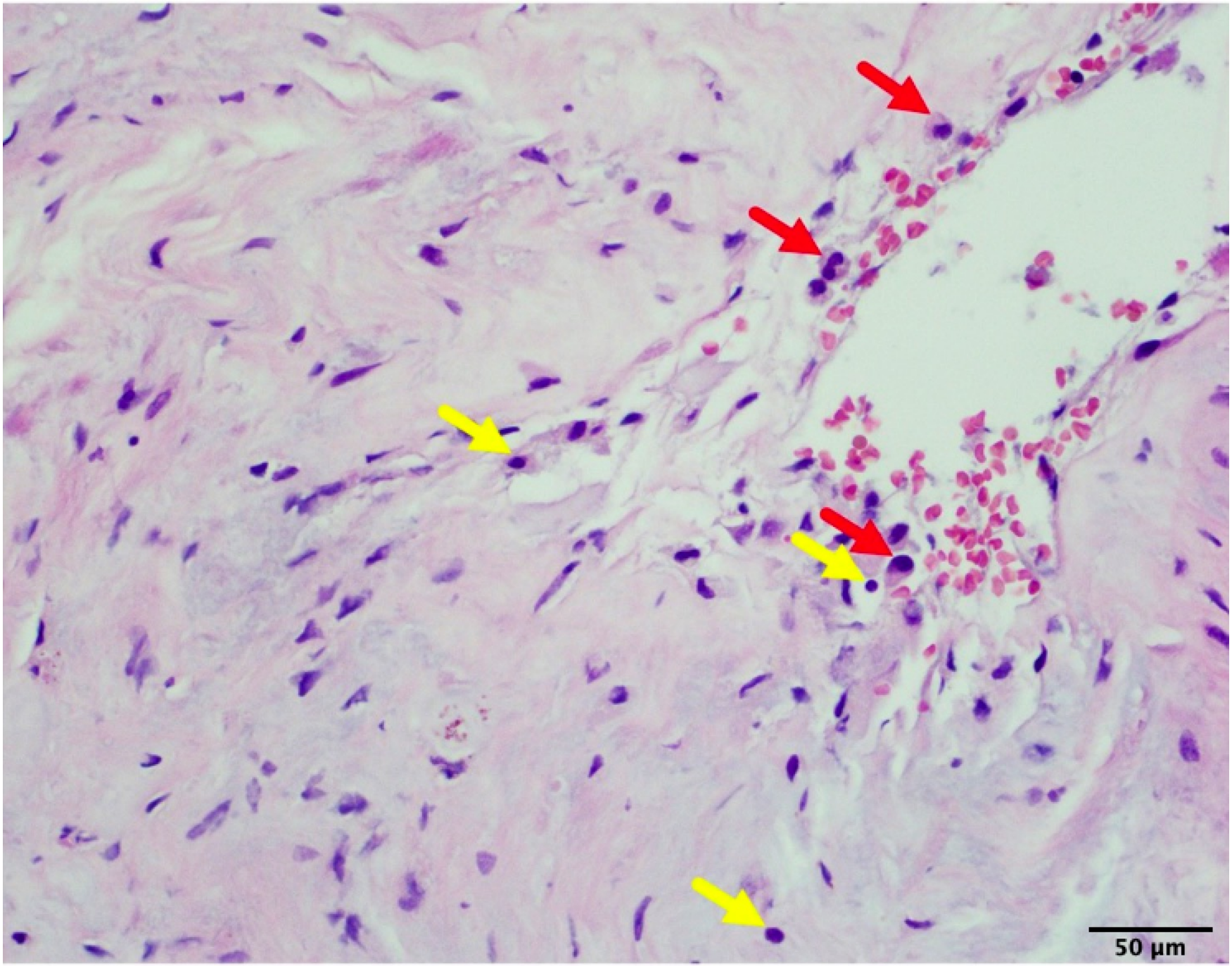

Table 1

Classification	MRI characteristics
Discitis	Regional inflammation involving intervertebral disc
	Disc space narrowing
	Low signal on T1-weighted image mixing high signal on T2-weighted image
Spondylitis	Regional inflammation involving adjacent vertebrae
	Vertebrae diffuse marrow edema
	Homogeneous or uneven low signal on T1-weighted image of vertebrae
Paraspinal/psoas abscess	Regional inflammation involving paraspinal or psoas
	Paravertebral abscess
	Psoas abscess
Appendicitis	Regional inflammation involving appendicitis
	Low signal on T1-weighted image
	High signal on T2-weighted image
Compound	Endemic inflammation involving two or more parts of vertebral and paravertebral structures
	T1-weighted image reveals incomplete heterogeneous hypointensity
	T2-weighted image reveals hyperintensity

This table has been modified from Bai et al.[22].

