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Microbiologic Diagnosis of Pyogenic Spondylitis

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ABSTRACT

Pyogenic spondylitis requires long-term antibiotics treatment and identification of the etiologic microorganism is essential. The first test in the microbiologic diagnosis of pyogenic spondylitis is a blood culture. Any microorganisms that grow in blood culture are highly likely to be the etiological microorganisms of pyogenic spondylitis. If the microbial etiology cannot be defined by the blood culture, a needle biopsy is performed on the inflamed tissues. Here, it is recommended that paraspinal tissues, rather than spinal tissues, are collected to increase the positive rate in tissue culture. If the microbial etiology cannot be defined by the first needle biopsy, another needle biopsy may be performed. The collected tissue sample is used in culture tests on bacteria and mycobacteria as well as pathological tests. If tuberculous spondylitis is suspected, polymerase chain reaction is carried out to detect *Mycobacterium tuberculosis*. In the case that the etiological microorganisms cannot be identified, the data of the patient regarding age, sex, vertebrae involved, history of spinal surgery or procedure, previous or concurrent urinary tract or intra-abdominal infection are analyzed. Based on this the most probable microbial etiology is determined to select the antibiotics to be used in the empiric treatment.

Keywords: Spondylitis; Diagnosis; Bacteria

INTRODUCTION

Infectious spondylitis is an infectious disease of the vertebral body, intervertebral disc, or paraspinal tissues. While it is specified based on the infection site, infectious spondylitis (vertebral osteomyelitis) or infectious spondylodiscitis, the two terms are often used without clear distinction. Infectious spondylitis is classified based on the microbial etiology, into pyogenic spondylitis, tuberculous spondylitis or fungal spondylitis. Despite the differences in the analyzed data, the reported incidence of pyogenic spondylitis approximates to 2.4 individuals per 100,000 with the incidence found to be higher for males and older individuals [1-3]. The most common underlying disease that accompanies pyogenic spondylitis is diabetes, as it is found in approximately 30% of patients, followed by malignant neoplasm, chronic kidney disease, liver cirrhosis, cerebrovascular disease, and congestive heart failure [4, 5]. With the increase in the number of spinal surgeries and procedures on spinal areas, the incidence of infectious spondylitis has also increased [3]. For the treatment of pyogenic

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spondylitis, a long-term antibiotics is required, and in the case of paralysis, anatomical instability of the vertebra, or aggravation during antibiotic treatment, a surgical treatment should also be performed [6]. As pyogenic spondylitis requires at least 6 weeks of antibiotics treatment, it is crucial that the microbial etiology is identified. If not, an empiric treatment is performed, and with unknown microbial etiology, long-term and broad-spectrum antibiotic treatment is unavoidable, and can result in unnecessary side effects and antibiotic resistance. This article reviews the diagnostic approaches to identify microbial etiology in patients with pyogenic spondylitis.

ETIOLOGIC MICROORGANISMS

The microorganisms reach the vertebra through hematogenous spread or during a spinal surgery, procedure, or directly from a site close to the vertebra. Microorganisms known to cause infectious spondylitis are diverse, with regional and periodic variation in distribution [3, 7]. The most common species causing infectious spondylitis in Korea are bacteria and *Mycobacterium tuberculosis*. Recently, the incidence of pyogenic spondylitis has increased, whereas the incidence of tuberculous spondylitis has decreased [7]. *Brucella* is a common etiologic microorganism of infectious spondylitis in the Mediterranean, Middle East, Latin America and West Asia, but it is rare in Korea [8, 9] with a very low incidence of spondylitis caused by non-tuberculous mycobacteria or fungi [10-12].

