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## Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology

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# Chapter 3

## **Culture yield of repeat percutaneous image-guided biopsy after a negative initial biopsy in suspected spondylodiscitis: a systematic review**

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## Abstract

### Purpose

To systematically review published data on the culture yield of repeated (second) percutaneous image-guided biopsy after initial negative biopsy in suspected spondylodiscitis.

### Materials and Methods

A systematic search was performed of the PubMed/Medline and Embase databases. Methodological quality of included studies was assessed. The proportions of positive cultures among all initial biopsies and second biopsies (after initial negative biopsy) were calculated for each study and assessed for heterogeneity (defined as  $I^2 > 50\%$ ).

### Results

Eight studies, comprising a total of 107 patients who underwent a second percutaneous image-guided biopsy after an initial culture-negative biopsy in suspected spondylodiscitis, were included. All 8 studies were at risk of bias and had concerns regarding applicability, particularly with regard to patient selection, flow of patients through the study and timing of biopsy. The proportions of positive cultures among all initial biopsies ranged from 10.3% to 52.5%, and were subject to heterogeneity ( $I^2 = 73.7\%$ ). The proportions of positive cultures among all second biopsies after initial negative biopsy ranged from 0% to 60.0%, and were not subject to heterogeneity ( $I^2 = 38.7\%$ ).

### Conclusion

Although a second percutaneous image-guided biopsy may have some value in patients with suspected spondylodiscitis, its exact value remains unclear given the available poor-quality evidence. Future well-designed studies are needed to determine the role of a second percutaneous image-guided biopsy in this setting. Such studies should clearly describe the spectrum of patients that was selected for a second percutaneous image-guided biopsy, the method of biopsy, and differences with the first biopsy, if any.

## Introduction

Spondylodiscitis refers to infection of the vertebrae and intervertebral disc [1]. The incidence of spondylodiscitis is approximately 2.4 cases per 100,000 population [2, 3], and is on a steady rise due to an aging population with inherent co-morbidities, and improved case ascertainment, particularly related to the widespread use of magnetic resonance imaging (MRI) [1]. Because of its nonspecific presentation, a delay of 6-8 weeks between the onset of symptoms and diagnosis is not unusual [1, 2]. However, because spondylodiscitis can be complicated by abscess formation, orthopedic complications (vertebral collapse and hyperkyphosis), neurologic complications (motor weakness or paralysis), and even death (in approximately 6%) [1, 2], timely diagnosis and treatment initiation are essential. Current Infectious Diseases Society of America (IDSA) guidelines recommend performing spine MRI and obtaining blood cultures in all patients with suspected spondylodiscitis [4-6]. The same guidelines also recommend an image-guided biopsy when a microbiologic diagnosis has not been established by blood cultures or serologic tests [4, 5]. A recent meta-analysis showed the culture yield of initial image-guided biopsy in spondylodiscitis to be approximately 48% [7]. However, when both blood and biopsy cultures remain negative, it is unclear whether empirical antibiotic therapy should be started, if a repeated (second) image-guided biopsy should be performed, or if more invasive procedures such as percutaneous endoscopic discectomy and drainage (PEDD) or open excisional biopsy should be considered [7]. The advantage of a second image-guided biopsy is that it is less invasive than PEDD or an open excisional biopsy. However, because of the limited number of studies on this topic with relatively small sample sizes and heterogeneous methodology, the culture yield of a second image-guided biopsy is still unclear. Theoretically, if patient spectrum and technical factors related to the biopsy are the same for the first and second attempt, the culture yields will be the same. However, this may not be the case in clinical practice. Information on the culture yield of a second image-guided biopsy, as performed in clinical practice, is crucial for evidence-based clinical decision making. Therefore, the aim of this study was to systematically review published data on the culture yield of a second percutaneous image-guided biopsy after a negative initial biopsy in patients with suspected spondylodiscitis.