Table 2

Symptoms	**Number of patients (%)**
Spinal symptoms	
-Back pain	31 (96.9%)
-Radiculopathy	22 (68.8%)
Constitutional symptoms	
-Fever	27 (84.4%)
-Sweating	18 (56.3%)
-Weakness of fatigue	14 (43.8%)
-Weight loss	9 (28.1%)
-Hepatomegaly	7 (21.9%)
-Arthralgia	4 (12.5%)

This table has been modified from Abulizi et al.[37].

Table 3

Parameters	Preoperative	Last follow-up	Improvement rate (%)	*P* value
VAS	5.19 ± 1.47	0.47 ± 0.67	90.9	<0.05
ODI	55.31 ± 9.16	10.72 ± 3.23	80.7	<0.05
JOA	12.38 ± 2.98	26.13 ± 2.58	82.7	<0.05

Scores were demonstrated as Mean ± Standard deviation. Abbreviations: VAS = visual analogue scale; ODI = Oswestry Disability Index; JOA = Japanese Orthopaedic Association. This table has been modified from Abulizi et al.[37].

Name of Material/Equipment	Company	Catalog Number
Absorbable gelatin sponge	Chuhe Medical Devices Co., Ltd.	AWZ-035-XSMJHM-AD.
Box curette	Rudischhauser GmbH	R16-BD2310-ST
Bone graft funnel	Rudischhauser GmbH	R19-K00000-FU
Bone pusher	Rudischhauser GmbH	R19-EK4110-00
Bone rongeur	Vet Direct & VETisco	EC-RG-BO-180
Iodophor (1%)	Beijing SanYao Science & Technology Development Co.	14975I
Nerve retractor	Rudischhauser GmbH	R16-HD1710-00
Osteotome 1	Rudischhauser GmbH	R16-CD2310-08
Osteotome 2	Rudischhauser GmbH	R16-CD2310-10
Pedicle screw	DePuy Synthes Companies	199723540
	DePuy Synthes Companies	199723545
	DePuy Synthes Companies	199723550
	DePuy Synthes Companies	199723640
	DePuy Synthes Companies	199723645
	DePuy Synthes Companies	199723650

	DePuy Synthes Companies	199723740	
	DePuy Synthes Companies	199723745	
	DePuy Synthes Companies	199723750	
Securo Drain	Dispomedica GmbH		1.33578
Sterile 0.9% Sodium Chloride Solution	Beijing SanYao Science & Technology Development Co.	15935S	
Straight rod	DePuy Synthes Companies	1797-62-480	
Streptomycin sulfate, Powder	Beijing SanYao Science & Technology Development Co.	P06-11025P	

Comments/Description
60 mm x 20 mm x 5 mm
Width: 7.5 mm; height: 5.9 mm; shaft: 6.0 mm (diameter); working length: 223 mm
Working length: 246.5 mm; End diameter: 42 mm; shaft: 6.4 mm (diameter)
Working length: 220 mm; shaft: 6.0 mm (diameter)
Length: 180 mm
Volume: 500 mL
Width: 10 mm; length: 145 mm; shaft: 5.0 mm (diameter)
Width: 8 mm; height: 3 mm; shaft: 6.0 mm (diameter); working length: 223 mm
Width: 10 mm; height: 3 mm; shaft: 6.0 mm (diameter); working length: 223 mm
Length: 40 mm; diameter: 5.0 mm
Length: 45 mm; diameter: 5.0 mm
Length: 50 mm; diameter: 5.0 mm
Length: 40 mm; diameter: 6.0 mm
Length: 45 mm; diameter: 6.0 mm
Length: 50 mm; diameter: 6.0 mm

Length: 40 mm; diameter: 7.0 mm

Length: 45 mm; diameter: 7.0 mm

Length: 50 mm; diameter: 7.0 mm

Size: 7 mm; Length of perforation: 15 cm; Total length: 80 cm; Reservior size: 150 ml

Volume: 500 mL

Length: 480 mm; diameter: 5.5 mm

Size: 1 g

Point-by-point response to the Editorial and Reviewers' comments

We are very glad to receive the comments from the Editor and Reviewers for our manuscript. We wish to thank the Editor and Reviewers very much for their constructive and cautious reviews and insightful comments to improve the quality of the manuscript. We have addressed all the concerns below and made changes to the manuscript where appropriate. We believe that the manuscript has been significantly improved and strengthened as a result of their recommendations. We appreciate the opportunity to submit the revised manuscript very much, and do hope that, with these changes and clarifications, our work might be suitable for publication in the *Journal of Visualized Experiments.*

Once again, we thank you for the time you put in reviewing our paper and look forward to meeting your expectations.

Sincerely,

Liang Gao, M.D., Ph.D.

Maierdan Maimaiti, M.D.

Editorial comment 1: Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling and grammar. Please define all abbreviations at first use and use American English.

Author response: We would like to thank the Editor for this important and useful comment. We thank the Editor very much for this opportunity to proofread the manuscript to cheek the spelling and grammar. We have defined all abbreviations at first use.

