THE NORTHERN HOSPITAL

BACTERIAL ENDOCARDITIS

Niccolo Machiavelli, by Santo di Tito, (1536 -1603) Palazzo Vecchio Florence

"As the doctors say of a wasting disease, to start with it is easy to cure but difficult to diagnose; after a time, unless it has been diagnosed and treated at the outset, it becomes easy to diagnose but difficult to cure. So it is in politics. Political disorders can be quickly healed if they are seen well in advance (and only a prudent ruler has such foresight); when for lack of a diagnosis, they are allowed to grow in such a way that everyone can recognize them, remedies are too late"

Niccolo Machiavelli, The Prince, 1513-1514.

Though not widely read during his life time Niccolo Machiavelli's "The Prince" has become one of the iconic literary masterpieces of the Western world. Many works before his, beginning with Plato's "Republic" and many since such as Jean Jacques Rousseau's "Emile" have tried to define what the "perfect" society ought to be. These works were based however on the wishful thinking of philosophers with little understanding of the "real world". Machiavelli's genius lay in his ability to assess and understand human nature as it truly is. Shocking to many of his time and since, it was work that for the first time in history told of how a prince could attain and maintain a perfect society not based on a starry eyed ideal but within the constraints of the real world. Drawing on his own vast experience as a diplomat within the treacherous and turbulent world of Renaissance Italy he stated uncompromisingly what to varying degree most governments actually do, but none profess to do. Having dealt at first hand with all levels of society from the Emperor Maximilian of the Holy Roman Empire, King Louis XII of France, Pope Julius II, the infamous Cesare Borgia and his equally infamous father Pope Alexander VI to Leonardo da Vinci, to the common soldier, local farm workers, actresses of "ill repute" soldiers and prostitutes, he came to know "human nature"

His earliest biographer Pasquale Villari, (1826-1917) wrote of him, "Of middle height, slender figure, sparkling eyes, dark hair, rather a small head, a slightly aquiline nose, a tightly closed mouth. All about him bore the impress of a wry accurate observer and thinker. He could not easily rid himself of the sarcastic expression continually playing round his mouth and flashing from his eyes, which gave him the air of a cold impassable calculator..."

His most recent biographer, Michael White, wrote of him, "...Machiavelli was a commanding presence in any company. He was cool calm astute, probing and wise. He could size up others very quickly with very little to go on. Most of the time he played his cards close to his chest, but he was never afraid to express a sincerely held opinion…he understood how the world worked and he could make piercing critical judgments with apparent ease"

We can do well to heed the wise words of Niccolo in the difficult case of endocarditis. Although readily treated if it is diagnosed early it can be an extremely difficult diagnosis to make in the first instance. Like the prudent ruler we must have foresight by maintaining a high index of suspicion for the condition especially in those who are predisposed. If this is not done the disease will surely progress, to the stage where the diagnosis will be obvious to everyone, but unfortunately by then it may be too late for our remedies to cure them.

BACTERIAL ENDOCARDITIS

Introduction

Infective endocarditis is a microbial infection of the endocardial surface of the heart.

There are a number of pathologies including fungal infections and rheumatologic diseases which may lead to endocarditis, but the most important is **bacterial endocarditis.**

It may be acute, or subacute / chronic.

The characteristic pathological lesion, the "**vegetation**", is composed of a collection of platelets, fibrin, microorganisms, and inflammatory cells.

It most commonly involves heart valves but may also occur at the site of a septal defect, on the chordae tendineae, or on the mural endocardium.

Bacterial endocarditis is a *commonly missed* diagnosis as symptoms and signs are very non-specific, and so called "classical" signs are frequently absent.

Most commonly patients will simply present as a PUO.

A high index of suspicion must be maintained especially for those patients who at at increased risk for the condition.

Bacterial endocarditis should be considered as a multisystem disease and not simply a cardiac disease. Septic embolic complications are legion and may be the major reason for initial presentation.