## Materials and Methods

### Search strategy

The PubMed/Medline and Embase databases were systematically searched for articles on the culture yield of a second percutaneous image-guided biopsy after an initial negative biopsy in suspected spondylodiscitis. The search comprised a combination of the search terms “spondylodiscitis OR spondylodiskitis OR discitis OR diskitis OR spondylitis OR spinal osteomyelitis OR vertebral osteomyelitis” AND “biopsy OR biopsies OR aspiration OR aspirations OR sample OR samples OR sampling OR samplings” AND “computed tomography OR computerized tomography OR CT OR CT-guided OR fluoroscopic OR percutaneous”. No date restriction was applied. The search was updated until 18 November 2017. References of articles that remained after the selection process were screened for potentially suitable additional articles.

### Study selection

Studies investigating the culture yield of a second percutaneous image-guided biopsy after a negative initial biopsy in suspected spondylodiscitis were eligible for inclusion. No language restriction was applied. Conference abstracts, case reports or series, editorials or letters, review articles, and meta-analyses were excluded. Articles that only reported the culture yield of initial percutaneous image-guided biopsy and that not did report or allow for the extraction of the culture yield of second biopsy after initial negative biopsy, were excluded. Articles that only included patients who underwent aspiration of postoperative paraspinal fluid collections or PEDD were excluded. When the same patient data were presented in more than one article, the article with the largest number of patients was selected. Three researchers (Ö.K, H.J.A.A., and T.C.K.) reviewed the titles and abstracts of the retrieved articles in consensus, applying the previously mentioned inclusion and exclusion criteria. Clearly ineligible articles were excluded at this stage. Subsequently, the same three researchers jointly reviewed the full text version of the remaining articles to determine their eligibility for inclusion.

### Study quality

Methodological quality of included studies was assessed using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS)-2 tool [8]. The QUADAS-2 tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing [8]. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of

concerns regarding applicability [8]. In the present study, image-guided biopsy and microbiological culture can be considered as both index test and reference test. Therefore, index test and reference standard were combined into one domain called “biopsy” for both risk of bias and applicability assessment. Risk of bias and concerns about applicability for each domain was judged as “high”, “unclear”, or “low”. If a study is judged as “low” on all domains relating to bias or applicability, then it is appropriate to have an overall judgment of “low risk of bias” or “low concern regarding applicability” for that study [8]. If a study is judged “high” or “unclear” in one or more domains, then it may be judged “at risk of bias” or as having “concerns regarding applicability” [8].

### Statistical analysis

The proportions of positive cultures (i.e. cultures with isolated bacteria in the biopsy) among all initial biopsies and second biopsies (after initial negative biopsy) were calculated for each individual study. Heterogeneity in positive culture yields across individual studies was assessed using the  $I^2$  statistic, with heterogeneity defined as  $I^2 > 50\%$  [9]. Statistical analyses were done using Comprehensive Meta-Analysis Version 3 software (Biostat, Englewood, Illinois, USA).

## Results

### Literature search

The systematic search yielded 1300 articles from PubMed/Medline and 920 articles from Embase. After reviewing titles and abstracts, 78 PubMed/Medline indexed articles and 62 Embase indexed articles remained. After discarding duplicates, 93 potentially eligible articles remained, and these were retrieved in full text format. After reviewing the full text article, 85 articles were excluded because they only reported the culture yield of initial percutaneous image-guided biopsy and did not report or allow for the extraction of the culture yield of repeated biopsy after initial negative biopsy. Finally, eight studies remained [10-17], comprising a total of 107 patients who underwent a second percutaneous image-guided biopsy after an initial negative biopsy in suspected spondylodiscitis. The characteristics of these studies are displayed in **Tables 1 and 2**.

