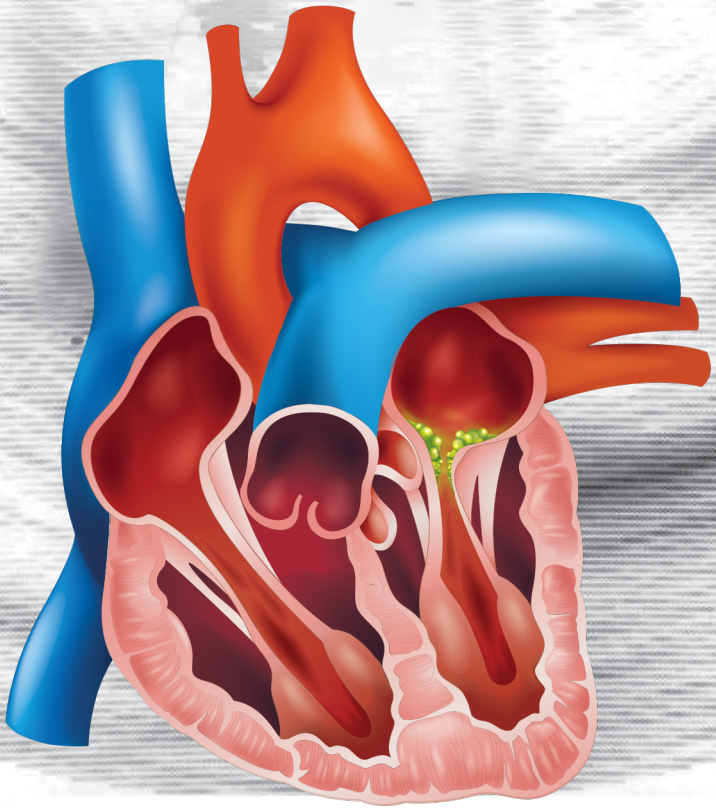
CLINICAL PRACTICE GUIDELINES FOR THE

PREVENTION, DIAGNOSIS & MANAGEMENT OF INFECTIVE ENDOCARDITIS



Ministry of Health Malaysia

National Heart Association of Malaysia

Academy of Medicine Malaysia

PUBLISHED BY:

Clinical Practice Guidelines (CPG) Secretariat
c/o Health Technology Assessment (HTA) Unit
Medical Development Division
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This document will be made available on the following websites:
http://www.moh.gov.my
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STATEMENT OF INTENT

These clinical practice guidelines are meant to be a guide for clinical practice. It is based on the best available evidence, knowledge and clinical experience at the time of development. These guidelines do not guarantee the best outcome in every case and the responsibility lies on the individual healthcare provider to manage his/her patient based on the clinical manifestations of the patient and the management options available locally.

PERIOD OF VALIDITY

These clinical practice guidelines were issued in 2017 and will be reviewed in 4 years (2021) or earlier depending on the availability of new evidence. NHAM will inform either the Chairperson of this current CPG committee or the National Advisor of the related specialties when the time for updating this CPG is due. Prior to commencement of updating this CPG, a discussion to determine the need for an update, including the scope of the CPG updates should be done. If there is a need for an update, as with this current committee, a multidisciplinary team will be formed for the specific purpose of updating this CPG.

TABLE OF CONTENTS

FORWARD BY THE DIRECTOR GENERAL OF HEALTH 4

INFECTIVE ENDOCARDITIS CLINICAL PRACTICE GUIDELINES EXPERT PANEL 5

EXTERNAL REVIEWERS 7

GRADES OF RECOMMENDATION AND LEVELS OF EVIDENCE 10

RATIONALE AND PROCESS OF THE INFECTIVE ENDOCARDITIS GUIDELINES DEVELOPMENT 11

SUMMARY OF THE CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF INFECTIVE ENDOCARDITIS 15

1.0 INTRODUCTION 24

2.0 EPIDEMIOLOGY 27

3.0 DIAGNOSIS 29

3.1 Clinical evaluation of suspected infective endocarditis 30
3.1.1 Pre-existing risk factors 30
3.1.2 Clinical manifestations 31

3.2 Investigations 34
3.2.1 Laboratory investigations 34
3.2.2 Microbiological diagnosis 34
3.2.3 Histopathological diagnosis 40

3.3 Imaging 43
3.3.1 Echocardiography 43
3.3.2 Other imaging modalities 50

3.4 Diagnostic criteria 53
3.4.1 The modified Duke criteria and its limitations 53

4.0 MANAGEMENT 57

4.1 Clinical management 57
4.1.1 Monitoring 58
4.1.2 Complications 60
4.1.3 Issues with anticoagulation 70
4.1.4 Referral for specialist care 74
4.1.5 Pre-discharge management 77

4.2 Antimicrobial therapy: principles and methods 78
4.2.1 General principles 78
4.2.2 Suggested regimes for treatment of native or prosthetic valve infective endocarditis 78
4.2.2.1 *Streptococcus viridans* 79
4.2.2.2 Nutritionally variant streptococci 82
4.2.2.3 *Staphylococcus aureus* and *Coagulase-negative staphylococcus* (CoNS) 84
4.2.2.4 *Enterococcus* species 88
4.2.2.5 HACEK microorganisms 91
4.2.2.6 *Candida* 92
4.2.2.7 Non-HACEK Gram-negative microorganisms 93
4.2.2.8 Other microorganisms 94
4.2.3 Empirical therapy 95
4.2.4 Outpatient parenteral antimicrobial therapy for infective endocarditis 99

5.0 SURGICAL INTERVENTION 100

5.1 Indications 100

5.2 Timing of surgery 102
5.2.1 Preventing systemic embolism 103

5.3 Surgery in specific conditions 104
5.3.1 Cerebral infarction or haemorrhage 104
5.3.2 Right-sided endocarditis 105
5.3.3 Prosthetic valve endocarditis 106

5.4 Principles of surgery 107
5.4.1 Aortic valve 109
5.4.2 Mitral valve 109
5.4.3 Tricuspid valve 109
5.4.4 Periannular extension 109

5.5 Surgery for infective endocarditis in congenital heart disease 110
5.5.1 Indications for surgery 110
5.5.2 Timing of surgery 111
5.5.3 Surgical techniques 113

6.0 OUTCOME AND FOLLOW-UP 114

7.0 SPECIFIC SITUATIONS 117

7.1 Infective endocarditis in congenital heart disease 117
7.1.1 Epidemiology 117
7.1.2 Mortality 118

7.1.3 Lesion specific incidence of infective endocarditis in congenital heart disease 118
7.1.4 Management of infective endocarditis in congenital heart disease 120
7.2 Infective endocarditis in paediatric patients 121
7.2.1 Infective endocarditis in neonates with normal heart structures 121
7.2.2 Clinical presentation 122
7.2.3 Management of paediatric infective endocarditis 123
7.3 Infective endocarditis in transcatheter valve implantations 124
7.3.1 Transcatheter pulmonary valve implantation 124
7.3.2 Transcatheter aortic valve implantation/ transcatheter aortic valve replacement 126
7.4 Infective endocarditis in cardiac implantable electronic devices 127
7.5 Infective endocarditis in pregnancy 129
8.0 ANTIMICROBIAL PROPHYLAXIS FOR INFECTIVE ENDOCARDITIS 130
8.1 Introduction 130
8.2 Cardiac conditions associated with the highest risk of infective endocarditis 130
8.3 Antimicrobial prophylaxis for specific procedures 131
8.3.1 Dental procedures 131
8.3.2 Non-dental procedures 132
8.4 Antimicrobial regimes for infective endocarditis prophylaxis 133
8.5 Preventive measures 135
8.5.1 Periodontal and dental disease 135
8.5.2 Cardiac implantable devices or prosthesis implantation 135
9.0 IMPLEMENTING THE GUIDELINES AND RESOURCE IMPLICATIONS 136
10.0 APPENDICES 137
REFERENCES 170
ACKNOWLEDGEMENT 179
DISCLOSURE STATEMENT 179
SOURCES OF FUNDING 179

FOREWORD BY THE DIRECTOR GENERAL OF HEALTH

Infective endocarditis (IE) is an uncommon and potentially lethal infection affecting patients at risk. Despite advances in medicine, IE still causes significant morbidity and mortality. This is due to the changing epidemiology of the disease, the wide spectrum of presentation extending from the neonate to the elderly, diagnostic difficulties, delayed surgical interventions and embolic complications. The advances in cardiothoracic surgery and cardiology over the years with the increasing use of prosthetic material, valves and intracardiac devices have also contributed to the challenges in managing IE in these patients.

Some important evolution in management strategies would be the development of an Endocarditis Team with multidisciplinary expertise in cardiology, cardiothoracic surgery, infectious disease and other subspecialties as indicated. This is encouraged to enable early diagnosis, optimise treatment and prevent complications in these patients. It also allows for smoother and more efficient referrals to specialised centres.

Previously, surgical intervention was delayed because of the high-risk and mortality but, recently published data have also shown that early surgical interventions in these patients decrease embolic complications and improve outcomes.

There have also been changes with regards to antimicrobial prophylaxis. The evidence currently shows that routine antimicrobial prophylaxis prior to dental procedures is not indicated for all cardiac patients and should be limited to high-risk cardiac patients only. Maintaining a good oral and skin hygiene routine is highly recommended in the prevention of IE.

With these recent developments in the prevention, diagnosis and management of IE, it is timely that we develop local clinical practice guidelines to update all respective healthcare providers with regards to the new management strategies.

I congratulate the committee for the effort and hope that these guidelines would serve to decrease the incidence of IE and its associated morbidity and mortality.

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GRADES OF RECOMMENDATION AND LEVELS OF EVIDENCE

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
IIa	Weight of evidence/opinion is in favour of its usefulness/efficacy.
IIb	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

LEVEL OF EVIDENCE	
A	Data derived from multiple randomised clinical trials or meta-analyses.
B	Data derived from a single randomised clinical trial or large non-randomised studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology. 2015.