In most regions, the most common microbial species that cause infectious spondylitis are bacteria and *M. tuberculosis*. While the treatment of pyogenic spondylitis requires at least 6-week of antibiotics, tuberculous spondylitis requires over 6-month of antituberculous drugs. This means differential diagnosis of the two diseases is critical. The signs, symptoms, blood test, and imaging results provide valuable data for the differentiation of the two diseases. Pyogenic spondylitis can be divided into culture-positive and culture-negative cases, depending on the microbial growth in blood and/or spinal tissues. Comparison of culture-positive pyogenic spondylitis and tuberculous spondylitis shows that the disease progression is faster in the former. Fever, diabetes, bacteremia is more commonly accompanied in patients with culture-positive pyogenic spondylitis [13, 14]. Patients with culture-positive pyogenic spondylitis show significantly higher levels of peripheral leukocyte count, proportion of neutrophil, and C-reactive protein (CRP) [13-15]. The most common infection site of pyogenic spondylitis is the lumbar spine, whereas that of tuberculous spondylitis is the lumbar as well as thoracic spine. A significantly larger number of vertebral bodies are affected in tuberculous spondylitis [13, 14]. When culture-negative pyogenic spondylitis is compared with tuberculous spondylitis, the frequency of accompanied fever is higher in the latter, while no difference is found in the peripheral leukocyte count, proportion of neutrophil, or CRP [16]. The proportion of concurrent extraspinal tuberculosis is significantly higher in patients with tuberculous spondylitis [13, 16]. The positive rate of interferon-gamma release assay (IGRA) varies greatly according to region. While the rate is generally higher for tuberculous spondylitis, a considerably higher rate may be found in patients with pyogenic spondylitis in regions with moderate or high prevalence of tuberculosis. Thus, IGRA might be useful in excluding tuberculous spondylitis but not in the differential diagnosis between tuberculous spondylitis and pyogenic spondylitis [16, 17]. The differential diagnosis of pyogenic and tuberculous spondylitis is based on the findings described so far, but for a definite diagnosis, blood culture, tissue culture, and polymerase chain reaction (PCR) for *M. tuberculosis* should be performed. If the microbial etiology remains unknown even after blood culture and tissue

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culture, the previously described findings are used to make a presumed diagnosis and the patient is given the respective treatment.

The microbial etiology of pyogenic spondylitis varies across different studies, but the most commonly reported etiologic species is *Staphylococcus aureus*, followed by *Streptococcus*. Gram-negative bacilli account for 7 – 33% of the entire microbial etiology, with *Escherichia coli* as the most common species [18-20] (**Table 1**). Coagulase-negative *Staphylococcus* (CNS) has also been identified but, as it could have originated from microbial contamination in the process of sample collection, the culture test results should be obtained from at least two samples. The distribution of etiologic microorganisms varies according to the area of vertebra including cervical, thoracic, lumbar and sacral spines; however, *S. aureus* is the most common species across all regions [4]. Among the etiologic microorganisms of pyogenic spondylitis, the proportion of Gram-negative bacilli is higher for those affecting thoracic or lumbar spine than for those affecting cervical or sacral spine [4]. The proportion of *S. aureus* increases as age decreases, while that of Gram-negative bacilli increases as age increases [4]. The proportion of Gram-negative bacilli is 16.4% in males and 32.1% in females [4]. CNS is the cause of 30 – 32% of pyogenic spondylitis in patients who received a spinal surgery or procedure. The proportion is significantly higher than in patients without past spinal surgery or procedure [21-23] (**Table 1**). *Streptococcus* or *Enterococcus* accounts for 5 – 20% of etiologic microorganisms of pyogenic spondylitis [3-5]. The cases where Gram-negative bacilli are suspected as the etiologic microorganisms of pyogenic spondylitis are as follows: a female patient and/or a patient with previous or concurrent urinary tract infection or intra-abdominal infection [18, 19]. The cases of pyogenic spondylitis caused by *Brucella* are suspected if the patient works in livestock industry or shows normal leukocyte count or sacroiliitis [9]. The cases of tuberculous spondylitis are suspected when the disease progression is slow over the period of several months, when extraspinal tuberculosis including pulmonary tuberculosis has been detected [13, 16]. For infectious spondylitis caused by non-tuberculous mycobacteria, the diagnosis is difficult at first due to its rarity, and it may be suspected if immunocompromised patient with infectious spondylitis is unresponsive to the treatment based on the diagnosis of pyogenic spondylitis or tuberculous spondylitis [11].

