

Histopathology of Infective Endocarditis

Bobbi S. Pritt, MD, MSc

Mayo Clinic, Rochester, MN

Introduction

There are several important principles for detection of infectious endocarditis. Unlike other infections, the patients are often on antibiotics prior to surgery and routine bacterial cultures are commonly negative. Therefore, histopathology, and occasionally molecular testing, plays an important role in confirming the presence of infection.

Causative Agents

Viridans streptococci and staphylococci are the most common causes of native valve endocarditis, while coagulase-negative staphylococci and *Staphylococcus aureus* are more commonly seen in cases of prosthetic valve endocarditis. Other causes of endocarditis include the HACEK group of organisms (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella* species), *Bartonella* spp., *Brucella* spp., *Coxiella* spp., *Tropheryma whipplei* and various fungi. Rarely, mycobacteria may also cause endocarditis.

Basic Diagnostic Principles

The following are basic principles regarding identification of organisms using microscopic and molecular analyses:

1. Histopathologic exam generally reveals a neutrophilic-predominant inflammatory infiltrate, as well as lymphocytes, histiocytes and, rarely, multinucleated giant cells.
2. Endocarditis due to intracellular or fastidious organisms (e.g., *Coxiella*, *Bartonella*, and *Brucella* species) shows more fibrosis with calcifications and mononuclear cell infiltrates.
3. Bacteria may be visible on H&E, and are often are basophilic (Figure 1). This does not necessarily correlate with their staining reaction on Gram stain (e.g. Gram positive or Gram negative). A Gram stain is needed to definitively access the Gram categorization.
4. The tissue Gram stain works the same way as it does in the microbiology lab with a few caveats:
 - a. High magnification is often needed for interpretation (e.g. 500 to 1000x with oil immersion), especially for characterizing bacterial morphology (Figures 2, 3).
 - b. Decolorization may occur, particularly when bacteria are at the edge of the slide.
 - c. Morphology may be difficult to appreciate in the thick regions; bacterial shape and size are best appreciated at the edges of growth.

- d. Bacterial morphology may undergo alterations with antibiotic treatment; bacteria may become enlarged (cocci) or elongated (bacilli), (Figures 4, 5).
 - e. Non-viable organisms (e.g. treated with antibiotics) may fail to take up the Gram stain and appear Gram “invisible”.
5. Gomori methenamine silver (GMS) and/or periodic acid Schiff (PAS) are useful stains for:
 - a. Highlighting non-viable, “Gram-invisible” organisms. GMS should be routinely performed for this purpose when infective endocarditis is suspected.
 - b. Fungi
 - c. *Tropheryma whipplei* (agent of Whipple’s disease); organisms are within macrophages and are strongly positive with PAS, including after diastase treatment.
 6. Whipple’s disease should be suspected when numerous foamy histiocytes are present (Figure 6). In these instances, a PAS stain will demonstrate numerous bacilli within histiocytes
 7. Molecular methods show greater sensitivity using fresh tissue and it therefore may be desirable to set aside a portion of the excised vegetation at the time of surgery for future molecular studies pending results of the bacterial cultures and histopathologic examination. Molecular testing is rarely positive when organisms are not visible on Gram- or GMS-stained sections, and therefore the results of the histopathologic examination should be used to evaluate the need for additional testing.

References:

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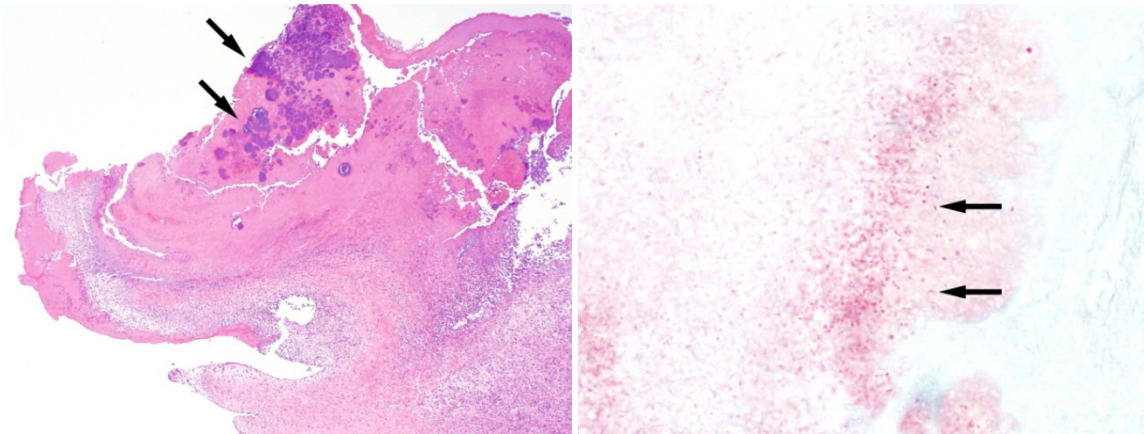


Figure 1. *Streptococcus pyogenes* endocarditis, showing a large vegetation with a fibrinous exudate on the free edge of the valve and associated bacteria in dark purple clusters (arrows). Numerous inflammatory cells are seen in the basal portion (H&E, 40x). Figure 2. Endocarditis due to *Haemophilus parainfluenzae*, one of the HACEK organisms, showing faintly staining Gram-negative bacteria (arrows) (Gram, 1000x).