**Table 1.** Characteristics of included studies and patients.

| Study (year)                | Country     | Data acquisition | No. of patients <sup>a</sup> | Age in years (range) <sup>b</sup>     | Gender (M/F) <sup>b</sup> | Patient spectrum <sup>a</sup>  | CRP levels in mg/L (range) <sup>a</sup> | Leukocyte count $\times 10^9$ (range) <sup>b</sup> |
|-----------------------------|-------------|------------------|------------------------------|---------------------------------------|---------------------------|--|---|--|
| Ahuja et al. [10] (2017)    | UK          | Retrospective    | 45                           | 62.3 <sup>b</sup> (28-87)             | 26/19                     | -Patients with suspected spinal infection based on clinical and MRI findings<br>-Postoperative spinal infections were excluded   | 58 <sup>c</sup> (30-90 <sup>b</sup> )   | 8.46 <sup>c</sup> (2.4-9)                          |
| Terreaux et al. [11] (2016) | France      | Retrospective    | 63                           | 68.2 <sup>b</sup> (NR)                | 34/29                     | -Patients with spontaneous spondylodiscitis and negative blood cultures<br>-Patients with postoperative spondylodiscitis, positive blood cultures before the development of spontaneous spondylodiscitis, spontaneous discitis with negative blood cultures investigated by surgical biopsy, tumors, and crystal deposition disease were excluded  | NR                                      | NR   |
| Gras et al. [12] (2014)     | France      | Retrospective    | 136                          | 58 <sup>c</sup> (47-69 <sup>d</sup> ) | 89/47                     | -Hospitalized patients $\geq 18$ years with spondylodiscitis, pre-biopsy negative blood culture(s), CT-guided biopsy by an interventional radiologist and one or more post-biopsy blood cultures (0-4 hours)<br>-Patients with continuous osteomyelitis due to decubitus ulcers, vertebral device, brucellosis, and tuberculous spondylodiscitis were excluded<br>-Patients receiving antibiotics within 2 weeks preceding the biopsy were also excluded | NR                                      | NR   |
| Kim et al. [13] (2013)      | South Korea | Retrospective    | 140                          | 65.1 <sup>b</sup> (16-89)             | 70/70                     | -Patients in whom fluoroscopy-guided biopsy was performed to confirm or rule out the clinical or radiological possibility of spondylodiscitis<br>-Patients who underwent biopsy for suspected primary bone tumor or metastases were excluded   | NR                                      | NR   |

Table 1 Continued

| Study (year)                   | Country | Data acquisition | No. of patients <sup>a</sup> | Age in years (range) <sup>b</sup> | Gender (M/F) <sup>c</sup> | Patient spectrum <sup>d</sup>  | CRP levels in mg/L (range) <sup>e</sup> | Leukocyte count $\times 10^9$ (range) <sup>f</sup> |
|--------------------------------|---------|------------------|------------------------------|-----------------------------------|---------------------------|--|---|--|
| Gasbarrini et al. [14] (2012)  | Italy   | Prospective      | 69                           | 60 <sup>b</sup> (5-85)            | 37/32                     | Patients in whom CT-guided biopsy was performed in case of infection indicated on MRI, elevated inflammation markers (ESR, CRP), with a thoracic, lumbar or sacral lesion (cervical lesions were excluded), the absence of bacteriological isolation elsewhere, the absence of indication for emergency surgery, and in whom no antibiotic therapy was initiated or who were outside the therapeutic window of a previously taken antibiotic | NR                                      | NR   |
| Lora-Iamayo et al. [15] (2011) | Spain   | Retrospective    | 72                           | 66 (NR)                           | 43/29                     | -Patients with pyogenic spondylodiscitis<br>-Postsurgical cases of pyogenic osteomyelitis, cases of facet joint infection with no involvement of intervertebral disc or vertebral bodies, and cases due to <i>Mycobacterium tuberculosis</i> , <i>Brucella</i> species, and fungus were excluded   | NR                                      | NR   |
| de Lucas et al. [16] (2009)    | Spain   | Retrospective    | 40                           | 58 <sup>b</sup> (1-88)            | 24/16                     | Patients with confirmed spondylodiscitis, based on imaging findings, positive cultures from CT-guided or surgical biopsy, or blood samples and satisfactory evolution after antibiotic treatment   | NR                                      | NR   |
| Friedman et al. [17] (2002)    | USA     | Retrospective    | 48                           | 68.2 <sup>b</sup> (NR)            | 26/22                     | Adult patients with spontaneous infectious spondylodiscitis who were treated by a single surgeon over a 5-year period and patients with postoperative discitis over the same time period   | NR                                      | NR   |

