C-reactive protein measurements. J Neurosurg Spine. 2010;13:158–164. doi:10.3171/2010.3.SPINE09403.
[2] Mok JM, Pekmezci M, Piper SL, Boyd E, Berven SH, Burch S, et al. Use of C-reactive protein after spinal surgery: comparison with erythrocyte sedimentation rate as predictor of early postoperative infectious complications. Spine. 2008;33:415–421. doi:10.1097/BRS.0b013e318163f9ee.
[3] Meyer B, Schaller K, Rohde V, Hassler W. The C-reactive protein for detection of early infections after lumbar microdiscectomy. Acta Neurochir (Wien). 1995;136:145–150.

Author: Bryan Alexander

QUESTION 4: Is there a role for molecular techniques such as polymerase chain reaction (PCR) or next-generation sequencing (NGS) for the diagnosis of spinal surgery infection? If so, in which group of patients should this be done?

RECOMMENDATION: It is reasonable to selectively incorporate these diagnostic modalities as an adjunct to standard methodologies where there is a history or high pre-test probability for culture negative infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 71%, Disagree: 14%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

Successful management of periprosthetic joint infections (PJI) is significantly enhanced with a prompt and accurate microbiological diagnosis. Conventional culture methods for diagnosis of PJI can be compromised and complicated by early antibiotic treatment, heterogeneity of surgical sampling, fastidious microorganisms difficult to grow in culture and non-planktonic pathogens utilizing biofilms. Therefore, modern molecular microbiologic methods have naturally been seen as very promising for increasing diagnostic yield in these circumstances. Technologies that have more recently been applied to PJI generally include ribosomal RNA sequencing, species-specific and multiplex PCR and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Specifically, with respect to spinal and vertebral infections, these varied technologies have demonstrated success in leading to an etiologic diagnosis. These methods have been used to identify a variety of pathogens, including *Staphylococcus spp.* [1–3], *Streptococcus spp* [3,4], *Enterococcus spp.* [4], Enterobacteriaceae [3–5], *Brucella spp.* [6], *Mycobacterium spp.* [2], atypical bacteria (*T. whipplei*) [7], *Mycoplasma spp.*) [8], anaerobes (*Clostridium spp.*) [3], *Fusobacterium spp.*) [4,9] and fungi (*Aspergillus spp.*) [10].

By far, the most experience with these techniques for spinal infections is in the diagnosis of Pott's disease (*Mycobacterium tuberculosis*) [2,6,11–15]. These reports generally demonstrate a high sensitivity and specificity of PCR modalities, though many of these studies have been completed in tuberculosis endemic geographic areas with likely higher inoculum infections and a well-defined pre-test probability.

False positive results from dead or colonizing/contaminating bacteria is a concern with these tests, and studies evaluating the appropriate number of samples to optimize sensitivity and specificity specific to these molecular methods are limited and not specific to spinal infections [16]. Another important concern with molecular techniques for PJI diagnostics is that they do not commonly allow for susceptibility testing to appropriately target antimicrobial therapy. Certain resistance mechanisms, such as methicillin resistance in *S. aureus* [1,17,18] or rifampin resistance in *M. tuberculosis* [12], are reliably expressed if genetically detected. This is not the norm, however, as resistance expression is generally a complex phenotype determined by multiple factors. Care should be taken not to overly rely on non-susceptibility-generating techniques, as they can just as easily lead to long courses of overly-broad therapy, as can no etiologic diagnosis at all, undermining patient safety and important principles of antimicrobial stewardship. In addition, it has been noted that utilizing molecular methods as an adjunct to and in combination with standard culture methodologies often serves to improve overall diagnostic yield [3].

A few studies have attempted to establish test sensitivity and specificity data when compared to routine culture for bone and joint specimens in general [4,15,19–23], however these efforts are limited by lack of a true gold standard diagnostic method for comparison, the variety of testing methodologies clinically employed and non-standardized clinical criteria for utilization of these methods. Predictably, results vary widely, with sensitivities reported between 50–92% and specificities between 65–94% [20]. No studies investigating sensitivity and specificity of these techniques specific only to spinal post-surgical infections have yet been reported. Therefore, an evidence-based evaluation of the appropriate clinical criteria for utilization of these techniques in spinal surgery patients is not currently possible. One study proposed a strategy for routine collection and potential use of molecular diagnostics in PJI [24]. There is no data investigating the cost effectiveness for any diagnostic schema incorporating molecular methods, however given their positive proof-of-concept and the significant clinical impact of spinal post-surgical infections, it seems reasonable to selectively incorporate the use of molecular methods into situations where there is a high pre-test probability for indolent or culture-negative infection as further studies are done to standardize their use.