Note: The grades of recommendations denoted throughout these guidelines reflect the strength of the evidence that each recommendation is based upon. It may not refer to the clinical significance of the recommendation. All patients with infective endocarditis should be managed together with the best clinical judgment of the healthcare provider.

RATIONALE AND PROCESS OF THE INFECTIVE ENDOCARDITIS GUIDELINES DEVELOPMENT

Rationale

Infective endocarditis (IE) causes substantial morbidity and mortality despite advances in antimicrobial therapy, methods of diagnosis and treatment of complications.

This first edition clinical practice guidelines (CPG) has been developed to guide the prevention, diagnosis and management of IE for use by Malaysian healthcare professionals. The writing committee consisting of experts in infectious disease, cardiology, cardiothoracic surgery, microbiology, pharmacy and dentistry from the Ministry of Health, the National Heart Institute (IJN), the Ministry of Education hospitals and private healthcare has developed these guidelines using as references, best practice recommendations from internationally recognised bodies and latest available evidence-based articles. The CPG was developed based on the local landscape of IE and has been reviewed by a multidisciplinary team of experts involved in the comprehensive management of this disease.

Objectives

To provide evidence-based guidance for the prevention, diagnosis and management of all patients with or at risk of IE with the aim to reduce related morbidity and mortality by:

- Facilitating the early diagnosis of IE, so appropriate treatment can be instituted early.
- Providing guidance on the principles of appropriate antimicrobial therapy based on the type of IE and the causative microorganisms.
- Determining the indications and optimal timing for cardiothoracic surgery in IE.
- Determining the indications for antimicrobial prophylaxis in the prevention of IE.

Process

An extensive search of the current medical literature on the prevention, diagnosis and management of IE was done based on the clinical questions developed by the expert panel. The electronic databases used were the Cochrane database of systemic reviews (CDSR), Medline/PubMed via Ovid, and Sumsearch2 with the following search criteria; to include all original articles (clinical trials, systemic reviews, meta-analysis and observational studies) published in English and to exclude publications in languages other than English, and animal studies. When local data were required, local publications in unindexed journals and unpublished data were used. Literature search was conducted till the most current available published data. The references ranged from years 1966 to the latest National Institute for Health and Care Excellence (NICE) update for the prophylaxis against IE in 2016.

The main search strategy was built around the following MeSH and free text terms used either singly or in combination:

^{18}F-FDG PET/CT, acute, adult, adverse effects, antiplatelet therapy, antibiotics, anticoagulant, anticoagulation, anti-fungal, antimicrobial, bacteraemia, blood culture, blood culture negative, blood culture negative infective endocarditis, blood culture positive, blood culture positive infective endocarditis, body piercing, *Candida*, cardiac implantable electronic device, challenges, classification, clinical, clinical manifestation, culture negative, *Coagulase-negative staphylococcus,* collection, complications, congenital heart disease, control, definition, dental, dental health services, diagnosis, diagnostic criteria, drug monitoring, echocardiogram, echocardiography, empirical, endocarditis, *Enterobacteriacae, Enterococcus,* epidemiology, follow-up, fungal, guidelines, HACEK, haemorrhagic stroke, health, healthcare, healthcare associated, heart failure, histopathology, incubation, indication, infective endocarditis, interpretation, intervention, intravenous drug user, investigation, ischaemic stroke, laboratory investigation, limitations, magnetic resonance imaging, management, microbiological, microbiology, modified Duke criteria, monitor, morbidity, mortality, multislice computed tomography, mycotic aneurysm, native valve, neonates, neurological, non-HACEK, nuclear imaging, nutritionally variant streptococci, out patient, out patient parenteral antibiotic therapy, outcomes, paediatric, parenteral therapy, perivalvular extension, persistent infection, positron emission tomography, post-discharge, pre-discharge, pre-procedural, predisposing risk, presentation, prevention, prognosis, prophylaxis, prosthetic valve, pseudoaneurysms, pulmonary valve implantation, referral, renal impairment, right-sided, sampling, *S. aureus, S. viridans,* services, side effects, signs and symptoms, single-photon emission computed tomography, single-photon

emission computed tomography white cell count, specialist care, specimen, stains, Staphylococci, Streptococci, *Staphylococcus Aureus, Streptococcus Viridans,* subacute, surgery, survival, systemic embolism, tattooing , therapy, timing, transcatheter aortic valve implantation, transcatheter aortic valve replacement, transcatheter pulmonary valve implantation, transcatheter valve implantation, transoesophageal echocardiography, transthoracic echocardiography, treatment, valvular.

From the searched literature, the relevant articles were picked based on the Critical Appraisal Skills Program (CASP). In addition, the reference lists of these relevant articles were searched to identify further studies. International guidelines on the prevention, diagnosis and management of IE e.g. from American Heart Association (AHA), European Society of Cardiology (ESC), NICE, the British Society for Antimicrobial Chemotherapy, and Australian Infective Endocarditis Prophylaxis Expert Group, and the Canadian revisions to the latest AHA guidelines were also used as reference points in the development of this CPG. These international guidelines were reviewed and assessed by the committee using the AGREE II tool prior to inclusion as reference.

The members of the expert panel appraised all the literature retrieved in a systematic manner. The expert panel and review committee agreed on all statements and recommendations formulated in the CPG. Where the evidence was insufficient the recommendations were derived by consensus of both groups. Disagreements were resolved by voting and the consensus decision of the majority was used.

These guidelines were presented to the Technical Advisory Committee for Clinical Practice Guidelines, the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

Clinical questions addressed

- What are the diagnostic criteria and its limitations in diagnosing IE?
- What are the appropriate microbiological investigations and procedures to diagnose IE?
- What are the appropriate imaging modalities in diagnosing IE?
- What are effective and safe antimicrobial therapies for treatment of IE?
- How to diagnose and appropriately manage complications of IE?
- What are the indications and timing for surgery in valvular IE?
- What are the indications and timing for surgery in congenital heart disease (CHD) IE?
- What are the risk factors for IE in CHD?
- Who are at risk of developing IE in the paediatric population?
- How is IE diagnosed and appropriately managed in these conditions:
  - > Patients with cardiac implantable electronic devices (CIED)?
  - > Patients with transcatheter pulmonary valve implantation (TPVI), transcatheter aortic valve implantation (TAVI) and transcatheter aortic valve replacement (TAVR)?
- Which high-risk cardiac conditions need antimicrobial prophylaxis?
- Which dental and other interventional procedures are high-risk for developing IE?
- If indicated, what is the effective and safe antimicrobial prophylaxis before an interventional procedure?
- What effective and safe preventive measures should be practiced by patients at risk of IE to reduce bacteraemia?

Target group

This CPG is applicable to all healthcare professionals and relevant stakeholders involved in the prevention and care of patients with high-risk of IE or, patients with suspected or proven IE.

Target population

These guidelines are targeted at all age groups in the population at risk of IE and/or those who present in any form and severity of IE.

Healthcare settings

These guidelines were developed for the prevention, diagnosis and management of IE in the primary, secondary and tertiary healthcare settings.

SUMMARY OF THE CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

General information

- Infective endocarditis (IE), even though uncommon, causes significant morbidity and mortality in both children and adults.
- The trend of IE has evolved to affect older patients with co-morbidities and no known structural heart disease.
- *Streptococcus* species is a common causative microorganism in young patients with pre-existing structural heart disease whilst *Staphylococcus aureus* (*S. aureus*) is more common in the older patients and those with healthcare associated IE.

Diagnosis

- Early and accurate diagnosis of IE is crucial to institute appropriate treatment and prevent complications. A high level of clinical suspicion of IE is warranted especially in those with pre-existing risk factors (refer Section 3.1.1).
- Due to the varied spectrum of the disease, a combination of clinical assessment, microbiological testing and imaging are required to make the diagnosis.
- **Blood culture** is a key investigation in the diagnosis of IE. Proper technique of blood culture collection is crucial, as this will reduce the rate of contamination and yield a true positive result (refer Appendix 3).
- Blood cultures should be drawn for patients with fever of unexplained origin and a heart murmur, a history of heart disease or previous endocarditis.
- Three sets of blood cultures should be obtained first before administering antimicrobials when a patient has fever and predisposing risk factors for IE.
- If blood cultures remain negative after 5 days of incubation and there is no history of prior antimicrobial use, consider blood culture negative infective endocarditis (BCNIE), which can be caused by fungi or fastidious microorganisms, and perform the appropriate microbiological tests (refer Table 3.2 and Figure 3a).

- **Histopathological examination (HPE)** of cardiac tissue/vegetations obtained during surgery is of diagnostic value and is recommended.
- A transthoracic **echocardiogram** (TTE) should be obtained without delay if the diagnosis of IE is suspected.
- Echocardiogram findings should be interpreted in the context of the clinical scenario and repeated if the clinical suspicion of IE persists despite a negative initial echocardiogram.
- Transoesophageal echocardiogram (TOE/TEE) should be done if initial TTE examination is negative, in patients with strong clinical suspicion of IE, in those with prosthetic valves/cardiac material and in those with high-risk features (refer Figure 3b).
- Echocardiography plays a crucial role in the diagnosis of IE, monitoring for complications and progression of valvular dysfunction, assessing the outcome of surgical repair and in the follow-up after completion of antimicrobials (refer to Table: Role of echocardiography in the diagnosis and management of IE, below).
- In patients with *S. aureus* bacteraemia from an unknown aetiology or persistent bacteraemia despite antimicrobials, echocardiography should be considered.
- Some newer imaging modalities (multislice computed tomography; MSCT, magnetic resonance imaging; MRI and nuclear imaging) can assist in diagnosing IE and its complications.
- The **modified Duke criteria** is used to diagnose IE but has limited diagnostic accuracy in the early phase of the disease and in those patients with prosthetic valve or cardiac implantable electronic device (CIED) endocarditis (refer Figure 3c).