Author action: We rewrote the following sentences with American English to read as "*Despite the research progress significantly in past decades, accurate and timely diagnosis of BS still post a challenge to clinicians due to its late-onset radiological findings, slow growth rate in blood cultures, and complexity of its serodiagnosis*." (lines 64-67)

"*Most bone destruction lesions at vertebral edges are small and occur on multiple areas. The hyperplastic and sclerotic lesions are more prominent and often admixed (Figure 1)*." (lines115-116)

"*MRI is the best imaging tool for BS diagnose human BS (Figure 1). The characteristic MRI findings can be classified into 5 subsets including discitis, spondylitis, paraspinal/psoas abscess, appendicitis, and compound (Table 1)*." (lines119-121)

"*Patients who have surgical indications will receive surgical intervention after two weeks of antibiotic treatment*." (lines147-148)

"*Expose the posterior spinal structures including lamina, facet joints, and transverse processes*." (lines 162-163)

"*NOTE: In order to achieve adequate debridement, the pedicle screws are placed closest to the superior or inferior endplate and away from infection lesions. Screws are fixed to a temporary rod (diameter: 5.5 mm) on the less involved side (see Table of Materials).”* (lines 168-170)

“Meanwhile, the nerve root needs to be protected with a nerve retractor (see Table of Materials).” (lines 176-177)

“*NOTE: The psoas abscess should be adequately drained from posterolateral under a blunt dissection as thoroughly as possible. Removed tissues and abscess should be sent for histopathologic examination*.” (lines 179-181)

“If the result of decompression and debridement is not satisfied after a unilateral facetectomy, the same procedure should be performed on the opposite side.” (lines 182-184)

“Absorbable gelatin sponge (60mm x 20mm x 5mm) saturated with 0.75 – 1.5g streptomycin is used for both hemostasis and local antibiotic treatment within the surgical area (see Table of Materials).” (lines 190-192)

“Drainage and lesion closure are performed accordingly (see Table of Materials).” (line 200)

“*Histopathologic examinations on biopsy samples obtained from the paravertebral tissue indicated noncaseating granulomatous lesions infiltrated by inflammatory cells (lymphocyte and monocytes) with various spatial extents (Figure 2).”* (lines 249-251)

“*The diagnosis of BS needs to be differentiated from spinal tuberculosis compared to which BS is relatively less bone destructive and usually responds effectively to the antibiotic treatment. In addition, noticeable neurological deficits, persistent pain, spinal instability, and paravertebral abscesses can be observed in BS patients in late stages. For patients who did not respond well to antibiotic treatment, surgical treatment should be considered as the last resort for these cases*.” (lines 294-299)

“*At this stage, single-stage transforaminal decompression, debridement, interbody fusion, and internal fixation via posterior-only approach is generally reported in the treatment of spinal tuberculosis.”* (lines 315-317)

"*The BS lesion mainly involves the structures within intervertebral space and yields less bony destruction compared to other infectious diseases that occur in the same region. Therefore, the posterior approach is suggested as more convenient and minimally invasive during the process to access the involved structures, allowing for a possible thoroughgoing removal of the lesion and complete decompression of bilateral nerve roots*." (lines 333-335)

Editorial comment 2: Unfortunately, there are sections of the manuscript that show overlap with previously published work. Please revise the following lines: 3.2 (143-145), note after 4.5 (lines 165-168), lines 219-232 (5.2-5.6: changing to imperative tense may reduce/eliminate overlap), figure 1 legend (lines 269-277). Tables 1 and 3 (and parts of Table 2) show a lot of overlap. Please obtain explicit copyright permission to reuse any tables and figures from a previous publication. Explicit permission can be expressed in the form of a letter from the editor or a link to the editorial policy that allows re-prints. Please upload this information as a .doc or .docx file to your Editorial Manager account. The Figure/Table must be cited appropriately in the Figure Legend/Table footnote, i.e. "This figure/table has been modified from[1]."

Author response: We would like to thank the Editor for this great comment.

Author action: We rewrote the above-mentioned sentences to read as "*1.2. Explain the other risks generally associated with using an implant (e.g., internal fixation system), such as allergic or immune system responses to the implanted materials*." (lines 96-97)

"*NOTE: In order to achieve adequate debridement, the pedicle screws are placed closest to the superior or inferior endplate and away from infection lesions. Screws are fixed to a temporary rod (diameter: 5.5 mm) on the less involved side (see Table of Materials).”* (lines 169-171)

“6.2. Monitor the activity of infection with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

6.3. Evaluate the interbody fusion by radiographs at the last follow-up.

NOTE: Assess the graft fusion with the radiologic criteria of Bridwell[38]. Perform the CT scans if there is an uncertainty on plain radiographies.

6.4. Utilize the visual analogue scale (VAS) to assess the back pain.

6.5. Evaluate the pain-related dysfunction with the Oswestry Disability Index (ODI).

6.6. Use the Japanese Orthopaedic Association (JOA) scale to evaluate the functional outcomes.” (lines: 225-237)

We submitted the links to the editorial policy that allows re-prints as a .docx file to my Editorial Manager account.

