

Infective Endocarditis due to *Achromobacter Xylosoxidans*

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Abstract: *Achromobacter xylosoxidans* was first described by Yabuuchi and Ohyama in 1971 from purulent ear discharge of patients with chronic, inflammatory otitis media. Endocarditis due to *Achromobacter xylosoxidans* species is a very rare yet serious, endovascular infection. Affected individuals are usually immunocompromised, but nosocomial outbreaks have also been defined. It has a near-fatal outcome without surgical intervention. The clinical presentation of IE is highly variable which makes its diagnosis very difficult. The diagnosis of infectious endocarditis requires multiple clinical (modified Duke Criteria), laboratory (microbiological), and imaging findings (CT scan, MRI etc.). The treatment of infections caused by this organism is difficult due to the lack of a standard therapy and resistance to several antibiotics.

Keywords: *Achromobacter xylosoxidans*, Endocarditis, immunocompromised, modified Duke Criteria

1. Introduction

Achromobacter xylosoxidans formerly called *Alcaligenes xylosoxidans* is a motile, Gram negative, aerobic rod bacterium. Due to its ability to easily oxidize xylose, it has been named *xylosoxidans*. It was first described by Yabuuchi and Ohyama in 1971 from purulent ear discharge of patients with chronic, inflammatory otitis media¹. It is primarily found in contaminated water or soil, but it is uncommon source of bloodstream infections in humans². Infections with the pathogen vary and are traditionally noted in immune compromised patients including those with tumors, blood diseases, hypogammaglobulinemia, or acquired immune deficiency syndrome (AIDS), or those who have undergone organ transplant but nosocomial outbreaks have also been defined. Though accepted as an opportunistic microorganism with low pathogenicity, *A. xylosoxidans* can lead to serious infections in immunocompromised individuals. The treatment of patients with *A. xylosoxidans* bacteraemia is challenging due to the fact that this microorganism carries both intrinsic and acquired mechanisms of resistance, often conferring a phenotype of multidrug resistance (MDR)^{3, 4}. In addition, current data on this uncommon entity is mostly limited to very small series or a single case report which makes the treatment even more difficult.

Infective endocarditis (IE) is defined as microbial infection of the endothelial surfaces of the heart or iatrogenic foreign bodies like prosthetic valves and other intracardiac devices. Infective endocarditis commonly involves heart valves, but may occur at sites of septal defects, chordae tendineae or mural endocardium. May also occur at arteriovenous (AV) shunts, arterioarterial shunts [patent ductus arteriosus (PDA)] or coarctation of aorta⁵. *Achromobacter* species infective endocarditis is associated with underlying immunodeficiencies or prosthetic heart valves and devices. Infective endocarditis is a serious and sometimes fatal illness. IE due to *Achromobacter xylosoxidans* is very rare only few cases are reported in whole world. *Achromobacter xylosoxidans* is of epidemiological significance due to its role as a hospital pathogen, its antimicrobial resistance profile and its implication in

outbreaks⁶. IE has an annual incidence of 3–10/100,000 of the population with a mortality of up to 30% at 30 days, and its diagnosis remains challenging since new etiologic agents have been increasingly reported. Similarly, the incidence of IE is increasing in the elderly population, which may present non-characteristic clinical symptoms, such as fatigue, malaise, and anorexia^{7, 8}.

Clinical Manifestations

The clinical presentation of IE is highly variable and may present as an acute, subacute or chronic condition reflecting the variable causative microorganisms, underlying cardiac conditions and pre-existing comorbidities. The presenting symptoms are a low-grade persistent fever without an obvious cause and fatigue and shortness of breath on exertion. Patients also may have joint pain (arthralgia) and muscle pain (myalgia) and their health care provider may hear a new or changing murmur. In addition, the following signs and symptoms occur:

- Heart murmur not previously present or a changed heart murmur (Presents in 80% of endocarditis patients)
- A higher fever of 100 – 103 degrees F
- Flu-like symptoms including chills
- Shortness of breath at rest
- Night sweats
- Chest pain while breathing
- Swelling in the feet, legs or abdomen
- Rapid heartbeat (tachycardia)
- Loss of appetite leading to weight loss
- Blood or blood cells in the urine (hematuria)
- Small red spots in the conjunctiva of the eyes and fingernails (splinter hemorrhages)
- Small painless spots on the palms of the hands or soles of the feet (Janeway lesions)
- Pain nodules in the fingertips (Osler nodes)

Infection on the heart valve results in destruction of the leaflet tissue, leaking of the valve and heart failure. Extension of infection into tissue next to valve may result in an abscess with rupture between different chambers of the heart. Clots (emboli) resulting from infective endocarditis may produce serious damage. Symptoms depend upon the

location of the clot. In 20-40% of individuals with infective endocarditis, clots lodge in the brain and may cause weakness on one side of the body, loss of vision or stroke. Clots may also cause abdominal pain, flank pain, or arterial insufficiency in an extremity. An eye doctor might see bleeding in the back of the eye (Roth spots). Damage from clots may be temporary or permanent^{9,10}.

Predisposing Risk Factors

Risk factors that contribute to the onset of Infective Endocarditis include:

- Intravenous drug use with a needle contaminated with bacteria or fungi
- Presence of an artificial (prosthetic) heart valve or other valve repair material
- Presence of a cardiac pacemaker lead
- Previous infective endocarditis
- Mitral valve prolapse with valve leakage
- An aortic valve with only 2 (instead of the normal 3 valve leaflets). This condition, called a bicuspid aortic valve, is present in about 1% of people.
- Narrowing (stenosis) of the aortic valve due to age-related calcification
- Other abnormal valves caused by rheumatic fever and degenerative conditions
- Congenital heart disease, especially if repaired with artificial material
- chronic kidney disease (particularly dialysis patients)
- chronic liver disease
- malignancy
- advanced age
- corticosteroid use
- poorly controlled diabetes
- indwelling line for venous access
- immunocompromised state (including HIV infection).

Diagnosis

The diagnosis of infectious endocarditis requires multiple clinical, laboratory, and imaging findings. Overdiagnosis and underdiagnosis of infectious endocarditis can be problematic; a missed diagnosis could prove fatal, whereas overdiagnosis can result in weeks of unnecessary antibiotic treatment. Diagnosis of infective endocarditis can be done based on pathology or by meeting certain clinical diagnostic criteria. These criteria are known as the modified Duke Clinical Criteria^{11, 12}. These have an overall sensitivity of 80% but this is significantly lower in cases of prosthetic valve endocarditis or implantable electronic device infections. Here, clinical suspicion, microbiological correlation and additional imaging may be required with whole body computed tomography (CT), cerebral magnetic resonance imaging (MRI) or increasingly 18F-labelled fluoro-2- deoxyglucose positron emission tomography (18F-FDG-PET) / CT^{13, 14}.

Endocarditis Diagnostic Criteria -- Modified Duke Criteria

2. Major Criteria

A. Supportive laboratory evidence

Typical microorganism for infective endocarditis from two separate blood cultures: viridans streptococci, *Staphylococcus aureus*, *Streptococcus bovis*, HACEK group (*Haemophilus spp.*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella spp.*, and *Kingella kingae*) or Community-acquired enterococci, in the absence of a primary focus

Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hours apart or

Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from all of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart.

Single positive blood culture for *Coxiella burnetii* or phase I antibody titer >1:800

B. Evidence of endocardial involvement

Echocardiogram supportive of infective endocarditis.