Management

- The management of IE is aimed at eradicating the infection, and preventing and treating both intra and extracardiac complications.
- Patients with complicated IE should preferably be referred to a **specialist centre**. Specialist centres are those with cardiothoracic, cardiac imaging and specialised cardiology services (refer Section 4.1.4).
- A **multidisciplinary team** approach involving infectious disease (ID) physicians, cardiologists, cardiothoracic surgeons and other relevant subspecialty experts is essential in the management of IE (refer Table 4.2).
- In all patients with suspected endocarditis, elicit risk factors for fastidious/intracellular pathogens (refer Table 3.2).
- The mainstay of treatment is appropriate and adequate **antimicrobial therapy** (refer Section 4.2). The minimum inhibitory concentration (MIC) should be done to ensure optimal antimicrobial therapy.

- For **penicillin susceptible (MIC ≤ 0.125 µg/ml) Viridans streptococci**:
  - Monotherapy with benzyl penicillin, ampicillin or ceftriaxone is adequate. [IIa/B]
  - Duration of therapy is for 4 weeks for native valve endocarditis (NVE) and 6 weeks for prosthetic valve endocarditis (PVE). [IIa/C]
- For **penicillin relatively resistant (MIC > 0.125 to 2 µg/ml) Viridans streptococci**:
  - Gentamicin has to be added to the regime. [IIa/B]
  - Duration of gentamicin is for 2 weeks for NVE and 6 weeks for PVE. [IIa/C]
- ***Granulicatella*** **and** ***Abiotrophia*** **(formerly nutritionally variant streptococci; NVS)** are fastidious and slow growing making it technically difficult to determine antimicrobial susceptibility.
  - Combination treatment of penicillin, ampicillin or ceftriaxone with gentamicin for at least the first 2 weeks, followed by continuation of chosen antimicrobial without gentamicin for 6 weeks is recommended. [II/B]
- ***Staphylococcus*** **endocarditis**:
  - Vancomycin is inferior to cloxacillin for methicillin-sensitive *Staphylococcal aureus* (MSSA) endocarditis.
  - Addition of gentamicin for native valve *staphylococcus* endocarditis is not recommended. [III/B]
  - Addition of gentamicin and rifampicin is recommended for prosthetic valve staphylococcal endocarditis. [I/C]
  - In order to prevent resistance, rifampicin should be started after 3-5 days of effective therapy or after blood cultures are negative.
- **HACEK microorganisms**:
  - Ceftriaxone monotherapy is recommended for endocarditis due to *Haemophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium, Eikinella* and *Kingella* (HACEK) microorganisms. [IIa/B]
  - Alternative drugs such as ampicillin-sulbactam or ciprofloxacin may be used provided the isolate is susceptible. [IIb/C]
- ***Candida*** **endocarditis**:
  - Valve surgery combined with anti-fungal therapy is required for adequate treatment of *Candida* endocarditis. [I/B]
  - Long-term suppressive therapy will be required if valve replacement is not performed.
- **Non-HACEK microorganisms**:
  - Combination therapy with β-lactam and aminoglycosides, or fluroquinolones is recommended for 6 weeks. [IIa/C]

- The **empirical antimicrobial treatment** in valvular endocarditis should cover for streptococci, enterococci and HACEK microorganisms if it is community acquired NVE or late PVE. Consider additional cover for MSSA in patients with acute presentation or with additional risk factors such as intravenous drug use (IVDU) and patients with prosthesis. If it is healthcare associated NVE or early PVE, methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci and non-HACEK Gram-negative microorganisms should be covered (refer Section 4.2 and Figure 4a).
- Patients with IE should be closely monitored for response to treatment and for complications (refer Section 4.1).
- Some **common complications** of IE are (refer Section 4.1.2):

  > Heart failure:
    - » Commonly associated with valve dysfunction.
    - » Surgery is indicated for those with acute decompensated heart failure due to valvular dysfunction.

  > Persistent infection and perivalvular extensions:
    - » Monitor for conduction abnormalities e.g. atrioventricular (AV) block.
    - » TEE should be performed to look for perivalvular extensions.

  > Systemic embolism:
    - » Usually occurs in left-sided IE and within the first 2 weeks of therapy.
    - » Common sites are the brain and spleen.
    - » Risk factors for embolism are associated with vegetation size (> 10 mm), mobility, location (anterior mitral valve leaflet) as well as the causative microorganism (*S. aureus*).

  > Neurological complications:
    - » Occurs early in the course of IE (first 2 weeks).
    - » Common complications are ischaemic or haemorrhagic stroke, and mycotic aneurysms.
    - » Management should be individualised and care plan decided by a multidisciplinary team that also includes neurologists and neurosurgeons.
    - » It is advisable to withhold anticoagulation in mechanical prosthetic valve endocarditis (MPVE) patients who have haemorrhagic neurological complications for at least 2 weeks with close monitoring of the valves and patient's clinical condition.
    - » The duration to withhold anticoagulation is dependent on the severity of the neurological complication and the patient's clinical condition (refer Table 4.1).

- **Anticoagulation** should be managed based on the individual patient's clinical status, presence of neurological complications and, on the presence or absence of indications for cardiac surgery (refer Section 4.1.3).
- Early **surgical intervention** is recommended especially in view of improving outcomes, preventing complications and increasing the success rate of valve reconstruction (refer Section 5.1).
- The main aim during surgery is to completely remove all infected tissue and to repair rather than replace the valve where possible.
- The timing for cardiac surgery is dependent on the patient's clinical condition, type of microorganism, size of vegetation and the presence of complications.
- The severity of clinical manifestations should not limit the decision for surgical intervention when indicated (refer Sections 5.1 & 5.2, and Table: Timing and indications for surgical intervention, below).

Timing and indications for surgical intervention

Timing of surgery	Clinical condition
Emergency ***(within 24 hours)***	Cardiogenic shock from severe valve dysfunction
Urgent ***(within 3-4 days)***	Pulmonary oedema but not in cardiogenic shock Very large vegetations (> 10 mm) Paravalvular abscess or heart block
Early ***(within 1-2 weeks)***	Fungal, *S. aureus* or other highly resistant microorganisms Persistent infection > 5-7 days after initiating antimicrobials Persistent or enlarging vegetations despite antimicrobials Recurrent emboli despite adequate antimicrobial therapy
Semi-elective ***(after 2 weeks of antimicrobials)***	PVE and relapsing infection
Elective ***(after 6 weeks of antimicrobials)***	Well-tolerated chronic severe valvular regurgitation with controlled infection

IE in specific conditions

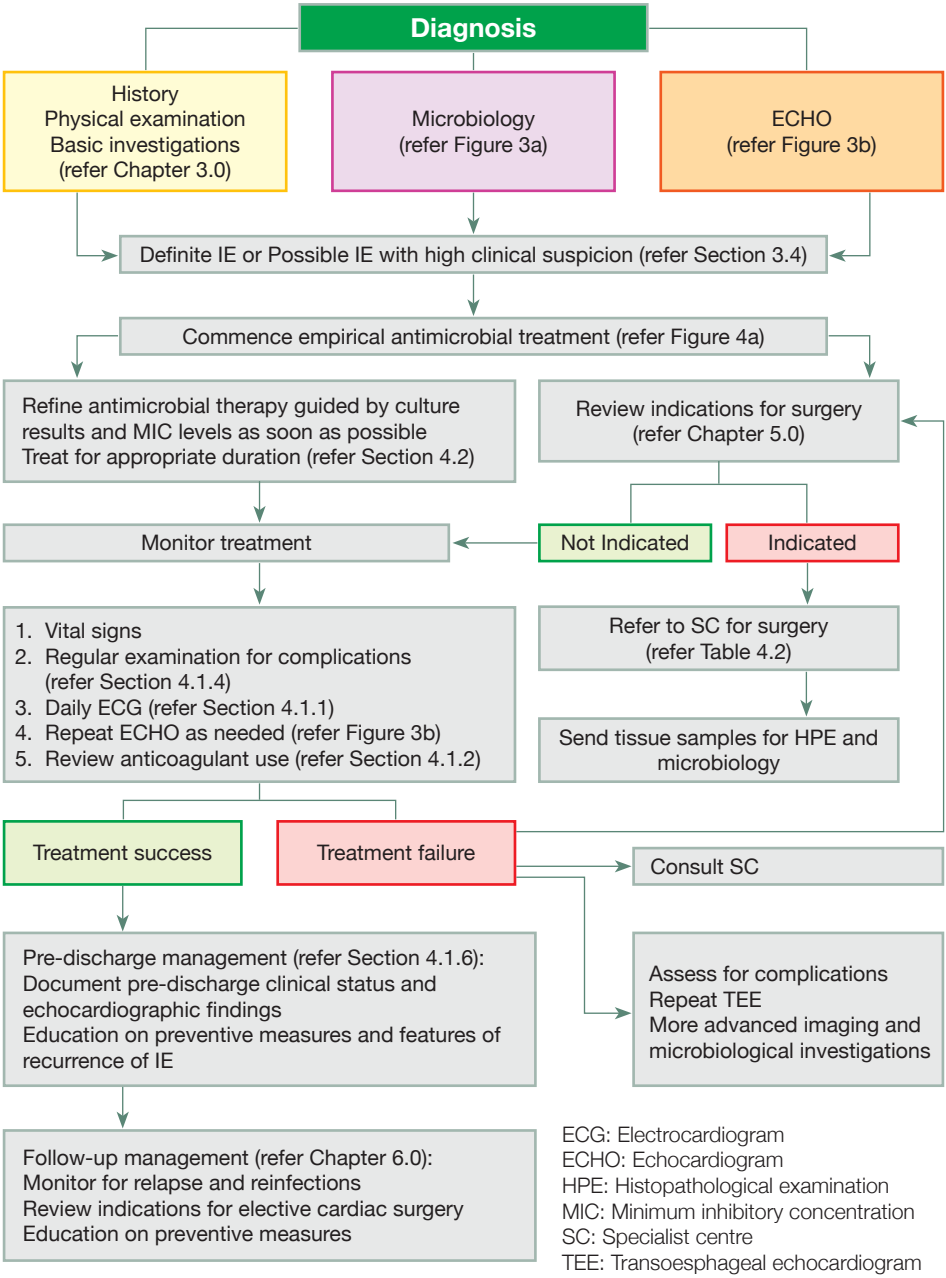
There are important considerations for IE in congenital heart disease (CHD), CIED and transcatheter valve implants:

- These conditions merit a high index of suspicion of IE (refer Sections 7.3 & 7.4).
- In these patients, once a diagnosis of IE has been established or if there is strong clinical suspicion of IE, the patient should be sent to a specialist centre (refer Section 4.1.4).
- The epidemiology of paediatric IE has evolved to reflect those with the advancement of interventions for CHD. It now broadly reflects the following groups:
  - Patients with prolonged use of central venous catheters in:
    - Corrected CHD during the post-operative period.
    - Neonates with normal heart structures who require intravenous treatment for other issues (refer Sections 7.1 & 7.2).
  - Adult and paediatric patients with:
    - Complex cyanotic CHD.
    - Unrepaired CHD.
    - Repaired CHD with prosthetic material.
    - Cardiac surgery or transcatheter device interventions done within the last 6 months (refer Section 7.2).

Prevention of IE

- Antimicrobial prophylaxis is not routinely recommended for cardiac patients undergoing invasive dental or other medical procedures and should be limited only for cardiac patients associated with the highest risk of adverse outcomes from IE (refer Chapter 8.0).
- Those with high predisposing risk for developing IE should be advised to maintain good oral and skin hygiene.

Summary of clinical management of IE (refer Section 4.1)



ECG: Electrocardiogram
ECHO: Echocardiogram
HPE: Histopathological examination
MIC: Minimum inhibitory concentration
SC: Specialist centre
TEE: Transoesphageal echocardiogram

Table: Role of echocardiography in the diagnosis and management of IE

Timing	Echocardiography assessment	Comments
Diagnosis	Presence and size of vegetation	If > 10 mm in diameter, there is excess risk of embolisation and surgery is indicated to prevent embolisation
	Valve function: mechanism and quantification of regurgitation or obstruction to flow	
	Valve damage: perforations or new dehiscence	
	Paravalvular extensions: fistula, abscess and pseudoaneurysms	
	Ventricular function and haemodynamics	
Monitoring during active IE	Valve function: worsening dysfunction or acute regurgitation	If present with acute/ worsening heart failure, surgery is indicated
	Monitoring of ventricular function	
	New development of paravalvular extension with or without new lesions	In the context of uncontrolled infection
	Changes in vegetation size and mobility	Risk of embolisation if > 10 mm in diameter
	Presence of pericarditis with or without myocarditis	Ideally this should be evaluated with cardiac magnetic resonance imaging (MRI)

Timing	Echocardiography assessment	Comments
Perioperative	Intraoperative TEE to assess: • Severity of valve dysfunction and pathology, and ventricular function • Outcome of the surgical intervention	
Pre-discharge	To establish a new baseline (most often a TTE is adequate)	Document baseline haemodynamic parameters and severity of any valvular lesions
On follow-up	Close monitoring especially in the first year post-IE to assess the severity and progression of residual valvular dysfunction For stable valvular lesions, to decide on timing of surgical intervention	If worsening, to consider on-going infection or need for early surgery Follow established guidelines for management of valvular heart disease[1]

1.0 INTRODUCTION

Infective endocarditis (IE) is defined as an infection of the endocardial surface of the heart (heart valves and mural endocardium) by microorganisms (mainly bacteria).

IE has evolved over the years as the prevalence of rheumatic heart disease declined. Advances in the treatment of congenital heart disease (CHD) and structural heart disease with the introduction of conduits, prosthetic materials and intracardiac devices has led to many patients surviving well into adulthood, hence making them more susceptible to infection in view of the presence of these foreign materials. Incidence of IE in patients with adult CHD is 3 times higher than that in the paediatric population. Increase in the ageing population has also led to older patients with multiple co-morbidities and no known structural heart disease being at risk of this disease too.

The spectrum of microorganisms involved with IE have also changed of late, with the increase in the presence of virulent and drug-resistant microorganisms such as Staphylococci and fungi that have contributed to the difficulties in the management of IE.

IE still remains a therapeutic challenge with a high morbidity and mortality despite advances in medicine and surgery. The changing trends in the epidemiology, the varied clinical manifestations and complications, and diagnostic difficulties with the uncertainties of appropriate timing for surgical interventions, have contributed to the poor prognosis of this disease.

The aim of these clinical practice guidelines (CPG) is to enable medical personnel at all levels of care to diagnose IE early and effectively manage these patients. It also stresses the importance of preventing IE in those with predisposing risk factors.

In keeping to this aim, this CPG attempts to highlight some of the more crucial areas in the diagnosis and management of IE:

- To enable early and accurate diagnosis:
  - > The chapter on diagnosis (refer Chapter 3.0) incorporates important information and recommendations pertaining to clinical, microbiological and imaging assessments to guide physicians in making an early diagnosis of IE.
  - > Included in this chapter is a comprehensive section (refer Section 3.2.2) on microbiological investigations focusing on increasing the yield in blood culture negative infective endocarditis (BCNIE).
  - > The role of echocardiography especially transoesophageal echocardiogram (TOE/TEE) and newer imaging modalities in the diagnosis of IE and its complications are detailed in Section 3.3.

- To improve and optimise the treatment of IE:
  - > As the clinical manifestations of IE can be varied, a good outcome depends on the combined management of a multidisciplinary team, which should include specialists such as cardiologists, cardiothoracic surgeons, infectious disease (ID) physicians and other relevant medical subspecialties.
  - > Early referral to a Specialist Centre (SC) for those patients with complicated IE is strongly recommended. A centre designated as a SC should have available expertise in basic and advance cardiac imaging with specialised cardiology and cardiothoracic services (refer Section 4.1.4).
  - > The section on antimicrobial therapy (refer Section 4.2) covers both paediatric and adult dosing regimes. Included is a focus on therapy for BCNIE and empirical therapy based on our local setting and experiences. Appropriate antimicrobials should be started promptly once 3 specimens of blood cultures have been taken, as delayed treatment could have poorer outcomes.
  - > The sections on indications and timing of surgery (refer Chapter 5.0) offer a paradigm shift as earlier surgical intervention has been shown to have a better outcome in IE patients in whom surgery is indicated.
  - > We have also included the management of IE in some specialised patient groups e.g. patients with CHD, cardiac implantable electronic device (CIED) and transcatheter implantable valves to accommodate the advances in medical interventions.

- To initiate appropriate antimicrobial prophylaxis:
  - > The committee has developed evidence-based recommendations for the prophylaxis of IE based on the predisposing risks and types of invasive procedures found in the local setting.
  - > The current emphasis is on maintaining good dental and gum hygiene, and preventing oral disease.

The recommendations developed in this CPG were based on the latest available data and evidence, taking into account the local healthcare system structure and patients. Though there are certain areas that would require a shift from the norm, the committee hopes that these evidence-based recommendations will not only serve to effectively manage IE patients but to also improve their outcomes.

2.0 EPIDEMIOLOGY

The annual incidence of IE in the adult population ranges between 3-9 per 100,000 subjects per year.[2-4] However, as most of the available data come from developed countries, its true incidence in developing countries is unknown. Variability in the epidemiology of IE also exists between countries and continents with regards to patient profile, microbiological aetiology, treatment and outcomes.

In the developed countries, IE tends to affect patients between the ages of 50-60 years, in contrast to developing countries where it is commonly seen in the 20-40 years old age group. This is primarily due to a more ageing society in developed countries that relies on increasing invasive medical care, the presence of degenerative valve disease and co-morbidities.[4-6] In developing countries, rheumatic heart disease is still the most common predisposing cause of IE.[6-9] About 50% of IE in developing countries occur in patients with no known history of valve disease.[4,8] Healthcare associated IE (refer to Appendix 1) is increasing with some studies reporting incidence of up to 25%.[5,10] The gender distribution of IE is male to female case ratio of more than 2:1.[4,5]

IE commonly affects native valves, usually involving the left-sided heart valves (2/3rd of the cases) with the mitral valve commonly affected.[5] *Streptococcus* species (spp.) is the most common microorganism causing IE in developing countries, in the younger age group and in those with pre-existing structural heart disease[6-8] compared to developed countries where Staphylococcal spp. tend to be more common.[4,5,11]

Complication rates of IE have been reported to be high (16-33%) leading to high mortality rates of up to 39% in certain studies.[5] In a prospective multicentre study, the following risk factors were shown to increase mortality in IE patients:[5]

- Paravalvular complications (odds ratio; OR: 2.25).
- Pulmonary oedema (OR: 1.79).
- *Staphylococcus aureus* (*S. aureus*) infection (OR: 1.54).
- Prosthetic valve involvement (OR: 1.47).
- Increasing age (OR: 1.30).
- Mitral valve vegetation (OR: 1.34).