We rewrote the Figure Legend footnote as “*This figure has been modified from previously published literature*.” (line 282)

We resubmitted the Tables with new footnotes as “*This table has been modified from previously published literature.*” (Table 1)

We resubmitted the Tables with new footnotes as “*This table has been modified from previously published literature.*” (Table 2, 3)

Editorial comment 3: Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution’s human research ethics committee. What are the patient selection criteria? Step 3 should be moved up.

Author response: We would like to thank the Editor for this useful comment.

Author action: We added the information of statement before the numbered protocol steps to read as "*The study was approved by the ethical committee of the First Affiliated Hospital of Xinjiang Medical University, China.*" (lines 87-88)

The patient selection criteria were expressed as the surgical indications in the manuscript as "*1.2.1. Persistent pain due to spinal instability which is caused by severe disc or/and vertebral destruction. 1.2.2. Severe or progressive neurologic dysfunction; attributed to the nerve root compression by inflammatory granuloma, epidural abscesses. 1.2.3. No response to the oral antibiotic therapy (e.g. doxycycline, rifampicin, streptomycin).”* (lines 133-141)

We have moved Step 3 up to Step 1. (lines 90-99)

Editorial comment 4: Please ensure that all text in the protocol section is written in the imperative tense as if telling someone how to do the technique (e.g., “Do this,” “Ensure that,” etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as “could be,” “should be,” and “would be” throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a “Note.” However, notes should be concise and used sparingly. Please include all safety procedures and use of hoods, etc.

Author response: We would like to thank the Editor for this useful comment.

Author action: We ensured that all text in protocol section was written in the imperative tense. We included all safety procedures and use of hoods.

Editorial comment 5: The Protocol should contain only action items that direct the reader to do something. Please move the discussion about the protocol to the Discussion.

Author response: We would like to thank the Editor for this great comment. We showed only action items in the Protocol section without discussion.

Author action: None.

Editorial comment 6: In the JoVE Protocol format, “Notes” should be concise and used sparingly. They should only be used to provide extraneous details, optional steps, or recommendations that are not critical to a step. Any text that provides details about how to perform a particular step should either be included in the step itself or added as a sub-step.

Author response: We would like to thank the Editor for this useful comment. We used the “Notes” following the JoVE Protocol format.

Author action: We highlighted the “Notes” to read as “*NOTE: In order to achieve adequate debridement, the pedicle screws are placed closest to the superior or inferior endplate and away from infection lesions. Screws are fixed to a temporary rod (diameter: 5.5 mm) on the less involved side (see Table of Materials).*” (lines 168-170)

“*NOTE: The psoas abscess should be adequately drained from posterolateral under a blunt dissection as thoroughly as possible. Removed tissues and abscess should be sent for histopathologic examination. Noncaseating granulomatous inflammation with predominant lymphocyte and monocytes infiltration is the typical histopathologic finding of BS. If the result of decompression and debridement is not satisfied after a unilateral facetectomy, the same procedure should be performed on the opposite side.*” (lines 179-184)

Editorial comment 7: Please note that your protocol will be used to generate the script for the video and must contain everything that you would like shown in the video. Please add more details to your protocol steps. Please ensure you answer the “how” question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. Please add more specific details (e.g. button clicks for software actions, numerical values for settings, etc) to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

Author response: We would like to thank the Editor for this useful comment.

Author action: We added more details (lines 157-158, 165-166, 186-188, 197-198) to our protocol steps and references (lines 112, 117, 120) published material specifying how to perform the protocol action.

Editorial comment 8: 1.1.1.2: As you have highlighted plain radiographs, please include enough details or add a statement indicating what will be filmed. Please reference Fig. 1 if this is appropriate here.

Author response: We would like to thank the Editor for this great comment.

Author action: We added the information to reference Fig. 1 to read as “*Central necrosis is mainly not present and the vertebral body is mostly morphologically intact **(Figure 1)**.*” (lines 111-112)

Editorial comment 9: 1.1.1.3: As you have highlighted CT, please include enough details or add a statement indicating what will be filmed. If you do not plan to demonstrate CT, then please cite a reference to help readers replicate this technique. If you plan to describe the features of CT images, please provide a figure or indicate what will be filmed.

Author response: We would like to thank the Editor for this useful comment.

Author action: We added the information to reference Fig. 1 to read as "*Most bone destruction lesions at vertebral edges are small and occur on multiple areas. The hyperplastic and sclerotic lesions are more prominent and often admixed **(Figure 1)**.*" (lines 115-117)

Editorial comment 10: 1.1.1.4: As you have highlighted MRI, please include enough details or add a statement indicating what will be filmed. If you do not plan to demonstrate MRI, then please cite a reference to help readers replicate this technique. If you plan to describe the features of MR images, please provide a figure or indicate what will be filmed. Would it be appropriate to reference Fig. 1 here?