Notes:

<sup>a</sup> (Based on the) total number of patients that was included in this study; <sup>b</sup> Mean

<sup>c</sup> Median; <sup>d</sup> Interquartile range

Abbreviations: CRP: C-reactive protein; NR: Not reported



**Table 2.** MRI and biopsy methods.

| Study (year)                  | Availability of MRI before tissue sampling | MRI criteria for spondylodiscitis  | MRI readers | Time between MRI and biopsy | Time between initial and second biopsy |
|-------------------------------|--|--|-------------|-----------------------------|--|
| Ahuja et al. [10] (2017)      | Yes  | NR   | NR          | NR                          | NR                                     |
| Terreaux et al. [11] (2016)   | Yes (in 60/63 [95%])                       | NR   | NR          | NR                          | 14.4 <sup>a</sup> ± 7.9                |
| Gras et al. [12] (2014)       | NR   | NR   | NR          | NR                          | NR                                     |
| Kim et al. [13] (2013)        | NR   | NR   | NR          | NR                          | NR                                     |
| Gasbarrini et al. [14](2012)  | Yes  | Hypointense on T1, hyperintense on T2, morphologic consistent with infection | NR          | NR                          | NR                                     |
| Lora-Tamayo et al. [15](2011) | NR   | NR   | NR          | NR                          | NR                                     |
| de Lucas et al. [16](2009)    | Yes (in 32/40 [80%])                       | NR   | Radiologist | NR                          | NR                                     |
| Friedman et al. [17](2002)    | NR   | NR   | NR          | NR                          | NR                                     |

Notes:

<sup>a</sup> Mean; <sup>b</sup> Aspiration; <sup>b</sup> Both biopsies and aspirations were performed

Abbreviations: CT: Computed tomography; MR: Magnetic resonance imaging; NR: Not reported; NA: Not applicable

### Methodological quality assessment

Results of the quality assessment using the QUADAS-2 tool are displayed in **Table 3**. Overall, all studies were at risk of bias and all studies had concerns regarding applicability. There was high risk of bias in the domain patient selection in seven studies [10-16], because only a minority of patients with initial negative biopsy cultures underwent second biopsy and it was unclear why these patients were selected for repeated biopsy. There was unclear risk of bias and applicability concern in the domain of biopsy in seven studies, because they did not describe sufficient details on how percutaneous image-guided biopsy was performed in terms of image guidance, needle size, and acquired number of biopsy samples [10-12, 14-17]. There was unclear risk of bias in the domain of flow and timing in all eight studies [10-17], because the time frame between MRI, the first biopsies and

| Type of image guidance for biopsy | Gauge, no. of samples         | Tissue targeted   | Second biopsy of the same area as first biopsy | Physician(s) who performed biopsy                              |
|-----------------------------------|-------------------------------|---|--|--|
| CT                                | NR, NR                        | NR  | NR   | Radiologist  |
| CT or fluoroscopic                | 11 to 14, NR                  | Disc  | NR   | NR   |
| CT                                | NR, 2.5 <sup>a</sup>          | Vertebral corpus  | NR   | Interventional radiologist                                     |
| Fluoroscopic                      | 15, >2                        | Vertebral corpus / disc / paravertebral abscess               | 22/26 same area<br>4/26 different area         | NR   |
| CT                                | 8 or 11, NR                   | Bone / disc   | NR   | Both interventional radiologist and surgeon, whenever possible |
| CT                                | 13.55 to 22 <sup>c</sup> , NR | Vertebral corpus / disc / abscess / paraspinal phlegmon       | NR   | Musculoskeletal radiologists                                   |
| CT                                | 20-22, NA <sup>b</sup>        | Vertebral corpus / disc / paravertebral soft tissue / abscess | NR   | NR   |
| NR                                | NR                            | Disc  | NR   | NR   |

second biopsies was not described. In addition, in seven studies it was unclear if patients received antibiotic treatment between the first and second biopsy [10-15, 17]. There was unclear applicability concern in the domain of patient selection in all eight studies [10-17], because it was unclear if patients with a previous history of spondylodiscitis were included, which patients were selected for second biopsy, and which of these patients had already been treated with antibiotics. In addition, in four studies it was unclear if MRI was performed at all [12, 13, 15, 17], in four other studies no (clear) MRI criteria for spondylodiscitis were reported [10, 11, 14, 16], and in two studies it was unclear if patients with positive blood cultures before biopsy were excluded [10, 16].