BLOOD CULTURE

Blood culture is the first test in the microbiologic diagnosis of pyogenic spondylitis. The reported positive rate varies in the range of 40 - 60% [3, 6]. For patients suspected of pyogenic spondylitis, at least two pairs of blood culture tests should be performed. While the positive rate of blood culture is higher for patients with fever, the test is equally recommended for patients without fever [3, 6, 24]. There is an ongoing debate on whether tissue biopsy should be performed upon detecting microbial growth in the blood culture of a patient suspected of pyogenic spondylitis. The Infectious Diseases Society of America recommends, tissue biopsy is recommended for all cases other than those where the growth of *S. aureus, Staphylococcus lugdunensis*, or *Brucella* is detected in blood culture [25]. In a retrospective study conducted on 141 patients with pyogenic spondylitis, whose blood and tissue culture tests showed microbial growth, the concordance rate of bacterial identification was 95.7% [26]. Cases of inconsistent results mostly showed the growth of a single microbial species in one sample, but multiple species, including the identified species in the other sample. The findings suggest that tissue biopsy is unnecessary for microbiologic diagnosis of pyogenic spondylitis if microbial growth is detected in the blood culture of a suspected patient. An increase in the positive rate of

Table 1. Microorganisms identified in patients with spontaneous or postoperative pyogenic spondylodiscitis [4, 22]

	Spontaneous pyogenic spondylitis (n = 586)	Postoperative pyogenic spondylitis (n = 104)
Gram positive cocci	426 (72.7%)	82 (78.8%)
Staphylococcus aureus	255 (43.5%)	35 (33.6%)
Methicillin-susceptible	157 (26.8%)	13 (12.5%)
Methicillin-resistant	98 (16.7%)	22 (21.2%)
Coagulase-negative staphylococci	31 (5.3%)	32 (31.0%)
Methicillin-susceptible	12 (2.0%)	4 (3.8%)
Methicillin-resistant	19 (3.2%)	28 (26.9%)
Enterococcus species	22 (3.8%)	4 (3.8%)
E. faecium	4 (0.7%)	1 (1.0%)
E. faecalis	17 (2.9%)	3 (2.9%)
E. gallinarum	1 (0.2%)	0 (0%)
Streptococcus species	118 (2.0%)	11 (10.6%)
S. pneumoniae	6 (1.0%)	0 (0%)
S. agalactiae	27 (4.6%)	3 (2.9%)
Viridans streptococci	70 (11.9%)	7 (6.7%)
Other streptococci	15 (2.6%)	1 (1.0%)
Gram-negative bacilli	132 (22.5%)	15 (14.4%)
Escherichia coli	69 (11.8%)	6 (5.8%)
Klebsiella pneumoniae	22 (3.8%)	1 (1.0%)
Klebsiella oxytoca	3 (0.5%)	0 (0%)
Klebsiella aerogenes	1 (0.2%)	0 (0%)
Pseudomonas aeruginosa	10 (1.7%)	4 (3.8%)
Enterobacter cloacae	5 (0.8%)	2 (1.9%)
Enterobacter asburiae	1 (0.2%)	0 (0%)
Serratia marcescens	3 (0.5%)	2 (1.9%)
Raoultella ornithinolytica	1 (0.2%)	0 (0%)
Salmonella (non-typhoidal)	2 (0.3%)	0 (0%)
Proteus mirabilis	2 (0.3%)	0 (0%)
Proteus penneri	1 (0.2%)	0 (0%)
Citrobacter koseri	1 (0.2%)	0 (0%)
Morganella morganii	1 (0.2%)	0 (0%)
Campylobacter fetus	3 (0.5%)	0 (0%)
Haemophilus influenzae	1 (0.2%)	0 (0%)
Vibrio cholerae non O1/O139	1 (0.2%)	0 (0%)
Ralstonia mannitolilytica	1 (0.2%)	0 (0%)
Achromobacter xylosoxidans	1 (0.2%)	0 (0%)
Burkholderia cepacia	2 (0.3%)	0 (0%)
Stenotrophomonas maltophilia	1 (0.2%)	0 (0%)
Anaerobes	11 (1.9%)	1 (1.0%)
Polymicrobial	9 (1.5%)	5 (4.8%)
Other[a]	8 (1.4%)	1 (1.0%)

[a]*Granulicatella adiacens*, *Erysipelothrix rhusiopathiae*, *Lactococcus gravieae* (2), *Listeria monocytogenes*, *Neisseria* species (2), *Moraxella* species.

blood culture performed immediately after tissue biopsy was reported in a previous study; however, no such increase was observed in the follow-up study, and thus, blood culture is not recommended to be performed after tissue biopsy [27, 28].