1. Type of study

TEE recommended as first test in the following patients: a) prosthetic valve endocarditis; or b) those with at least "possible" endocarditis by clinical criteria; or c) those with suspected complicated endocarditis, such as paravalvular abscess. **TTE recommended as first test in all other patients**

2. Definition of positive findings: oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation or myocardial abscess or new partial dehiscence of prosthetic valve

C. New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

Minor Criteria

Predisposing heart condition or intravenous drug use

Fever ≥ 38.0 C (100.4 F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor

Positive blood culture not meeting major criterion as noted previously (Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with infective endocarditis

Definite infective endocarditis

Pathologic criteria

- 1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- 2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria

- 1) 2 major criteria; or
- 2) 1 major criterion and 3 minor criteria; or
- 3) 5 minor criteria

Possible infective endocarditis

- 1) 1 major criterion and 1 minor criterion; or
- 2) 3 minor criteria

Rejected

- 1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
- 2) Resolution of infective endocarditis syndrome with antibiotic therapy for <4 days; or
- 3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for <4 days; or
- 4) Does not meet criteria for possible infective endocarditis, as above¹⁴⁻¹⁷

Treatment of Infective Endocarditis due to *Achromobacter xylosoxidans*

Successful treatment of infective endocarditis (IE) relies on microbial eradication by antimicrobial drugs. Surgery plays a major role in the treatment of IE¹⁸, by removing infected material and draining abscesses. Bacteria are present in vegetations and biofilms, e.g., in prosthetic valve endocarditis (PVE), and justify the need for prolonged therapy (6 weeks) to fully sterilize infected heart valves. In both native valve endocarditis (NVE) and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery¹⁹. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

Empirical Antimicrobial Therapy

Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30 min intervals before initiation of antibiotics. The initial choice of empirical treatment depends on these considerations:

- a) Whether the patient has received prior antibiotic therapy or not;
- b) Whether the infection affects a native valve or a prosthesis (and, if so, when surgery was performed [early vs late PVE]);

In some centers, empiric therapy and blood culture negative infective endocarditis (BCNIE) treatments are different depending on whether they are community or nosocomial acquired (increased risk of staphylococcus and Fungi).

Protocol

- a) Community-acquired NVE and late PVE (>1 year): Amoxicillin 12 g/day + Gentamicin 3 mg/kg/day (one shot)
- b) Early PVE (<1 year), Device-related IE : Vancomycin 30 mg/kg/j + Gentamicin 3 mg/kg/day (one shot)

According to existing reports, *A. xylosoxidans* has a high resistance against antibiotics, making treatment difficult, with recent research describing intrinsic beta-lactamases and efflux pumps as mechanisms of resistance²⁰. It has been suggested that the most active antibiotic agents against *A. xylosoxidans* are imipenem, piperacillin-tazobactam, ceftazidime, tigecycline, colistin and trimethoprim-sulfamethoxazole. Resistance was found in second- or third-generation cephalosporins except ceftazidime and fluoroquinolones²¹. Resistances to aminoglycosides are quite

common. Antimicrobial combinations such as piperacillin plus gentamycin, azitromycin plus doxycycline, and azitromycin plus TMP-SMZ have been tested with favorable results. Susceptibility to the fluoroquinolones is variable. High concentrations of colistin inhibit most strains²². Surgical intervention became very important in case the antibiotics does not work. Due to its high resistance against antibiotics surgery is often needed.

3. Conclusion

Infective endocarditis secondary to *Achromobacter xylosoxidans* is very rare, till 2017 only 18 cases of *A. xylosoxidans* endocarditis in the English language are reported. Due to this lack of data the treatment of IE due to *Achromobacter xylosoxidans* is also very difficult, it has a near-fatal outcome without surgical intervention. Other things that make the treatment of patients with *A. xylosoxidans* endocarditis challenging is due to the fact that this microorganism carries both intrinsic and acquired mechanisms of resistance, often conferring a phenotype of multidrug resistance (MDR). Diagnosis of IE is very difficult which increases the mortality rate of patient. The only way to decrease the mortality rate is by early diagnosis and rational use of antibiotic to treat the infection. Optimal use of empirical antibiotic therapy is also necessary.

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