**Table 3.** Quality assessment of included studies using the QUADAS-2 tool [8].

| Study (year)                   | Risk of bias      |         |                 | Applicability concerns |         |
|--------------------------------|-------------------|---------|-----------------|------------------------|---------|
|                                | Patient selection | Biopsy  | Flow and timing | Patient selection      | Biopsy  |
| Ahuja et al. [10] (2017)       | High              | Low     | Unclear         | Unclear                | Low     |
| Terreaux et al. [11] (2016)    | High              | Low     | Unclear         | Unclear                | Low     |
| Gras et al. [12] (2014)        | High              | Low     | Unclear         | Unclear                | Low     |
| Kim et al. [13] (2013)         | High              | Low     | Unclear         | Unclear                | Low     |
| Gasbarrini et al. [14] (2012)  | High              | Low     | Unclear         | Unclear                | Low     |
| Lora-Tamayo et al. [15] (2011) | High              | Low     | Unclear         | Unclear                | Low     |
| de Lucas et al. [16] (2009)    | High              | Low     | Unclear         | Unclear                | Low     |
| Friedman et al. [17] (2002)    | Low               | Unclear | Unclear         | Unclear                | Unclear |

Note:

The following signaling questions were used to assess the risk of bias and applicability concerns (which were then scored as high risk, low risk, or unclear):

*Risk of bias:*

1. Patient selection. Did most patients with initial negative biopsy cultures undergo a repeated biopsy? Was it reported why patients were selected for repeated biopsy?
2. Biopsy. Could the conduct or interpretation of biopsy have introduced bias?
3. Flow and timing. Was MRI performed within two months before tissue biopsy? Was the repeated biopsy performed within one month of the initial biopsy and was no therapy administered between the initial and repeated biopsy?

*Applicability concerns:*

4. Patient selection. Were patients with a previous history of spondylodiscitis excluded? Were patients with positive blood cultures before biopsy excluded? Was MRI performed before biopsy and were the criteria for positivity reported? Which patients underwent a repeated biopsy after an initial negative biopsy?
5. Biopsy. Was fluoroscopic or CT guidance used? What needle size was used? How many biopsy samples were acquired?

### Culture yield of repeated biopsy

Culture yields of initial and second biopsies for each individual study are displayed in **Table 4**. The proportions of positive cultures among all initial biopsies (n=507) ranged from 10.3% to 52.5% (with  $I^2=73.7%$ ). The proportions of positive cultures among all second biopsies (n=107) ranged from 0% to 60.0% (with  $I^2=38.7%$ ) (**Figure 1**).