Author response: We would like to thank the Editor for this great comment.

Author action: We added the information to reference Fig. 1 to read as "*MRI is the best imaging tool for BS diagnosis **(Figure 1)***." (lines 119-120)

Editorial comment 11: As you have highlighted 1.1.2, please specify actions and details that will enable filming these steps.

Author response: We would like to thank the Editor for this useful comment. We showed the details of the confirmed diagnosis details in Step 2.1.2 in the video from 1 minute 17 seconds to 1 minute 52 seconds.

Author action: None.

Editorial comment 12: Step 4: for all operative procedures, please specify what surgical instruments to sterilize and use, the specifications of the pedicle screws, how is C-arm fluoroscopy performed (4.5), how is facetectomy to be performed (4.6), please provide details for histopathological examination (if to be filmed)-how will slides be prepared, magnification to observe, what is a "large amount of saline" (in 4.8)?

Author response: We would like to thank the Editor for this great comment.

Author action: We added relevant references to specifying how to perform the protocol action to read as "*4.5. Place the pedicle screws (diameter: 5 – 7 mm, length: 20 – 65 mm) into both sides of the affected vertebra with the assistance of C-arm fluoroscopy (see Table of Materials)*." (lines 165-166)

"*4.6. Perform the facetectomy at the involved level on the side where neurologic and radiological manifestations are more severe*.*"* (lines 173-174)

We also added the relevant references to show the preparation of slides and the magnification to observe to read as "*Removed tissues and abscess should be sent for histopathologic examination*." (lines 180-181)

In surgery, we use normal saline to irrigate the surgical area to clear the residual Brucellar lesion. The amount of the saline used depends on the size of the surgical area. In our protocol, we used 1000-2000 ml of 0.9% sodium chloride solution for irrigation. We rewrote Step 4.8 to read as *"4.8. After adequate removal of the lesions and decompression of the neural elements, 1000 – 2000 ml of 0.9% sodium chloride solution is utilized for surgical area irrigation to clear the residual Brucellar lesion (see Table of Materials)."* (lines 186-188)

Editorial comment 13: 4.9: please replace 60mm*20mm*5mm with 60 mm x 20 mm x 5 mm.

Author response: We would like to thank the Editor for this useful comment.

Author action: We rewrote the information to reads as "*Absorbable gelatin sponge (60mm x 20mm x 5mm) saturated with 0.75 – 1.5g streptomycin is used for both hemostasis and local antibiotic treatment within the surgical area (see Table of Materials).*" (lines 190-192)

Editorial comment 14: How are 4.10, 4.11, and 4.12 to be performed?

Author response: We would like to thank the Editor for this comment.

Author action: For Step 4.10, we collected the autogenous bone from the facetectomy (Step 4.6). The autogenous bone fragments were separated into granules by rongeur. If the bone granules were insufficient to fill the defect space, the allogeneic bone could be used.

For step 4.11, we added relevant references to specifying how to perform the protocol action to read as "*Pedicle screws (diameter: 5 – 7 mm, length: 20 – 65 mm) on both sides are fixed to the pre-contoured rods (diameter: 5.5 mm) under a slight compression (see Table of Materials).”* (lines 198-199)

For step 4.12, we added relevant reference to specifying how to perform the protocol action to read as *“Drainage and lesion closure are performed accordingly (see Table of Materials). ”* (line 201)

All the details of Step 4.10-Step 4.12 was showed in the video from 4 minutes 38 seconds to 5 minutes 06 seconds.

Editorial comment 15: As we are a methods journal, please revise the Discussion to explicitly cover the following in detail in 3-6 paragraphs with citations:
a) Critical steps within the protocol
b) Any modifications and troubleshooting of the technique

Author response: We would like to thank the Editor for this useful comment.

Author action: We rewrote several critical steps to read as "*The first critical step in the treatment of BS is to make the right diagnosis*." (line 293)

"*The second critical step is to utilize transforaminal lumbar interbody fusion (TLIF) technology in operation, which refers to a modification of posterior lumbar interbody fusion. It can minimize traction force on the dura and nerve root during surgery, therefore, decrease the risk of postoperative complications.*" (lines 310-312)

"*The third critical step is to plant the pedicle screw into the affected vertebra to achieve a shorter segmental fixation.*" (lines 332-333)

Editorial comment 16: Please do not abbreviate journal titles in the reference list.

Author response: We would like to thank the Editor for this great comment.

Author action: We changed the reference list with full journal name.

Editorial comment 17: Please sort the materials alphabetically in the Table of Materials.

Author response: We would like to thank the Editor for this useful comment.

Author action: We have sorted the materials alphabetically in the Table of Materials.

Reviewer#1 comments:

Manuscript Summary:

The authors presented a practical guide of the diagnosis and surgical treatment of human Brucellar Spondylodiscitis. This study explained the detail of the initial and confirmed diagnosis. Furthermore, crucial surgical steps are also explained. This clinical algorithm yielded substantially satisfactory outcomes, which can also be introduced for large-scale applications to manage human Brucellar Spondylodiscitis.