REFERENCES

[1] Tsuru A, Setoguchi T, Kawabata N, Hirotsu M, Yamamoto T, Nagano S, et al. Enrichment of bacteria samples by centrifugation improves the diagnosis of orthopaedics-related infections via real-time PCR amplification of the bacterial methicillin-resistance gene. BMC Res Notes. 2015;8:288. doi:10.1186/s13104-015-1180-2.
[2] Sheikh AF, Khosravi AD, Goodarzi H, Nashibi R, Teimouri A, Motamedfar A, et al. Pathogen identification in suspected cases of pyogenic spondylodiscitis. Front Cell Infect Microbiol. 2017;7:60. doi:10.3389/fcimb.2017.00060.
[3] Fuursted K, Arpi M, Lindblad BE, Pedersen LN. Broad-range PCR as a supplement to culture for detection of bacterial pathogens in patients with a clinically diagnosed spinal infection. Scand J Infect Dis. 2008;40:772–777. doi:10.1080/00365540802119994.

[4] Fihman V, Hannouche D, Bousson V, Bardin T, Lioté F, Raskine L, et al. Improved diagnosis specificity in bone and joint infections using molecular techniques. J Infect. 2007;55:510–517. doi:10.1016/j.jinf.2007.09.001.
[5] Shibata S, Tanizaki R, Watanabe K, Makabe K, Shoda N, Kutsuna S, et al. Escherichia coli vertebral osteomyelitis diagnosed according to broad-range 16S rRNA gene polymerase chain reaction (PCR). Intern Med. 2015;54:3237–3240. doi:10.2169/internalmedicine.54.5066.
[6] Colmenero JD, Morata P, Ruiz-Mesa JD, Bautista D, Bermúdez P, Bravo MJ, et al. Multiplex real-time polymerase chain reaction: a practical approach for rapid diagnosis of tuberculous and brucellar vertebral osteomyelitis. Spine. 2010;35:E1392–E1396. doi:10.1097/BRS.0b013e3181e8eeaf.
[7] Altwegg M, Fleisch-Marx A, Goldenberger D, Hailemariam S, Schaffner A, Kissling R. Spondylodiscitis caused by Tropheryma whippelii. Schweiz Med Wochenschr. 1996;126:1495–1499.
[8] Flouzat-Lachaniette C-H, Guidon J, Allain J, Poignard A. An uncommon case of Mycoplasma hominis infection after total disc replacement. Eur Spine J. 2013;22 Suppl 3:S394–S398. doi:10.1007/s00586-012-2511-9.
[9] Sanmillán JL, Pelegrín I, Rodríguez D, Ardanuy C, Cabellos C. Primary lumbar epidural abscess without spondylodiscitis caused by Fusobacterium necrophorum diagnosed by 16S rRNA PCR. Anaerobe. 2013;23:45–47. doi:10.1016/j.anaerobe.2013.06.014.
[10] Dayan L, Sprecher H, Hananni A, Rosenbaum H, Milloul V, Oren I. Aspergillus vertebral osteomyelitis in chronic leukocyte leukemia patient diagnosed by a novel panfungal polymerase chain reaction method. Spine J. 2007;7:615–617. doi:10.1016/j.spinee.2006.08.005.
[11] Sharma K, Meena RK, Aggarwal A, Chhabra R. Multiplex PCR as a novel method in the diagnosis of spinal tuberculosis-a pilot study. Acta Neurochir (Wien). 2017;159:503–507. doi:10.1007/s00701-016-3065-0.
[12] Held M, Laubscher M, Zar HJ, Dunn RN. GeneXpert polymerase chain reaction for spinal tuberculosis: an accurate and rapid diagnostic test. Bone Joint J. 2014;96-B:1366–1369. doi:10.1302/0301-620X.96B10.34048.
[13] Pandey V, Chawla K, Acharya K, Rao S, Rao S. The role of polymerase chain reaction in the management of osteoarticular tuberculosis. Int Orthop. 2009;33:801–805. doi:10.1007/s00264-007-0485-8.
[14] Sun Y, Zhang Y, Lu Z. [Clinical study of polymerase chain reaction technique in the diagnosis of bone tuberculosis]. Zhonghua Jie He He Hu Xi Za Zhi. 1997;20:145–148.
[15] Van der Spoel van Dijk A, MCleod A, Botha PL, Shipley JA, Kapnoudhis MA, Beukes CA. The diagnosis of skeletal tuberculosis by polymerase chain reaction. Cent Afr J Med. 2000;46:144–149.
[16] Marín M, Garcia-Lechuz JM, Alonso P, Villanueva M, Alcalá L, Gimeno M, et al. Role of universal 16S rRNA gene PCR and sequencing in diagnosis of prosthetic joint infection. J Clin Microbiol. 2012;50:583–589. doi:10.1128/JCM.00170-11.
[17] Choe H, Aota Y, Kobayashi N, Nakamura Y, Wakayama Y, Inaba Y, et al. Rapid sensitive molecular diagnosis of pyogenic spinal infections using methicillin-resistant Staphylococcus-specific polymerase chain reaction and 16S ribosomal RNA gene-based universal polymerase chain reaction. Spine J. 2014;14:255–262. doi:10.1016/j.spinee.2013.10.044.
[18] Dubouix-Bourandy A, de Ladoucette A, Pietri V, Mehdi N, Benzaquen D, Guinand R, et al. Direct detection of Staphylococcus osteoarticular infections by use of Xpert MRSA/SA SSTI real-time PCR. J Clin Microbiol. 2011;49:4225–4230. doi:10.1128/JCM.00334-11.
[19] Borde JP, Häcker GA, Guschl S, Serr A, Danner T, Hübner J, et al. Diagnosis of prosthetic joint infections using UMD-Universal Kit and the automated multiplex-PCR Unyvero i60 ITI(®) cartridge system: a pilot study. Infection. 2015;43:551–560. doi:10.1007/s15010-015-0796-4.
[20] Malandain D, Bémer P, Leroy AG, Léger J, Plouzeau C, Valentin AS, et al. Assessment of the automated multiplex-PCR Unyvero i60 ITI® cartridge system to diagnose prosthetic joint infection: a multicentre study. Clin Microbiol Infect. 2018;24:83.e1–e83.e6. doi:10.1016/j.cmi.2017.05.017.
[21] Bémer P, Plouzeau C, Tande D, Léger J, Giraudeau B, Valentin AS, et al. Evaluation of 16S rRNA gene PCR sensitivity and specificity for diagnosis of prosthetic joint infection: a prospective multicenter cross-sectional study. J Clin Microbiol. 2014;52:3583–3589. doi:10.1128/JCM.01459-14.
[22] Grif K, Heller I, Prodinger WM, Lechleitner K, Lass-Flörl C, Orth D. Improvement of detection of bacterial pathogens in normally sterile body sites with a focus on orthopedic samples by use of a commercial 16S rRNA broad-range PCR and sequence analysis. J Clin Microbiol. 2012;50:2250–2254. doi:10.1128/JCM.00362-12.
[23] Fenollar F, Roux V, Stein A, Drancourt M, Raoult D. Analysis of 525 samples to determine the usefulness of PCR amplification and sequencing of the 16S rRNA gene for diagnosis of bone and joint infections. J Clin Microbiol. 2006;44:1018–1028. doi:10.1128/JCM.44.3.1018-1028.2006.
[24] Lévy P-Y, Fenollar F. The role of molecular diagnostics in implant-associated bone and joint infection. Clin Microbiol Infect. 2012;18:1168–1175. doi:10.1111/1469-0691.12020.