**Table 4.** Results of included studies.

| Study (year)                | No. of culture-positive initial biopsies | Cultured micro-organisms of initial biopsy  | No. of culture-positive second biopsies after initial negative biopsy* | Cultured micro-organisms on repeated biopsy*  |
|-----------------------------|--|---|--|---|
| Ahuja et al. [10] (2017)    | 19/45 (42.2%)                            | <ul style="list-style-type: none"> <li>-<i>Escherichia coli</i> (n=2)</li> <li>-<i>Propionibacterium acnes</i> (n=2)</li> <li>-<i>Staphylococcus aureus</i> (n=2)</li> <li>-<i>Candida albicans</i> (n=1)</li> <li>-Coagulase negative staphylococci (n=1)</li> <li>-<i>Enterococcus faecium</i> (n=1)</li> <li>-Group B haemolytic <i>Streptococci</i> (n=1)</li> <li>-<i>Klebsiella oxytoca</i> (n=1)</li> <li>-Methicillin-resistant <i>Staphylococcus aureus</i> (n=1)</li> <li>-<i>Mycobacterium tuberculosis</i> = (n=1)</li> <li>-<i>Pseudomonas aeruginosa</i> = (n=1)</li> <li>-<i>Staphylococcus capitis</i> = (n=1)</li> <li>-<i>Streptococcus sanguis</i> = (n=1)</li> <li>-<i>Staphylococcus aureus</i> and <i>propionibacterium acnes</i> (n=1)</li> <li>-Coagulase-negative <i>Staphylococci</i> and <i>Propionibacterium acnes</i> and <i>Streptococcus mutans</i> (n=1)</li> <li>-Non-haemolytic <i>Streptococci</i> and <i>Propionibacterium</i> sp. (n=1)</li> </ul> | 1/7 (14.3%)  | <ul style="list-style-type: none"> <li>-<i>Staphylococcus epidermidis</i> and <i>Propionibacterium acnes</i> (n=1)</li> </ul>   |
| Terreaux et al. [11] (2016) | 33/63 (52.4%)                            | <ul style="list-style-type: none"> <li>-Methicillin-susceptible <i>Staphylococcus aureus</i> (n=9)</li> <li>-<i>Staphylococcus epidermidis</i> (n=8)</li> <li>-<i>Mycobacterium tuberculosis</i> (n=3)</li> <li>-<i>Streptococcus constellatus</i> (n=3)</li> <li>-<i>Propionibacterium acnes</i> = (n=2)</li> <li>-Methicillin-resistant <i>Staphylococcus aureus</i> (n=1)</li> <li>-<i>Enterococcus hirae</i> (n=1)</li> <li>-<i>Klebsiella pneumoniae</i> (n=1)</li> <li>-<i>Staphylococcus caprae</i> (n=1)</li> <li>-<i>Streptococcus mutans</i> (n=1)</li> <li>-<i>Streptococcus dysgalactiae</i> (n=1)</li> <li>-<i>Streptococcus milleri</i> type 2 (n=1)</li> <li>-<i>Escherichia coli</i> (n=1)</li> </ul>   | 6/10 (60.0%)   | <ul style="list-style-type: none"> <li>-<i>Streptococcus</i> (n = 3)</li> <li>-<i>Prevotella denticola</i> (n=1)</li> <li>-<i>Pseudomonas aeruginosa</i> (n = 1)</li> <li>-<i>Mycobacterium tuberculosis</i> (n=1)</li> </ul> |