Although surgery can be associated with high risks,[12] it has been shown to reduce mortality in complicated cases (hazard ratio; HR 0.33).[6] Based on the available evidence, surgical intervention was required in about 50% of IE patients.[5,13] Prendergast *et al*. stated surgery was required in 25-50% of cases during acute infection and in 20-40% during convalescence.[12]

A recent local study done in Hospital Kuala Lumpur[14] (a tertiary inner city hospital) reported 36 cases of definite IE diagnosed over a period of 2 years (2013-2014). Eighty percent were male (male to female ratio 4:1) and the median age at presentation was 36 years (interquartile range; IQR 23). The predominant race affected was the Malays (60%). In this urban inner city cohort,[14] IE mainly affected normal valves (39%), and intravenous drug use (IVDU) was the commonest predominant risk factor (36%).

Methicillin-sensitive *Staphylococcus aureus* (MSSA) was the predominant microorganism grown from blood cultures (30%). All patients were treated with antimicrobials; with 91% on antimicrobial therapy for a duration of 42 days or less. Five patients died (13.9%) primarily due to overwhelming sepsis. Fifty-three percent of patients had indications for surgical intervention, however none had surgery within the index hospitalisation.[14]

3.0
DIAGNOSIS

As this disease affects multiple organ systems, patients with IE can present with very diverse clinical presentations making its diagnosis challenging. The clinical course of the disease can vary from subacute to acute infection, and each will manifest differently. Patients often visit multiple health practitioners before a correct diagnosis is made.

Making a clinical diagnosis of IE requires:

- Careful and thorough clinical history taking and physical examination.
- Laboratory investigations.
- Microbiological investigations.
- Histopathological examinations; HPE (when possible).
- Imaging, namely echocardiography and radiological investigations.

In difficult cases, consultation with other experts such as ID specialists, cardiac imaging specialists and microbiologists may be required.

3.1 Clinical evaluation of suspected infective endocarditis

The most common symptom at presentation (up to 87%) is fever associated with chills, poor appetite and weight loss. Heart failure may be present at admission (up to 58%) and there may be a new or altered cardiac murmur (50-85%).[15,16] Embolic events may also cause presenting symptoms (27-30%) and these events may be singular or multiple in nature.[13,16,17]

3.1.1 Pre-existing risk factors

A high level of suspicion of IE is warranted in patients with fever and pre-existing risk factors who present with non-specific symptoms. These are:[15,18-21]

- Previous history of IE.
- Pre-existing cardiac disease.
- Presence of prosthetic valves or prosthetic cardiac material.
- Presence of intracardiac devices.
- History of IVDU.
- Presence of chronic intravenous access (e.g. haemodialysis catheters, chemoports and neonate/paediatric patients with indwelling central venous catheters).
- Presence of CHD (refer Section 7.1).
- Elderly or immunocompromised patients.[22]
- Co-existing conditions such as diabetes, human immunodeficiency virus (HIV) infection and malignancy.

3.1.2 Clinical manifestations

Patients do not often present with classic textbook manifestations of subacute or chronic endocarditis. Therefore medical personnel should bear in mind that the symptoms and signs of IE can be general and/or system specific as presented in Table 3.1 below.

Table 3.1: Symptoms and signs of IE

	Symptoms and signs	Site	Comments
General	• Night sweats and chills • Weight loss • Fatigue • Body aches • Poor appetite		
	• Fever		• Temperature may be normal or subnormal in: > Subacute cases > Elderly > Immunocompromised patients • Fever is usually very high in acute IE
	• Anaemia		• In subacute cases this may be anaemia of chronic disease or microcytic anaemia
Peripheral	• Splinter haemorrhages	• Nail beds of the fingers or toes	• Examine all digits of upper and lower limbs • Exclude workplace trauma
	• Osler's nodes > Painful subcutaneous nodules (red-purple, slightly raised, tender lumps and with a pale centre)	• Pulps of the fingers or toes	• Pain precedes the development of the visible lesion by up to 24 hours • Can occur at any time during the course of endocarditis (usually subacute) • Lasts from hours to several days
	• Janeway lesions > Non-tender lesions > 1-4 mm in diameter > Often haemorrhagic	• On the palms and soles	• Lasts days to weeks • Commonly seen in acute endocarditis • The histology is usually consistent with septic microembolism

	Symptoms and signs	Site	Comments
	• Digital clubbing		• Usually seen in patients who have an extended period of untreated IE[23]
	• Subconjunctival haemorrhages		• Examine both eyes
	• Generalised petechiae	• Conjunctivae • Dorsa of the hands and feet • Anterior chest wall • Abdominal wall • Oral mucosa • Soft palate	
	• Embolic lesions	• Fingers and toes	
	• Arthritis		• Asymmetrical • Single or multiple joints
Central	• Roth spots (white-centred retinal haemorrhages)	• Retina	• Examine both eyes
	• Splenomegaly		• Occurs with long-standing subacute disease • May not resolve after treatment
	• Haematuria		• Due to glomerulonephritis
	• Septic embolisation	• Lung embolisation	• Occurs in right-sided IE causing pneumonia or lung abscess
		• Abdominal embolisation	• Splenic abscesses or infarcts
Cardiac	• Murmurs		• Appearance of new murmur • Usually regurgitant • Right-sided IE may not have a murmur
	• Heart failure		• Usually due to valve dysfunction/regurgitant lesions
	• Bradycardia		• Indicates aortic root abscess interfering with cardiac conduction pathways

	Symptoms and signs	Site	Comments
Neurological	• Focal signs: hemiparesis, aphasia and others	• Cerebral septic embolisation	• May be due to ischaemic/ haemorrhagic lesions or cerebral abscess
	• Delirium in meningitis, meningoencephalitis and encephalopathy		• Occurs from purulent meningitis especially with acute IE
	• Intracranial bleeding > Manifests as: » Confusion » Drowsiness » Reduced consciousness » Vomiting » Seizures		

It is very rare for IE patients to present with the full spectrum of physical signs and there may be only one or two of these clinical features present. For the primary care physician, general practitioner or emergency room physician, the diagnosis of IE may be missed or delayed because of the failure to recognise certain clinical manifestations of the disease.

In the presence of fever, IE should be considered as part of the differential diagnosis in the following conditions:

- Unexplained embolic phenomena to the brain, liver or spleen (left-sided IE), or to the lung (right-sided IE).
- Focal neurological signs of unknown aetiology.
- Heart failure that cannot be accounted for.
- Haemorrhages in unusual locations.

KEY MESSAGE:

1. IE can present with very diverse clinical presentations which makes its diagnosis challenging.
2. A high level of suspicion of IE is warranted in patients with fever and pre-existing risk factors who present with non-specific symptoms.

3.2 Investigations

3.2.1 Laboratory investigations

Laboratory tests for infection may aid the diagnosis of IE. These include:

- Inflammatory markers:
  - > Elevated C-reactive protein (CRP).
  - > Elevated erythrocyte sedimentation rate (ESR).
  - > Procalcitonin (PCT):
    - » > 2 and < 10 ng/ml: severe systemic inflammatory response or sepsis.
    - » > 10 ng/ml: severe bacterial sepsis or septic shock.

PCT is available in Hospital Universiti Kebangsaan Malaysia (HUKM) and University Malaya Medical Centre (UMMC).

- Complete blood count (CBC)/full blood count (FBC):
  - > Raised white cell count.
  - > Low haemoglobin.
- Urine full examination and microscopic examination (UFEME):
  - > Microscopic haematuria.
- Blood culture and sensitivity (refer Section 3.2.2).

With the exception of blood cultures, the **above tests are not specific** and may indicate other causes of sepsis.

3.2.2 Microbiological diagnosis

The microbiological diagnosis of IE can be divided into:

- Blood culture positive IE.
- Blood culture negative IE.

3.2.2.1 Blood culture positive infective endocarditis

Blood cultures should be taken before the commencement of empiric antimicrobial agents as it is critical to the diagnosis and treatment of patients with IE. In order to obtain high yield of positive blood cultures, the following considerations are crucial:[24]

A. Timing of blood cultures

- The blood cultures can be obtained at anytime:[24]
  - > This is due to the continuous nature of bacteraemia associated with IE.
  - > There is no necessity to wait for spikes of fever.
  - > Blood cultures should be taken at 30-minute intervals between samples.[24]

B. Number of blood culture sets and the blood volume

- At least three sets of blood cultures:[25]
  - > To distinguish between 'false positive' blood cultures due to skin contaminants from 'true positive' blood cultures.
  - > Increases the volume of blood cultured, which is the most important factor in the recovery of microorganisms from blood.
- Microorganisms that are skin contaminants include:
  - > Coagulase negative staphylococci.
  - > *Bacillus* spp.
  - > *Corynebacterium* spp. (diphteroids).
  - > *Propionibacterium* spp., viridans group of streptococci (VGS).
  - > *Aerococcus* spp.
  - > *Micrococcus* spp.

These microorganisms may be considered as significant pathogens when they are cultured from 2 or more blood cultures drawn on separate occasions.

- If the initial 3 blood culture sets are negative at 24 hours, obtain 2 more sets of cultures, for a total of 5 sets overall.[25]

- A set includes 1 aerobic and 1 anaerobic bottle[25] with samples taken from a single venepuncture site:
  - > The anaerobic culture is vital for the growth of nutritionally variant streptococci (NVS) and facultative anaerobic microorganisms such as *Enterobacteriaceae* (refer Appendix 2).
- Each bottle should contain 10 ml of blood for adults and 1-3 ml of blood for paediatric patients (using the appropriate paediatric blood culture bottles).
  - > Adequate volume is the most important factor in the recovery of microorganisms in IE.
- If the blood cultures are negative, BCNIE should be considered (refer Section 3.2.2.2).

C. Sampling sites of blood cultures

- Strict aseptic techniques should be observed (refer Appendix 3).
- Blood should be sampled from separate peripheral venepuncture sites.
- Avoid sampling from central venous or indwelling catheters. Catheter-drawn blood cultures have increased risk of contamination[25] and thus may give rise to misleading interpretation.