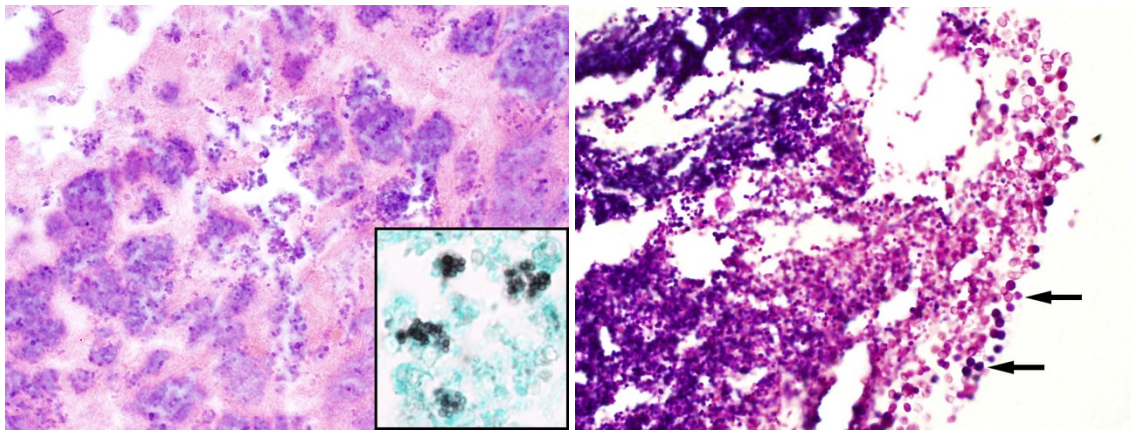


Figure 3. *Streptococcus pyogenes* endocarditis, showing numerous coccoid bacteria in dark purple clusters (H&E, 1000x). The organisms are somewhat larger than expected, likely due to antibiotic effect. The inset demonstrates the organisms on GMS stain. Figure 4. Another case of *S. pyogenes* endocarditis showing enlarged cocci (right side, arrows) due to antibiotic effect (Gram, 1000x).

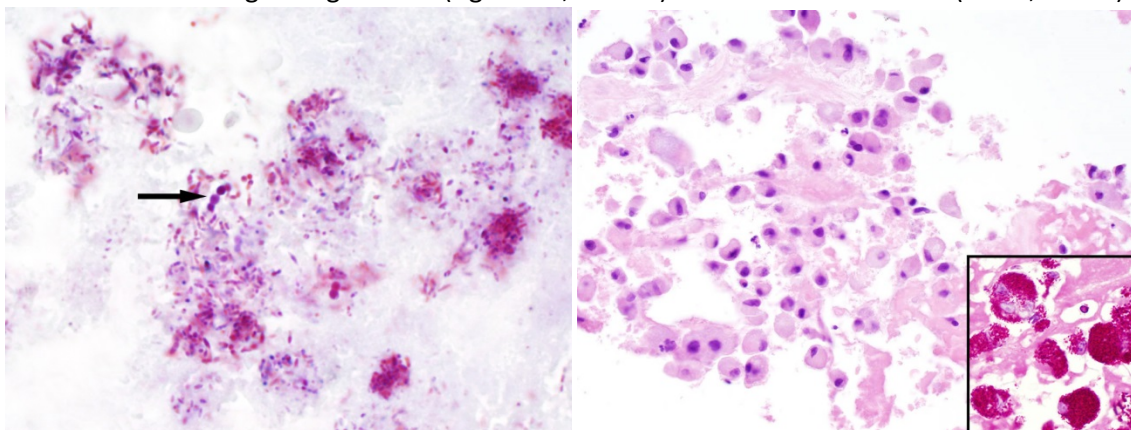


Figure 5. Viridans streptococcus endocarditis, showing pleomorphic Gram-positive bacteria, including typical-appearing short chains of Gram-positive cocci (arrow) and atypical elongated and Gram-negative forms (Gram, 1000x). Figure 6. *Tropheryma whipplei* endocarditis, showing foamy macrophages within the vegetation (H&E, 400x). Intracellular bacilli were highlighted using a PAS stain with diastase (inset, 1000x).