Epidemiology

The condition seems to be most prevalent in the fifth and sixth decades, however it can occur an any age if a predisposing condition exists.

Prosthetic valve endocarditis accounts for up to 30 % of cases.

In developing countries, **rheumatic fever** remains the commonest risk factor for infective endocarditis.

Intravenous drug use is a particular risk factor in Australia.

Pathophysiology

Organisms:

The 3 principal causative organisms are:

1. **Staphylococcus aureus**:

- Is now the commonest cause.
- It is especially seen in intravenous drug users, and accounts for the majority of cases of right sided endocarditis)

2. Streptococcus species:
    - Including S. viridans, in particular in cases of poor dental hygiene.
3. Enterococci are seen in older age groups (> 60 years)

Many other organisms have been implicated, but are rare.

Predisposing factors

1. Any structural valvular lesion will predispose to this condition.

    The following are prominent risk factors:
    - Rheumatic heart disease
    - Mitral valve prolapse
    - Prosthetic valves
    - Congenital heart disease, including septal defects.
    - Cardiomyopathies
    - Previous infective endocarditis.
2. Intravenous drug use:
    - Resulting most commonly in right sided valve lesions.
3. Foreign bodies:
    - Intracardiac pacemakers
    - Central venous lines
4. Immunosuppression:
    - Diabetes mellitus
5. Poor dental hygiene

Complications:

Important complications include:

1. Destruction of the heart valve, with consequent acute severe heart failure.

2. Conduction abnormalities:

    - Extension into the septum can result in electrical conduction abnormalities.

3. Septic embolization:

    - Unexplained stroke
    - Septic arthritis
    - Organ abscesses:
        - ♥ Liver, kidney, splenic, gut (from **left sided** lesions).
        - ♥ Lung abscess (from **right sided** lesions)
    - Organ infarctions:
        - ♥ Arterial occlusion from emboli.
    - Generalized septicemia

3. Anemia

Clinical Features

Infective endocaditis should be considered as a multisystem disease.

The symptoms and signs are largely non specific, which makes diagnosis difficult.

To make the diagnosis a high index of suspicion must be maintained

Endocarditis should always be suspected in patients with a PUO and a predisposing condition.

Symptoms usually occur within 2 months of the event responsible for the initiation of bacteremia, although this can be difficult to identify.

Clinical features include:

1. Fever:

- Fever is usually presence, but its absence does not rule out the diagnosis.
- Fever of **unknown origin** is the commonest presenting feature.

2. Constitutional symptoms:

   Non-specific "constitutional" symptoms, as for any infection, can be seen:

   - Headache
   - Anorexia
   - Myalgias
   - Lethargy / malaise

3. Valvular incompetence murmurs:

   - There is *classically* a new valvular incompetence murmur or a changed old one.
   - An acute murmur is actually an uncommon finding, but when present is highly suggestive.
   - Absence of a murmur does **not** exclude a diagnosis of endocarditis.

4. Septic emboli:

   - Distant systemic emboli from the **left side** of the heart can result in:
     - ♥ Abscesses in virtually any organ
     - ♥ Infarction in virtually any organ
   - Systemic emboli are not seen with tricuspid lesions, rather multiple pulmonary abscesses are seen.

5. Peripheral stigmata:

   The classically described "peripheral stigmata" described in textbooks are extremely rare and should **not** be relied on as evidence of endocarditis.

   These include:

   - Petechiae in the palpebral conjunctiva.
   - Splinter hemorrhages, (under finger or toe nails, initially red for several days then brownish)

- Osler's nodes (painful tender subcutaneous nodules of the finger tip pulps or toes or over the thenar eminence).
- Janeway lesions (small hemorrhages on the palms and soles)
- Roth spots (retinal hemorrhages with a pale centre)

6. Splenomegaly is seen in up to 30% of cases.

Investigations

Blood tests:

1. FBE:
   - There will often be a normchromic normocytic anemia.
   - Leukocytosis is seen in acute cases but may be absent in subacute cases.
   - Thrombocytopenia may occur, but is uncommon.
2. Inflammatory markers:
   - CRP is elevated.
   - ESR is elevated (in virtually all cases).
3. U&Es and glucose.
4. LFTs
5. **Blood cultures**:

   These are crucial to making the diagnosis of bacterial endocarditis.