Table 4. Continued

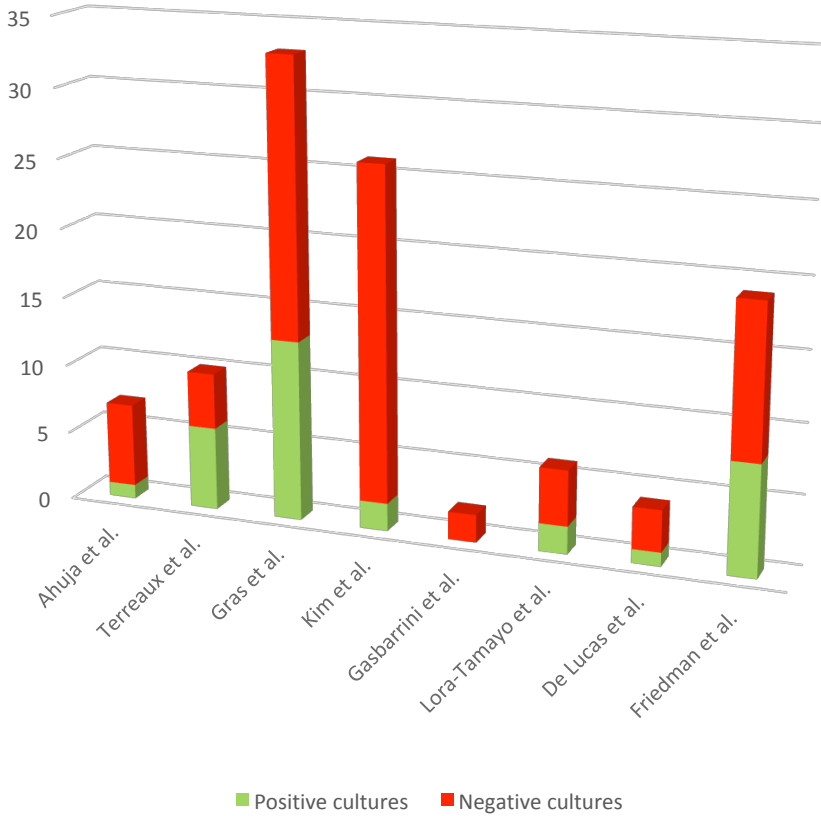
| Study (year)                   | No. of culture-positive initial biopsies | Cultured micro-organisms of initial biopsy   | No. of culture-positive second biopsies after initial negative biopsy <sup>a</sup> | Cultured micro-organisms on repeated biopsy <sup>a</sup>                          |
|--------------------------------|--|--|--|---|
| Gras et al. [12] (2014)        | 59/136 (43.4%)                           | NR   | 13/33 (39.4%)  | NR  |
| Kim et al. [13] (2013)         | 51/170 (30.0%)                           | - <i>Mycobacterium tuberculosis</i> (n=26)<br>- <i>Staphylococcus aureus</i> (n=13)<br>- <i>Streptococcus agalactiae</i> (n=4)<br>- <i>Streptococcus viridans</i> (n=2)<br>-Coagulase-negative <i>Staphylococcus</i> organisms (n=1)<br>- <i>Escherichia coli</i> (n=1)<br>- <i>Enterococcus faecalis</i> (n=1)<br>- <i>Enterobacter cloacae</i> (n=1)<br>- <i>Staphylococcus epidermidis</i> (n=1)<br>- <i>Klebsiella</i> (n=1) | 2/26 (7.7%)  | - <i>Mycobacterium tuberculosis</i> (n=1)<br>- <i>Staphylococcus aureus</i> (n=1) |
| Gasbarrini et al. [14] (2012)  | 11/24 (45.8%) <sup>b</sup>               | - <i>Mycobacterium tuberculosis</i> (n=3)<br>- <i>Staphylococcus hominis</i> (n=2)<br>-Methicillin-resistant <i>Staphylococcus aureus</i> (n=1)<br>-Methicillin-susceptible <i>Staphylococcus aureus</i> (n=1)<br>- <i>Streptococcus</i> spp (n=1)<br>- <i>Streptococcus stellatus</i> (n=1)<br>- <i>Pseudomonas aeruginosa</i> (n=1)<br>- <i>Escherichia coli</i> (n=1)<br>NR   | 0/2 (0.0%)   | NA  |
| Lora-Tamayo et al. [15] (2011) | 3/29 (10.3%)                             |  | 2/6 (33.3%)  | NR  |
| de Lucas et al. [16] (2009)    | NR <sup>c</sup>                          |  | 1/4 (25.0%) <sup>d</sup>   | - <i>Mycobacterium tuberculosis</i> (n=1)   |
| Friedman et al. [17] (2002)    | 21/40 (52.5%)                            |  | 8/19 (42.1%)   | NR  |

## Notes:

<sup>a</sup> No other diagnoses than spondylodiscitis (if present) were reported after initial or second biopsy; <sup>b</sup> Including one case that was culture-negative, but in whom *Mycobacterium tuberculosis* was molecularly detected by polymerase chain reaction.; <sup>c</sup> Initial and second CT-guided biopsy results could not be separated with certainty; <sup>d</sup> Antibiotics were given after the first negative biopsy in 3 cases, and no antibiotics were given to the other case that turned out to be culture-positive

## Abbreviations:

NR: not reported; NA: not applicable



**Figure 1.** Number of positive and negative cultures on repeated biopsy (after initial negative biopsy) in suspected spondylodiscitis, for each of the 8 included studies.