Authors: Glenn S. Russo, Daniel Tarazona

QUESTION 5: For which investigations should samples obtained by image-guided biopsy be sent?

RECOMMENDATION: A priority should be placed on obtaining bacterial cultures and pathohistology. In the appropriate epidemiological setting, mycobacterial, fungal and brucellar cultures can be considered.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RESPONSE

There is limited data available in the literature to help establish clear evidence-based parameters for treatment. However, there are society-based clinical guidelines such as the 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults, which provide assistance in decision-making. Highlights from this statement recommend the acquisition of image-guided aspiration biopsy in patients with suspected vertebral osteomyelitis when a microbiologic diagnosis for a known associated organism has not been established by blood cultures or serologic tests. Further, they recommend for the addition of fungal, mycobacterial or brucellar cultures on image-guided biopsy and aspiration specimens in patients with suspected vertebral osteomyelitis if epidemiologic, host risk factors or characteristic radiologic clues are present, or if testing to appropriately stored bacterial specimens reveal no growth [1].

There is some data to suggest that standard samples should be sent for both microbiology and pathohistology. Pathologic evaluation is meaningful, particularly in culture negative cases where the presence of leukocytes can indicate pyogenic osteomyelitis, or visualization of granulomas can suggest mycobacterial infection or brucellosis [2]. Pathology can also support ruling out diagnoses like ankylosing spondylitis, hemodialysis-associated spondyloarthropathy or neuropathic Charcot joint deformities [3]. Furthermore, crystal deposits can aid in the diagnosis of pseudogout [4].

REFERENCES

[1] Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26–e46. doi:10.1093/cid/civ482.
[2] Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med. 2010;362:1022–1029. doi:10.1056/NEJMcp0910753.