TISSUE CULTURE

Tissue culture is performed if microbial growth is not shown in the blood culture of the patient suspected of pyogenic spondylitis. The sample for the test can be collected through biopsy from the infected spinal or paraspinal tissues. After collecting the tissue samples, the culture tests are performed regarding aerobes, anaerobes, mycobacteria, and fungi,

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followed by the pathological tests. In a region with a high incidence of *Brucella* infection, the respective serological tests should be performed, and a request should be made to the lab to extend the culture period to four weeks. Although fungal spondylitis is extremely rare, it may occur in patients whose immunity is compromised due to the administration of immunosuppressants. Thus, for patients showing a causal factor, fungal tissue culture should be performed [25]. While it is difficult to identify the microbial etiology of pyogenic spondylitis through pathological tests, such tests as nucleic acid amplification test (NAAT), fungal staining, or acid-fast bacilli staining may be performed. Pathologic examination also may assist in the differential diagnosis of non-infectious diseases such as tumors. The method of biopsy may be using a needle (needle biopsy) or involving skin incision to collect tissue samples (open biopsy). The positive rate of tissue culture in open biopsy is higher than that in needle biopsy; however, open biopsy often necessitates general anesthesia with a risk of wound infection or bleeding, so that in practice, needle biopsy is frequently performed for the purpose of microbiologic diagnosis [29]. The reported positive rate of needle biopsy falls in the range of 40 – 80% [6, 30]. The areas from which tissue samples can be collected in needle biopsy are broadly divided into spinal and paraspinal tissues. In a study conducted on 136 patients with pyogenic spondylitis, the reported positive rate of tissue culture using biopsy samples was 39.7% (29/73) for spinal tissues and 63.5% (40/63) for paraspinal tissues [31]. Thus, if needle biopsy is to be performed for the microbiologic diagnosis of pyogenic spondylitis in patients showing concurrent paraspinal inflammation or abscess, it is recommended that the samples be collected from paraspinal rather than spinal tissues. The positive rate of tissue culture is reported to be high for cases showing paraspinal abscess, high CRP, or after open biopsy [30]. In the case of antibiotics treatment prior to biopsy, the positive rate of tissue culture decreased in some studies, while the rate was unaffected in others [32-35]. Nevertheless, it is more frequently reported that the positive rate falls if antibiotic treatment precedes biopsy. Some experts recommend that for a patient with pyogenic spondylitis, and with a history of antibiotics exposure but no evidence of sepsis or severe sepsis, a certain intervals of time should pass before performing the biopsy [6]. In a previous study, tissue biopsy was recommended to be performed 1 - 2 weeks after the discontinuation of antibiotic if the patient remained stable. Nonetheless, in a retrospective study conducted on 58 patients with pyogenic spondylitis and with antibiotic exposure within the last two weeks, the positive rate of tissue biopsy did not significantly differ between the case with washout period over five days and the case with less than two days [36]. What the results indicated was that the positive rate of tissue culture may not increase when biopsy is performed after a certain antibiotic washout period, despite theoretical validity. Further studies should be conducted regarding the necessary length of washout period on a larger number of patients as the number of subjects in previous studies was small.

Once the etiological microorganisms have been identified through needle biopsy, the respective antibiotics may be initiated for the treatment. However, if the microbial etiology remains unidentified, the empiric treatment may begin or the biopsy may be repeated [30]. For the second biopsy, either needle or open biopsy may be performed. If the microbial etiology is identified by the second biopsy, the respective antibiotics may be initiated for the treatment. If not, open biopsy should be performed or the empiric treatment should begin. The positive rate of tissue culture in the second needle biopsy is reported to be similar to that in the first needle biopsy [28], while open biopsy is known to have a higher positive rate [29, 37]. The possible side effects of needle biopsy include hemorrhage and damage on the surrounding organs, although it is extremely rare for side effects to occur [3, 38, 39].