   The patient's best chance of recovery is dependent on isolation of the causative organism, which then enables optimal therapy.

   If no prior antibiotics have been given, blood cultures are positive in 90-95 % of cases, often in the first two sets.

   - **Three sets of aerobic and anaerobic blood cultures** should be taken from separate venepuncture sights within the first 1 - 2 hours of presentation prior to the start of empirical antibiotics.

     The timing of this, however, depends entirely on how unwell the patient is.

- When severe illness demands urgent antibiotics, the 3 sets may be taken over 20 minutes, before they are given.

  In very urgent cases 3 sets of cultures can be taken from 3 separate venepuncture sites not separated in time.

- Blood cultures should be taken regardless of the patient's temperature. The often quoted dictum "blood culture when the patient has fever", does not apply with endovascular infections when bacteremia is continuous.

- If an unusual organism is suspected (e.g. fungal), inform laboratory staff to ensure optimal culture methods.

- Arterial and venous blood are equally likely to be infected.

- The polymerase chain reaction can be used to identify unculturable organisms in excised vegetations or systemic emboli.

Reasons for **negative cultures** include:

- Prior antibiotic treatment.

Or

- "Fastidious" organisms:

  These can include:

  - ♥ Brucella
  - ♥ Bartonella
  - ♥ Coxiella burnetti (Q fever)
  - ♥ Chlamydia
  - ♥ Legionella
  - ♥ Mycoplasma
  - ♥ Fungal species

CXR

Cardiomegaly, signs of cardiac failure.

ECG

Arrhythmias.

Echocardiography

Echocardiography: apart from blood cultures this is the next most important investigation.

- TTE may be diagnostic.
- TOE has much higher sensitivity and specificity for endocarditis and should be done if TTE is inconclusive.
- A negative TOE study, however, does not absolutely exclude the diagnosis or the need to start treatment if clinical suspicion remains high.

Making the Diagnosis

The diagnosis is usually made on the triad of:

1. A high index of clinical suspicion.
2. Blood cultures.
3. Echocardiographic investigations.

Formal diagnosis is based on the "Modified Duke's Criteria", (see Appendix 2 below).

Management

1. Empiric antibiotic treatment:

   Staphylococcus aureus is commonly the pathogen in fulminant bacterial endocarditis.

   Antibiotics need to be given intravenously, in high dose and for prolonged periods, (**general 4 - 6 weeks**).

   The recommended empirical regime for community acquired infective endocarditis of a native valve is:

   - **IV flucloxacillin**

   And

   - **IV benzyl penicillin**

And

- **IV gentamicin**

Vancomycin (& gentamicin) is indicated if:

- The patient has a prosthetic cardiac valve, pacemaker or intracardiac device in situ
- The patient has a health care - associated infection
- The patient has immediate penicillin hypersensitivity.
- Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) is suspected. (CA-MRSA endocarditis is still rare, although other CA-MRSA infections are becoming increasingly common.)

For full prescribing details, see latest edition of Antibiotic Guidelines.

2. Surgery:

Surgical intervention needs to be considered in certain circumstances.

- Acute valvular destruction with consequent congestive cardiac failure or frank pulmonary edema.
- Uncontrolled infection despite optimal medical treatment.
- Relapse after optimal therapy in prosthetic valve endocarditis.
- Unstable prosthesis
- Vegetations larger than 10 mm.
- Perivalvular extension of endocarditis.