D. Duration of incubation of blood cultures

- Within 5 days, most clinically important microorganisms including *Haemophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium, Eikinella* and *Kingella* (HACEK) will be isolated.[26]
- If all blood cultures are negative at 5 days and the diagnosis of IE is still being pursued consider:
  - > BCNIE (refer Section 3.2.2.2).
  - > Fungal IE.
- Longer incubation time for a total of 2 weeks and appropriate selective culture media may be required when fungaemia or bacteraemia caused by fastidious microorganisms e.g. *Legionella, Brucella* or *Nocardia* spp. is suspected.

E. Identification of the microorganisms and antimicrobial susceptibility testing

- Identification must be rapid and done up to the level of the bacterial species.
- A newly available state-of the-art technology in rapid bacterial identification is based on peptide spectra by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF) which is able to provide direct identification of bacteria in the blood culture supernatant.[27] This has improved the turnaround time of bacterial identification tremendously.
- For decisions on optimal therapy in IE, especially for infections involving streptococci spp. and multidrug resistant microorganisms, it is recommended to test for susceptibility of antimicrobials by determining the minimal inhibitory concentration (MIC) of the drug.

3.2.2.2 Blood culture-negative infective endocarditis

In general, BCNIE indicates IE which has no microorganism grown following inoculation of at least 3 independent blood samples when using the usual currently available culture methods in clinical laboratories after 5 days of incubation.

- BCNIE can be due to 3 main reasons:
  - > Partially treated IE by previous antimicrobial treatment, which is the most common cause (usually due to usual endocarditis-causing bacteria, i.e. streptococci, more rarely staphylococci, or enterococci).
  - > For the isolation of fastidious bacteria such as *Brucella, Nocardia* spp., NVS and fungi other than yeasts, blood culture incubation may need to be extended for two weeks before a negative result is released. Specimens other than blood, e.g. excised tissue and aspirated intracardiac pus, incubation of the inoculated agar media beyond 48 hours may be needed. Special media and prolonged incubation is required for the isolation of *Legionella pneumophilia*.
  - > "True" BCNIE due to intracellular bacteria that cannot be routinely cultured in blood with currently available techniques (e.g. *Bartonella* spp., *Coxiella burnetti* and *Tropheryma whipplei*).
- Diagnosis of BCNIE (refer to Table 3.2):
  - > Serological testing and molecular techniques such as polymerase chain reaction (PCR) assay aid in establishing the causative agent in BCNIE.

However limitations when using such assays are as follows:

- Serology:
  - > Cross reaction of serological assays (e.g. IE caused by *Bartonella* and *Chlamydia* spp. are often indistinguishable).[28]
- PCR:
  - > Low sensitivity of PCR when using blood specimens. It is however more sensitive when performed directly on cardiac valvular tissue[16,29-31] or surgical material.
  - > PCR findings should not be used to guide duration of therapy and should be interpreted in the context of other clinical information. This is due to persistence of bacterial deoxyribonucleic acid (DNA) even after eradication of viable microorganisms, causing false positive results.

Table 3.2: Fastidious and intracellular microorganisms, epidemiology and investigations

Microorganism	Predisposing risk factors, epidemiology and exposure risks	Laboratory investigation
***Aspergillus* and other non- *Candida* fungi**	Prosthetic valves	Culture: Blood culture Serology: Galactomanan PCR: Blood or cardiac valvular tissue/ vegetations HPE**: Cardiac tissue or emboli
***Bartonella* spp.**	Cat contact or ownership (*Bartonella henselae*), chronic alcoholism, contact with human body louse and homeless shelters (*Bartonella quintana*)	Culture: Blood culture Serology: IgG/IgM/total antibodies HPE**: Cardiac valvular tissue
***Brucella* spp.**	Ingestion of unpasteurised milk or cheese, contact with or occupational exposure to farm animals	Culture: Blood culture (requires extended incubation as 80% of cultures become positive with an incubation time of 4-6 weeks) and tissue Serology: IgG/IgM and total antibodies PCR: Blood
Coxiella burnetti	Ingestion of unpasteurised milk or cheese, contact with or occupational exposure to farm animals, or visit to farms	Serology: IgG/IgM HPE**: Cardiac valvular tissue/ vegetations
***Legionella* spp.**	Prosthetic valves	PCR: Cardiac valvular tissue/ vegetations HPE**: Cardiac valvular tissue/ vegetations
Nutritionally variant streptococci	Slow indolent course	Culture: Blood culture (culture on supplemented media or growth as satellite colonies around *S. aureus* streak)

**HPE consists of:
- Haematoxylin and Eosin (H&E) stain for basic morphology.
- Special stains which aid in the identification of the causative microorganisms of IE (refer Table 3.3).

IgG: immunglobulin G; IgM: immunoglobulin M; HPE: histopathological examination.

Adapted from Mandell JE, et al. 2015.[32]

The directory of laboratories that perform the serological and PCR tests of the rare aetiological agents of IE is given in Appendix 4.

3.2.3 Histopathological diagnosis

Patients with IE often undergo surgery to repair or replace their heart valve. Histopathology when available is of diagnostic value.[33,34] If excised tissue is obtained during cardiac surgery, it must be sent for HPE and culture.

Tissue specimens that can be sent are:

- Resected valvular tissue.
- Endocardial vegetation.
- Excised intracardiac abscess wall.

A diagnosis can be made from the pathological specimens if:

- Microorganisms are demonstrated by culture or on HPE.
- HPE shows active endocarditis.

The various special stains that are used to detect the infectious agents of interest in valvular tissue are shown in Table 3.3. For the preparation and transportation of cardiac tissue for HPE refer Appendix 5.

Table 3.3: Special stains which aid in the identification of the causative microorganisms of IE from cardiac tissue specimens

Tissue stain	Detected microorganism
General stain	
Acridine orange	Any bacterium
Giemsa	Any bacterium
Tissue Gram **Brown-Hopps** **Brown- Brenn**	 Gram-positive bacteria Gram-negative bacteria
Specific stains	
Periodic acid-Schiff	*Tropheryma whipplei* Fungi
Warthin-Starry	*Bartonella* spp.
Ziehl-Nielsen	Acid-fast bacilli
Gimenez	*Coxiella burnetti* *Legionella* spp.
Specific stains	
Kinyoun, Machiavello	*Chlamydia* spp.
Gomori-Grocott	Fungi

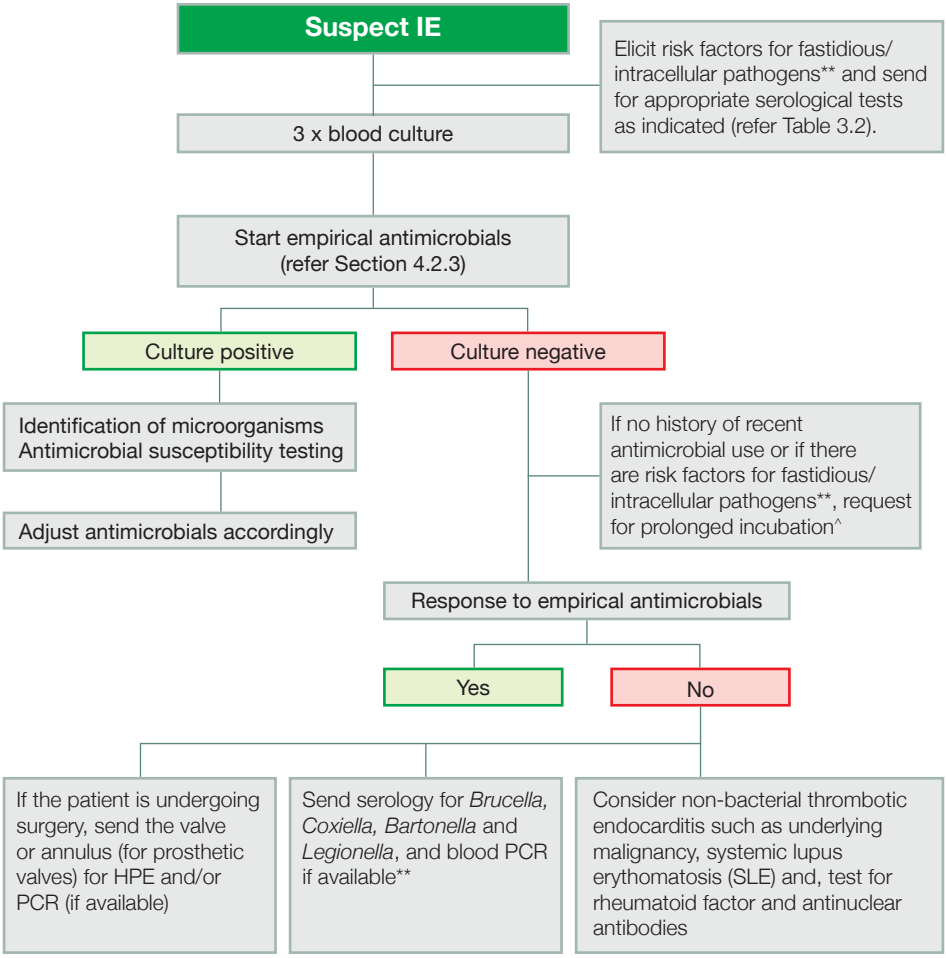
Adapted from P. Houpikian, D. Raoult 2003.[33]

Recommendations

Processes to ensure successful microbiological diagnosis:

1. At least 3 sets of blood cultures to be taken at least 30 minutes apart. In adult patients, each bottle should contain 10 ml of blood. [IIa/C]
2. For optimal recovery of diverse aetiological agents, each set of blood cultures should include paired aerobic and anaerobic blood culture bottles. [IIa/C]
3. Sampling should be obtained from a peripheral vein rather than from a central venous catheter. [IIa/C]
4. An incubation period of blood cultures for 5 days is adequate for the detection of the majority of pathogens including those from the HACEK group. [IIa/C]
5. Pathological specimens obtained during cardiac surgery which are of diagnostic value, should be sent for HPE. [IIa/C]

Figure 3a: Approach to microbiological diagnosis of IE



**Refer Table 3.2 for the risk factors for fastidious/intracellular pathogens.
^*Legionella, Brucella, Nocardia* spp., fungi and NVS e.g. *Gemella, Grnaulicatella* and *Abiotrophia* may require longer incubation periods.