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NUCLEIC ACID AMPLIFICATION TEST (NAAT)

Performing NAAT together with tissue culture using the spinal tissue samples collected through needle or open biopsy is helpful in microbiologic diagnosis. For NAAT, the PCR test for 16S rDNA is often used. The diagnostic utility of NAAT is well-known for other infectious diseases, as it is frequently used in the diagnosis of respiratory or gastrointestinal viral infection. Despite the general lack of studies regarding the diagnostic values of NAAT in patients with pyogenic spondylitis, the available data suggests that the sensitivity of NAAT is higher than tissue culture and it may thus be used as a complementary test to the microbial culture tests [40-42].

EMPIRIC TREATMENT

If a patient suspected of pyogenic spondylitis is not in condition of sepsis or severe sepsis, it is appropriate to identify the etiological microorganisms first before initiation of empiric antibiotics [25]. In the case of unidentified microbial etiology despite blood or tissue biopsy, the empiric treatment should begin based on the most probable microbial etiology. The most common microbial species that cause pyogenic spondylitis is *S. aureus* although its distribution varies according to the patient's age, sex, infection site, and past spinal surgery or procedure [4, 22]. If the patient is female, elderly, or has previous or concurrent urinary tract infection or intra-abdominal infection, Gram-negative bacilli may be suspected as the etiologic microorganism of pyogenic spondylitis [18, 19]. Gram-negative bacilli accounts for a relatively higher percentage among the etiologic species in thoracic or lumbar spine than in cervical or sacral spine. The distribution of etiological microorganisms of pyogenic spondylitis after spinal surgery or procedure differs from that in patients without a history of surgery or procedure [22]. *S. aureus* and CNS are the main etiologic species causing pyogenic spondylitis in patients with a history of spinal surgery or procedure, with CNS showing a higher proportion (30%). Another notable fact is the high rate of methicillin resistance shown by *S. aureus* and CNS isolated in patients with a previous spinal surgery or procedure [20, 22, 43].

To select the most suitable empiric antibiotics for a patient with pyogenic spondylitis of unidentified microbial etiology, the medical history, demographic characteristics, clinical characteristics, and imaging results should be taken into consideration. If the patient has never received a spinal surgery or procedure in the past, empiric antibiotics need not include vancomycin, based on the low probability of methicillin-resistant *S. aureus* or methicillin-resistant CNS. The suitable selection of antibiotics in this case includes the first generation cephalosporins, fluoroquinolone + rifampin, fluoroquinolone + clindamycin, or fluoroquinolone + beta-lactam/beta-lactamase inhibitor [44]. If the patient has previous or concurrent urinary tract infection or intra-abdominal infection, Gram-negative bacilli may be suspected and the empiric antibiotics should be selected accordingly. For pyogenic spondylitis in patients who have received a spinal surgery or procedure in the past, the microbial etiology shows a high percentage of *S. aureus* or CNS, and based on their high rate of methicillin resistance, vancomycin should be included as empiric antibiotics.

CONCLUSION

For the treatment of pyogenic spondylitis, at least 6-weeks of antibiotics treatment is required. Thus, to prevent prolonged use of unnecessary broad-spectrum antibiotics, it

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is essential that the etiological microorganisms are identified. For patients suspected of pyogenic spondylitis, blood culture is carried out, and if the microbial etiology cannot be determined based on the result, needle biopsy is performed so that a tissue sample can be collected from the infection site and used in culture tests on bacteria, mycobacteria, and fungi. NAAT should also be used where it is possible. If the microbial etiology is defined by the first needle biopsy, the appropriate antibiotics could be initiated. If not, the patient is treated with empiric antibiotics, or the second needle biopsy is performed. If the microbial etiology is thus defined, the appropriate treatment may begin for the patient; otherwise, an open biopsy is performed or the patient is treated with empiric antibiotics. For selecting the empiric antibiotics, patient's age, sex, infection site, and previous or concurrent urinary tract infection or intra-abdominal infection, are taken into consideration.

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