Author response: We would like to thank the Reviewer for the kind comments.

Author action: None.

Reviewer#1 comments:

Major Concern 1: The description of the first paragraph of Introduction is lengthy, please rephrase.

Author response: We would like to thank the Reviewer for this useful comment.

Author action: We adjusted the structure of Introduction to read as "*Human Brucellosis, with more than half a million new cases annually, has become a public health concern and remains an enormous burden worldwide. Brucellar spondylodiscitis (BS) as the most common and severe osteoarticular manifestation of human Brucellosis involves multiple structures, including vertebral bodies, intervertebral disc, and paraspinal structures. It occurs frequently in the lumbosacral zone and needs to be differentiated from other infectious disease due to the*

nonspecific clinical characteristics. Despite the research progress significantly in past decades, accurate and timely diagnosis of BS still post a challenge to clinicians due to its late-onset radiological findings, slow growth rate in blood cultures, and complexity of its serodiagnosis. Therefore, human BS remains clinically under-diagnosed and underreported.

The past decades have seen increasingly rapid advances in the introduction and popularization of several therapeutic guidelines, however, the consensus of optimal management modality is still lacking. Frequent relapses, treatment failure, sequelae are reported constantly. Of note, BS can be severely debilitating and disabling even if it is rarely fatal. Possible serious sequelae might be induced, if it is not treated appropriately, including persistent back pain, neurological deficiency, and even kyphotic deformity. Antibiotic therapy is the core in the treatment of BS and yields generally promising outcomes. Though, certain patients may require surgical treatment, if they are associated with neurological dysfunction, spinal instability, abscess formation, intractable pain and previous unsatisfactory response to conservative treatments. Yet, surgical intervention still remains controversial. Different surgical procedures for debridement and fusion have been described for the infectious disease of lumbar spine including anterior-only, posterior-only and combined approaches."(lines 59-80)

Reviewer#1 comments:

Major Concern 2: Lines 92-3: Please describe the clinical manifestations and symptoms in detail, such as the type of fever, duration of fever. It is helpful for the differential diagnosis.

Author response: We would like to thank the Reviewer for this great comment. We described the detailed fever as "undulant fever" according to the Reviewer's suggestion. The duration of undulant fever remains uncertain in different patients. Therefore, the differential and confirmed diagnoses depend mainly on medical imaging and laboratory tests.

Author action: We rewrote the information to read as "*The clinical manifestations and symptoms mainly include back pain, undulant fever, malaise, profuse night sweating, weight loss, polyarthralgia, and generalized myalgias."* (lines 106-107)

Reviewer#1 comments:

Major Concern 3: A new study (PMID: 17977995) reveals that quantitative real-time PCR (RT-qPCR), with a high sensitivity and specificity, may be a good method to diagnose BS. Please give your opinion.

Author response: We would like to thank the Reviewer for this important comment. The RT-qPCR is a valuable technique in determining the quantification of nucleic acids rapidly from individual blood samples. PCR approaches have advantages for the diagnosis of human brucellosis, such as speed, safety, high sensitivity and specificity[2]. However, PCR protocols lack standardization. As new methods for *Brucella spp.* identification and typing, PCR tests are still being developed and still await validation for use with clinical samples. This technique will be a more effective method for diagnosis of human Brucellosis in the future[3].

Author action: None.

Reviewer#1 comments:

Major Concern 4: According to the results (lines 257-8), ESR and CRP should have considerable clinical significance for BS diagnosis. Why didn't you consider using routine laboratory examinations as a diagnostic basis (line 88, diagnosis of BS section)?

Author response: We would like to thank the Reviewer for this meaningful comment. In our study, the activity of infection is monitored with the routine laboratory examinations as ESR and CRP. However, ESR and CRP results show a significant increase in inflammation and other infectious diseases (e.g., spinal tuberculosis),

lacking specificity. Therefore, the clinical diagnosis of brucellosis is mainly based on serological and etiological diagnosis results.

Author action: None.

Reviewer#1 comments:

Major Concern 5: Lines 110: Confirm that diagnosis needs to meet all three following criteria?

Author response: We would like to thank the Reviewer for this question. To avoid misdiagnosis with other infectious diseases (e.g., spinal tuberculosis), the confirmed diagnosis of Brucellar spondylodiscitis should satisfy all three criteria[4].

Author action: None.

Reviewer#1 comments:

Major Concern 6: Triple therapy of doxycycline, rifampicin and streptomycin appears to be an effective treatment for BS in some studies (PMID: 20518794). However, only doxycycline and rifampicin were used in this study (lines 131-2, lines 203-5). Could you please give more details to compare the relative advantages and disadvantages of these two strategies?