Adapted from Habib G, et al. Eur Heart J. 2015.

3.3 Imaging

3.3.1 Echocardiography

3.3.1.1 Echocardiography in diagnosis of infective endocarditis

Echocardiography plays a key role in the diagnosis of IE. The first line imaging investigation in suspected IE is usually transthoracic echocardiography (TTE) as it is non-invasive and widely available. TEE should be performed subsequently if indicated.

- In native valves, the sensitivity of TTE in diagnosing vegetations is 44-63%.[35-38]
- For prosthetic valves, the diagnostic yield of TTE is much lower, 36-69% due to acoustic shadowing from the prosthetic material and a higher chance of annular infection which cannot be seen clearly on TTE.[38]
- TEE enhances diagnostic sensitivity between 90-100% for native valves and 86-94% for prosthetic valves.[38]
- The specificity of TTE and TEE exceeds 90% for both native and prosthetic valves whilst the specificity of TEE for vegetation on prosthetic valves is 88-100%.[38]

Indications for TEE in patients with IE or those with pre-existing risk factors include:[39]

- Poor or suboptimal transthoracic window (e.g. morbid obesity, chronic obstructive pulmonary disease; COPD and previous sternotomy).
- High clinical suspicion of IE but negative TTE (e.g. typical microorganism of IE found on blood cultures).
- Staphylococcal bacteraemia if community acquired without an obvious focus of infection (e.g. cellulitis).[40,41]
- All cases of IE with prosthetic valves and prosthetic material such as conduits.
- High-risk features for complications (e.g. new atrioventricular; AV block on electrocardiogram; ECG which may indicate a periannular extension of infection).
- Perioperative TEE to assess mechanism and severity of valve dysfunction, perivalvular extensions and the success of surgery/ presence of residual lesions.[42]

Echocardiographic findings suggestive of IE include (refer Table 3.4):[1,43]

- Vegetation.**
- Abscess.**
  - > Abscess formation is a dynamic process, which starts with aortic root thickening that can be seen on TEE. If this finding is noted, a TEE should be repeated at a later time to confirm the diagnosis as the lesion progresses with formation of a cavity with no flow within.
- Pseudoaneurysms.
- New dehiscence of a prosthetic valve.
- Fistula.
- Perforation.
- Valve leaflet aneurysm.

**Documentation of vegetation or abscess sizes should be made by measuring their largest diameters in at least 2 dimensions rather than measuring the circumference. The view in which the measurement was made should also be documented.

Other important information to gather from an echocardiogram include:

- Haemodynamic and ventricular functional assessments:
  - > Transthoracic Doppler echocardiogram is used to assess haemodynamic dysfunction as it is more reliable and reproducible compared to TEE.
  - > For *left ventricular systolic dysfunction*, assessment of ejection fraction by using modified Simpson's method and others such as tissue Doppler imaging is recommended.
  - > For *diastolic function*, using pulse wave Doppler and tissue Doppler imaging is recommended. However, in situations where there are significant regurgitant lesions, the estimation of ventricular filling pressures by Doppler method is not accurate.
  - > For *right ventricular function*, assessing systolic function visually or by using quantitative parameters, e.g. tricuspid annular systolic plane excursion (TAPSE) or fractional area change (FAC) can be used.

- Pulmonary artery pressure assessment by estimation of:
  - > Right atrial pressure.
  - > Tricuspid regurgitation peak velocity.
  - > Pulmonary regurgitation end diastolic velocity.
- Assessment and quantification of valve regurgitation.
- Presence and quantification of pericardial effusion.

3.3.1.2 Interpretation of echocardiography

Echocardiography in IE can be challenging. This may be due to the absence of vegetations despite a high index of clinical suspicion or the presence of masses on the endocardial surface that are not due to infective vegetation. Therefore the results of the echocardiographic study must be interpreted with caution, taking into account the patient's clinical presentation and the likelihood of IE. The limitations of echocardiography in the diagnosis of IE should be noted as follows:

- The sensitivity and specificity of TTE and TEE are not 100%.
- A negative echocardiogram does not rule out IE.
- In some situations, a repeat TTE or repeat TEE may be necessary.
- Results of an echocardiogram must be interpreted with caution, as it is possible to have a false positive study (refer Table 3.5).

Table 3.4: Findings suggestive of IE and their anatomical and echocardiographic definitions

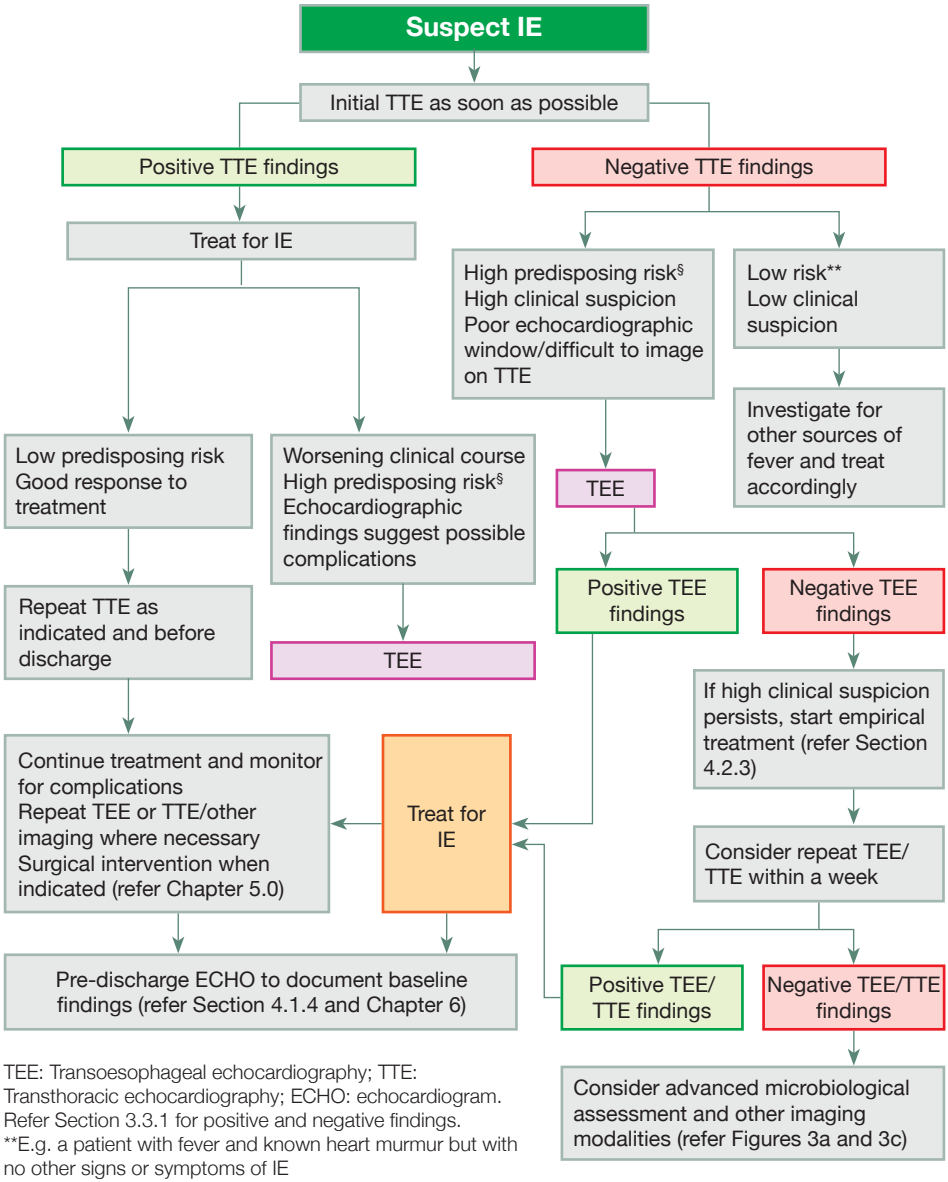
	Surgical or autopsy findings	Echocardiography findings
Vegetation	Infected mass attached to an endocardial structure or on implanted intracardiac material	Oscillating or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen	Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance
Pseudoaneurysms	Perivalvular cavity communicating with the cardiovascular lumen	Pulsatile perivalvular echocardiographic-free space, with colour-Doppler detected
Perforation	Interruption of endocardial tissue continuity	Interruption of endocardial tissue continuity traversed by colour-Doppler
Fistula	Communication between two neighbouring cavities through a perforation	Colour-Doppler communication between two neighbouring cavities through a perforation
Valve aneurysm	Saccular outpouching of valvular tissue	Saccular bulging of valvular leaflet tissue
Dehiscence of a prosthetic valve	Dehiscence of the prosthesis	Paravalvular regurgitation identified by TTE/TEE, with or without rocking motion of the prosthesis

Adapted from Habib G, et al. Eur J Echocardiogr. 2010.[43]

Table 3.5: Challenges in echocardiography interpretation in the context of IE

False positive echocardiogram ("vegetation" seen but diagnosis is NOT IE)	False negative echocardiogram ("vegetation" not seen but diagnosis IS IE)
This may be due to: • Thrombus • Papillary fibroelastoma • Lambl's excrescences • Cusp prolapse • Chordal rupture • Degenerative or myxomatous valve disease • Strands • Systemic lupus (Libman-Sacks) lesions • Primary antiphospholipid syndrome • Rheumatoid lesions or marantic vegetations • Prominent Chiari network or Eustachian valve in the right atrium	This may be due to: • Vegetations that have embolised • Initial/incipient abscess (if imaged early in the disease may appear like non-specific thickening) • Presence of pre-existing valvular lesions such as mitral valve prolapse and degenerative calcified valve disease • Prosthetic valves • Small vegetations (< 2-3 mm) • Non-vegetant IE • Intracardiac devices (this is difficult even with the use of TEE) • Sutures, suture pledgets and free floating chords in post-surgical patients (discuss with the operating surgeon) **If the clinical suspicion is high but initial imaging is negative, a repeat TTE or TEE is warranted within a week or even earlier in cases positive for *S. aureus*.**

Figure 3b: Use of echocardiography in the diagnosis and management of IE



TEE: Transoesophageal echocardiography; TTE: Transthoracic echocardiography; ECHO: echocardiogram. Refer Section 3.3.1 for positive and negative findings.
**E.g. a patient with fever and known heart murmur but with no other signs or symptoms of IE
§Includes presence of prosthetic valves, various CHD, appearance of new murmur, presence of heart failure, or other signs and symptoms of IE

Adapted from Baddour LM, et al. Circulation. 2015.