Disposition:

There should be also be referral and close collaboration with:

- The microbiology department.
- Infectious diseases physician.
- Cardiologist.
- ICU, if the patient is significantly unwell.

Appendix 1

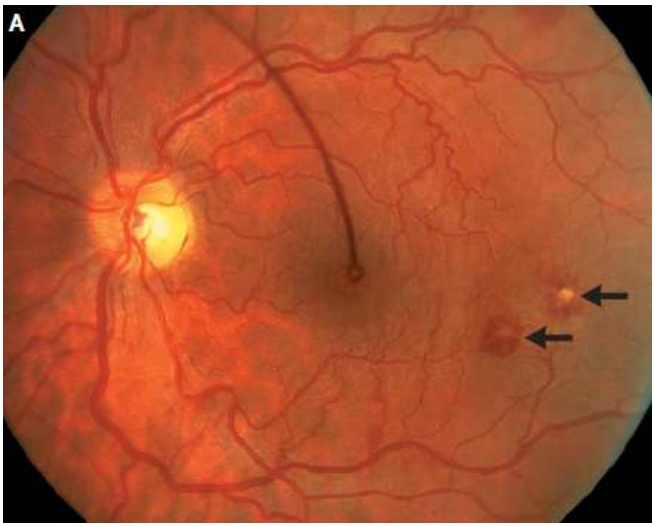
A

C

B

D

Some "classically" described lesion in bacterial endocarditis; A. Splinter hemorrhages. B. Conjunctival petechiae. C. Osler's nodes D. Janeway lesions. [1]



“Roth spots”

Roth’s spots, or white-centered retinal hemorrhages, may be seen in a variety of conditions, including leukemia, subacute bacterial endocarditis, ischemic events associated with elevated venous pressure, and systemic vascular conditions with capillary fragility, (Images in Clinical Medicine, NEJM, September 8, 2005)

Appendix 2

Duke Criteria for Infective Endocarditis: [1]

To make a diagnosis of infective endocarditis, the following is required:

1. 1 major criteria

Or

2. 1 major and 3 minor criteria

Or

3. 5 minor criteria

Major criteria:

1. Positive blood culture for Infective Endocarditis:

   - Typical microorganism consistent with IE from 2 separate blood cultures, as noted below:

     Viridans streptococci, Streptococcus bovis, or HACEK group, or community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus.

   Or

   - Microorganisms consistent with IE from persistently positive blood cultures defined as:

     2 positive cultures of blood samples drawn >12 hours apart,

     Or

     All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart)

2. Evidence of endocardial involvement:

   Positive echocardiogram for IE defined as :

   - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation,

   Or

- Abscess

Or

- New partial dehiscence of prosthetic valve

Or

- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria:

1. Predisposing factors:
   - Cardiac condition
   - IVDU
2. Fever, (> 38 degrees Celsius)
3. Vascular phenomena:
   - Systemic arterial emboli
   - Septic pulmonary infarcts
   - Mycotic aneurysm
   - Intracranial hemorrhage
   - Conjunctival hemorrhages
   - Janeway lesions
4. Immunologic phenomena:
   - Glomerulonephritis
   - Osler’s nodes
   - Roth spots
   - Rheumatoid factor
5. Microbiological evidence:

- Positive blood culture but does not meet a major criterion as noted below or serological evidence of active infection with organism consistent with IE

- Excludes single positive cultures for coagulase-negative staphylococci, diphtheroids, and organisms that do not commonly cause endocarditis.

6. Echocardiographic findings:

   Consistent with IE but do not meet a major criterion as noted above.

See also the MedCalc Website:

- https://www.mdcalc.com/

References:

1. Kevin KC Hung, Colin A. Graham. Infective Endocarditis in Heart Valve Emergencies in Textbook of Adult Emergency Medicine, Cameron et al 4th ed 2015.

2. Antibiotic Guidelines 15th ed in eTG March 2017.

Dr J Hayes

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