Author response: We would like to thank the Reviewer for this great comment. The advantage of the combination of two antibiotics is to reduce side effects[5]. The disadvantage of the combination of two antibiotics is that to avoid therapeutic failures and the risk of relapse, prolonged treatment is recommended[6]. For triple therapy, the advantage is to reduce treatment time and the risk of relapse. However, the disadvantage of triple therapy is the increased risk for adverse effects[5].

Author action: None.

Reviewer#1 comments:

Major Concern 7: To my knowledge, human Brucellar Spondylodiscitis is also found in children. What's the chemotherapy regimen for the Brucellar Spondylodiscitis in children?

Author response: We would like to thank the Reviewer for this great comment. According to the latest World Health Organization (WHO) treatment options[7], the treatment of uncomplicated brucellosis in adults and children eight years of age and older are as follows:

1. Doxycycline (a long acting tetracycline analogue) is given in a dose of 100 mg every 12 hours orally and is administered for a period of six weeks.
2. Streptomycin (1 g/day intramuscularly) administered for two to three weeks has long been the aminoglycoside of choice when used in combination with tetracycline or doxycycline.

However, the treatment should be personalized according to patient characteristics. Therefore, we suggest making the treatment options with the assistance of the pediatrician.

Author action: None.

Reviewer#1 comments:

Major Concern 8: It might be worthwhile to discuss the diagnosis of human Brucellar Spondylodiscitis in more detail in the Discussion.

Author response: We would like to thank the Reviewer for this useful comment.

Author action: We rewrote the Discussion with additional details of the diagnosis of human Brucellar Spondylodiscitis to read as "*The first critical step in the treatment of BS is to make the right diagnosis. The diagnosis of BS needs to be differentiated from*

spinal tuberculosis compared to which BS is relatively less bone destructive and usually responds effectively to the antibiotic treatment. In addition, noticeable neurological deficits, persistent pain, spinal instability, and paravertebral abscesses can be observed in BS patients in late stages. For patients who did not respond well to antibiotic treatment, surgical treatment should be considered as the last resort for these cases" (lines 293-298)

Reviewer#1 comments:

Minor Concern 1: Lines 60-2: "Brucellar spondylodiscitis (BS) as the most common and severe osteoarticular manifestation of human Brucellosis involves multiple structures, including vertebral bodies, intervertebral disc, and paraspinal structures." The description of the disease characteristics needs a supporting reference.

Author response: We would like to thank the Reviewer for this useful comment.

Author action: We added a supporting reference to read as "*Brucellar spondylodiscitis (BS) as the most common and severe osteoarticular manifestation of human Brucellosis involves multiple structures, including vertebral bodies, intervertebral disc, and paraspinal structures.*" (lines 60-62)

Reviewer#1 comments:

Minor Concern 2: Lines 60-2: According to the surgical video, I guess iodophor was used in the surgery, not iodine, please make sure (line 155).

Author response: We would like to thank the Reviewer for this great comment.

Author action: We changed the iodine to iodophor in the manuscript to read as "*4.2. Disinfect the surgical area with 1% iodophor and then cover with standard surgical towels.*" (lines 157-158)

Reviewer#1 comments:

Minor Concern 3: Some information appears misaligned in Table 2.

Author response: We would like to thank the Reviewer for this great comment.

Author action: We adjusted the information in Table to make it aligned.

Reviewer#2 comments:

Manuscript Summary:

This paper provides a detailed one-stage posterior protocol of surgical treatment of human BS, Which the authors believed could be introduced for the large-scale application to manage human BS, especially in endemic regions.

Author response: We would like to thank the Reviewer for this comment.

Author action: None.

Reviewer#2 comments:

Major Concern: As one-stage posterior surgical treatment for Lumbar Brucella Spondylitis has been proved to be effective and safe (Chen Y, Yang JS, Li T, Liu P, Liu TJ, He LM, Qian LX, Hao DJ. One-stage Surgical Management for Lumbar Brucella Spondylitis by Posterior Debridement, Autogenous Bone Graft and Instrumentation: A Case Series of 24 Patients. Spine (Phila Pa 1976). 2017 Oct 1;42(19): E1112-E1118. doi: 10.1097/BRS.0000000000002093. PMID: 28157811.), the novelty of this manuscript should be detailed provided.

Author response: We would like to thank the Reviewer very much for highlighting this important paper. Chen et al. reported an effective and safe surgical procedure for Brucella Spondylitis, including debridement and intervertebral bone graft fusion via a posterior approach.

Author action: We added additional paragraph in Discussion to discuss the novelty of our method to read as "*Unlike spinal tuberculosis, destruction in BS occurs mainly around and within the intervertebral disc, and vertebral collapse and local kyphosis are less likely to occur. Therefore, debridement and intervertebral bone graft fusion via a posterior approach is an effective and safe procedure for BS. It has been revealed that brucellosis can affect the facets, which may be the reason for severe back pain in those patients. Accordingly, a facetectomy followed by intervertebral debridement and fusion may be more effective than traditional posterior approach*."