## Discussion

The systematic review included eight studies comprising a total sample size of 107 patients who underwent a second image-guided biopsy after a culture-negative initial biopsy in suspected spondylodiscitis. The positive culture yield of a second CT-guided biopsy ranged between approximately 10% and 50% among included studies. However, these percentages should be interpreted cautiously because the overall quality of included studies was poor to moderate, with several important methodological concerns. First, in seven studies only a minority of patients with initial negative biopsy cultures underwent second biopsy [10-16]. Since six of these seven studies were performed retrospectively [10-13, 15,

16], the decision to rebiopsy was most likely based on clinical and radiological grounds, which may include insufficient treatment response and disease extent on MRI (e.g. presence of large paravertebral phlegmon and/or abscess). These factors might overestimate the culture yield if extrapolated to all patients with an initial negative biopsy culture. Although the culture-positive rebiopsy yields do reflect clinical practice, the exact reasons why the patients in these studies were rebiopsied, remain unclear. Furthermore, from the eight included studies it was unclear how many of the patients with initial culture-negative biopsies eventually had positive blood cultures, how many underwent PEDD or open biopsy, and how many received empirical antibiotic therapy without any further diagnostic interventions [10-17]. Second, there was poor reporting on the use and interpretation of MRI before biopsy. MRI is regarded as the imaging method of choice for the detection of spondylodiscitis and the discrimination from other conditions such as noninfectious inflammatory and degenerative disease that may simulate spinal infection [18]. For these reasons, IDSA guidelines recommend to perform spine MRI before biopsy in all patients with suspected spondylodiscitis [4-6]. However, four studies did not report if MRI was performed [12, 13, 15, 17] and the four other studies did not report (clear) MRI criteria for spondylodiscitis [10, 11, 14, 16]. In addition, none of the eight included studies reported the time interval between MRI and biopsy. This rather poor prebiopsy MRI assessment may have negatively affected the culture yields because of potential data contamination with spondylodiscitis mimickers such as Modic type I degeneration, acute Schmorl node, and (osteoporotic) fractures [18]. Third, none of the eight studies reported if patients with a previous history of spondylodiscitis were excluded. MRI findings in these patients are non-specific, correlate poorly to clinical and laboratory findings, and may overestimate the diagnosis of spondylodiscitis [19]. This issue may have affected culture yields. Fourth, seven of eight included studies reported variable anatomic targets for biopsy (disc, vertebral corpus, and/or paravertebral soft tissue) [11-17], whereas one study did not report which anatomic target was biopsied [10]. Variation in anatomic targets may also have affected culture yields. On the other hand, a previous study has shown that there were no statistically significant differences between the yields of endplate-disc, disc-only, and paravertebral soft-tissue biopsies [20]. Despite the variations in patient populations and methodology among included studies, proportions of positive culture yields among second biopsies were statistically homogeneous, but this may be due to the relatively small sample sizes of included studies.

This systematic review had several limitations. First, although 93 potentially eligible articles were considered after screening titles and abstracts, only eight studies with 107 patients who underwent repeated biopsy, remained for analysis. Second, due to the low number of studies and underreported data, it was not possible to perform further subgroup analyses to determine if any clinical, laboratory, and/or imaging parameters are associated with positive repeated biopsy cultures. Third, although the culture yield of second biopsy was determined, it remains unclear which strategy (i.e. additional blood culture, second biopsy, PEDD, open biopsy, and/or empirical antibiotic therapy without any further diagnostic interventions) is most (cost-)effective in patients with an initial culture-negative biopsy. Thus, future prospective studies with larger sample sizes are needed.

In conclusion, although a second percutaneous image-guided biopsy may have some value in patients with suspected spondylodiscitis, its exact value remains unclear given the available poor-quality evidence. Future well-designed studies are needed to determine the role of a second percutaneous image-guided biopsy in this setting. Such studies should clearly describe the spectrum of patients that was selected for a second percutaneous image-guided biopsy, the method of biopsy, and differences compared with the first biopsy, if any.



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# **PART II**

## **Pediatric oncology**