Reviewer#2 comments:

Minor Concern 1: Line 27: No response to the oral antibiotic therapy (e.g. doxycycline, rifampicin, streptomycin). What does the author think about triple therapy?

Author response: We would like to thank the Reviewer for this great comment. According to previous studies, triple therapy is an effective conservative treatment for Brucellar spondylodiscitis patients[5,8]. The advantage of triple therapy is to reduce treatment time and the risk of relapse. However, the disadvantage of triple therapy is the increased risk for side effects (i.e. immune thrombocytopenia)[5].

Author action: None.

Reviewer#2 comments:

Minor Concern 2: Line 134: Surgical candidates exhibit surgical indications, and surgical intervention should be performed after two weeks of antibiotic treatment...How to deal with patients with progressive nerve dysfunction?

Author response: We would like to thank the Reviewer for this great comment. For patients with progressive nerve dysfunction, we will arrange surgery immediately while administering antibiotic treatment. Neurotrophic drugs and functional exercise should

be arranged postoperatively. Adjust the treatment regimen according to the regular follow-up[9].

Author action: None.

Reviewer#2 comments:

Minor Concern 3: Line 235: A prospective, non-randomized, controlled study of 32 consecutive BS patients who were treated...Can the author provide the proportion of patients who need surgical treatment?

Author response: We would like to thank the Reviewer for this great comment. From February 2000 to April 2020, a total of 619 Brucellar spondylodiscitis patients were diagnosed in our institution. Among them, 83 patients underwent surgical treatment for Brucellar spondylodiscitis. Altogether 536 patients received conservative medical treatments. Patients who received surgical treatment accounted for 13.41% of all confirmed patients.

Author action: None.

Reviewer#2 comments:

Minor Concern 4: Line 279: Fig.2 Can the author provide positive findings of intracellular brucella by Giemsa staining?

Author response: We would like to thank the Reviewer for this useful comment. Tekkök Brucellar spondylodiscitis diagnostic criteria[4]:

1) Positive blood or bone marrow puncture culture.

2) Positive serum agglutination test (titer of antibodies to Brucella of ≥1/160).

3) Plain radiographs, computed tomography, magnetic resonance imaging or bone scan evidence for spinal involvement.

4) Pathological non-tuberculous granulation tissue.

We did the H&E staining in our study, and the result showed microgranulomatous proliferation with histiocytes and without caseous necrosis, which met the diagnostic criteria for Brucellar spondylodiscitis. Therefore, we didn't perform the Giemsa stain for intracellular brucella test.

Author action: None.

Reviewer#2 comments:

Minor Concern 5: Line 328: the accurate and timely diagnosis of BS is vital to reduce its global burden. Can this conclusion be drawn from the content of this article ?

Author response: We would like to thank the Reviewer for this useful comment. This conclusion cannot be drawn directly from the content of this article. Therefore, we rewrote the conclusion part.

Author action: We rewrote the conclusion to read as: "*In conclusion, application of the afore-mentioned protocol to timely diagnosis and treat BS patients can achieve satisfactory short-term clinical outcomes. Further popularization of this single-stage surgery for the large-scale surgical candidates, especially in the endemic regions, might be helpful to reduce its global burden.*"

References

1 Zong, Z. W. *et al.* Chinese expert consensus on echelons treatment of pelvic fractures in modern war. *Mil Med Res.* **5** (1), 21, (2018).

2 Navarro, E., Casao, M. A. & Solera, J. Diagnosis of human brucellosis using PCR. *Expert Review of Molecular Diagnostics.* **4** (1), 115-123, (2004).

3 Wang, Y. *et al.* Polymerase chain reaction–based assays for the diagnosis of human brucellosis. *Annals of Clinical Microbiology and Antimicrobials.* **13** (1), 31, (2014).

4 Tekkök, I. H., Berker, M., Ozcan, O. E., Ozgen, T. & Akalin, E. Brucellosis of the spine. *Neurosurgery.* **33** (5), 838-844, (1993).

5 Ioannou, S. *et al.* Efficacy of prolonged antimicrobial chemotherapy for brucellar spondylodiscitis. *Clin Microbiol Infect.* **17** (5), 756-762, (2011).

6 Alp, E. & Doganay, M. Current therapeutic strategy in spinal brucellosis. *Int J Infect Dis.* **12** (6), 573-577, (2008).

7 Corbel, M. J., Food, Agriculture Organization of the United, N., World Health, O. & World Organisation for Animal, H. (World Health Organization, Geneva, 2006).

8 Koubaa, M. *et al.* Spinal brucellosis in South of Tunisia: review of 32 cases. *Spine J.* **14** (8), 1538-1544, (2014).

9 Katonis, P., Tzermiadianos, M., Gikas, A., Papagelopoulos, P. & Hadjipavlou, A. Surgical Treatment of Spinal Brucellosis. *Clinical Orthopaedics and Related Research®.* **444**, (2006).

Video

Click here to access/download

Supplemental Coding Files

BS video.mp4