Recommendations

The use of echocardiography in diagnosing IE:

1. Echocardiography should be performed as soon as possible in all patients suspected of having IE. [I/B]
2. If there is a high suspicion of IE despite an initial negative TTE/TEE, then a repeat TTE/TEE is recommended within a week or if clinical findings change. [I/C]
3. TEE should be done if initial TTE images are negative or inadequate in patients for whom there is a persistent suspicion for IE. [I/B]
4. TEE is advised in cases with prosthetic valves, prosthetic cardiac material or cases with high-risk features. [I/B]
5. The echocardiographic measurement of the size of the vegetation at its longest diameter is preferable rather than its circumference. Documentation of the window in which the measurement was done will be useful. [IIa/C]
6. Intraoperative TEE recommended for all cases of IE undergoing surgery. [I/B]
7. It may be reasonable to perform TTE at the time of antimicrobial therapy completion to record baseline features. [IIa/C]

3.3.2 Other imaging modalities

A. Multislice computed tomography

Multislice computed tomography (MSCT) in the context of IE maybe useful in the following situations:

- To:
  - > Detect abscesses/pseudoaneurysms in the heart.[44,45]
  - > Assess the extent and consequences of any perivalvular extension, including the anatomy of pseudoaneurysms, abscesses and fistulae.[44,45]
- To detect and assess extracardiac complications:
  - > Concomitant pulmonary disease, e.g. abscesses and infarcts in right-sided/pulmonary endocarditis.
  - > Evaluation for central nervous system (CNS) lesions (e.g. mycotic aneurysm).
  - > Intra-abdominal lesions (e.g. silent splenic abscesses).
  - > Peripheral vascular complications of IE (e.g. extracerebral mycotic aneurysms) and their follow-up.[46]
- To aid in surgical planning:
  - > Pre-operative coronary assessments in unstable patients who are to undergo cardiac surgery for IE complications.[47]
  - > To define the size, anatomy and calcification of the aortic valve, root and ascending aorta, in cases of IE affecting the aorta.

Limitations of MSCT:[44]

- Exposure to radiation.
- Nephrotoxicity associated with contrast dye.
- Relative lack of sensitivity to demonstrate valve perforations.

B. Magnetic resonance imaging

Magnetic resonance imaging (MRI) has a higher sensitivity than computed tomography (CT) in detecting cerebral embolic events, majority of which are clinically silent.[48] Studies have shown that systematic cerebral MRI during acute IE has consistently reported frequent cerebral embolic lesions, in 60-80% of patients.[48-50]

Most commonly seen abnormalities are:[50]

- Ischaemic lesions (50-80%).
  - > Small ischaemic lesions are more frequent than larger territorial infarcts.
- Parenchymal or subarachnoidal haemorrhage (≤ 10%).
- Abscesses or mycotic aneurysms (< 10%).

In IE patients with neurological symptoms:[51]

- Cerebral MRI has no impact on the diagnosis of IE.
- It is often abnormal and more sensitive than CT in detecting lesions causing stroke, transient ischaemic attack (TIA) and encephalopathy.
- MRI may impact the therapeutic strategy, particularly the timing of surgery.

However in IE patients with no neurological symptoms:

- At least 50% show cerebral lesions on MRI, mostly ischaemic in nature.
- The detection of cerebral lesions on MRI adds 1 minor Duke criteria.[52,53]

Systematic abdominal MRI:[53]

- Has shown to detect lesions in one of three IE patients.
- Lesions occur most often in the spleen and commonly include splenic infarcts, abscesses and haemorrhagic lesions.

Whenever cerebral MRI findings are present, abdominal MRI is not indicated for the diagnosis of IE. However, it may play a role in further management (e.g. to detect intra-abdominal occult abscesses although CT abdomen would be the preferred investigation for this).

C. Nuclear imaging

New modalities in nuclear imaging like single-photon emission computed tomography (SPECT)/CT and positron emission tomography (PET)/CT are evolving as important supplementary assessments for patients with suspected IE and diagnostic difficulties. Several reports have shown promising results for radiolabelled white blood cell (WBC) SPECT/CT and fluorine-18 (F-18) fluorodeoxyglucose (FDG); ^{18}F-FDG PET/CT imaging in IE. Nuclear imaging may be of added value in refining a 'possible IE' to a 'definite IE' based on the Duke criteria by detecting peripheral embolic and metastatic infectious lesions.[54,55] There is also growing evidence that cardiac nuclear imaging can play a key role in the diagnosis and management of patients with suspected prosthetic valve endocarditis. Recent European Society of Cardiology (ESC) guidelines for the management of IE updated in 2015 have added ^{18}F-FDG PET/CT or radiolabelled WBC SPECT/CT as a new major criterion if abnormal uptakes are found around the area of prosthetic valve implantation in patients with a prosthesis implanted for more than 3 months.[16] However, the limited availability of these modalities in the local setting also limits its usage in the diagnosis and management of IE (refer Appendix 6).

KEY MESSAGE:

1. MSCT can be used to assess for perivalvular extensions and extracardiac complications and/or embolism.
2. MRI is more sensitive than CT in diagnosing cerebral embolic lesions many of which are silent.
3. Radiolabelled WBC SPECT/CT and ^{18}F-FDG PET/CT may have a supplementary role in detecting peripheral embolic or metastatic infectious lesions in those with high clinical suspicion of IE and diagnostic difficulties. They may also be useful in diagnosing prosthetic valve endocarditis.

3.4 Diagnostic criteria

3.4.1 The modified Duke criteria and its limitations

The Duke criteria was first proposed in 1994 by Durack *et al.* from the Duke University Medical Centre, North Carolina, United State of America (USA). This was a diagnostic schema that stratified patients with suspected IE into 3 categories; definite, possible and rejected. In the year 2000, taking into account further evidence, the Duke criteria was refined further into the modified Duke criteria[56] (refer Table 3.7) which is currently widely used in clinical practice.

The Duke criteria should be used as a research tool rather than a clinical tool for diagnosing IE, therefore clinicians should treat each individual patient appropriately. In very ill patients and patients in whom the diagnosis of IE is likely, empirical treatment should be started before blood culture results are available. This classification has a sensitivity of approximately 80% overall, when the criteria are evaluated at the end of patient follow-up in epidemiological studies.[57]

Table 3.7: Definition of IE according to the modified Duke criteria

Definite IE	*Pathological criteria:* Microorganisms demonstrated by culture or HPE of a vegetation, a vegetation that has embolised, or an intracardiac abscess specimen; **or** pathological lesions; vegetation or intracardiac abscess confirmed by HPE showing active endocarditis
	Clinical criteria: 2 major criteria **or** 1 major criterion and 3 minor criteria **or** 5 minor criteria
Possible IE	1 major criterion and 1 minor criterion **or** 3 minor criteria
Rejected IE	Firm alternative diagnosis explaining evidence of IE **or** resolution of IE syndrome with antimicrobial therapy for ≤ 4 days **or** no pathological evidence of IE at surgery or autopsy with antimicrobial therapy for ≤ 4 days **or** does not meet criteria for possible IE as above

Major Criteria	Blood culture positive for IE	Typical microorganisms consistent with IE from 2 separate blood cultures: • VGS, *Streptococcus bovis*, HACEK group, ***S. aureus*** • **Or** community-acquired enterococci in the absence of a primary focus • **Or** microorganisms consistent with IE from persistently positive blood cultures defined as follows: > At least 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 at least 1 hour apart) • Single positive blood culture from *Coxiella burnetii* or phase 1 IgG antibody titres > 1:800
	Evidence of endocardial involvement	Echocardiogram positive for IE defined as follows: • 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 • Abscess • **Or** new partial dehiscence of prosthetic valve • **Or** new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient) **(TEE is recommended for patients with prosthetic valves rated as at least possible IE by clinical criteria, or complicated IE (paravalvular abscess)**
Minor criteria	Predisposition: predisposing heart condition or IVDU	
	Fever: temperature > 38°C	
	Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway lesions	
	Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots and rheumatoid factor	
	Microbiological evidence: positive blood cultures but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and microorganisms that do not cause endocarditis) or serological evidence of active infection with microorganism consistent with IE	

Adapted from Li JS, et al. Clin Infect Dis. 2000.[56]

Limitations of the modified Duke criteria include a lower diagnostic accuracy especially in:

- Early diagnosis.
- Prosthetic valve endocarditis (PVE) with sensitivity of TTE 36% and TEE 82%.[58]
- Pacemaker or defibrillator lead IE with sensitivity of TTE 23% and TEE 94%.[59]

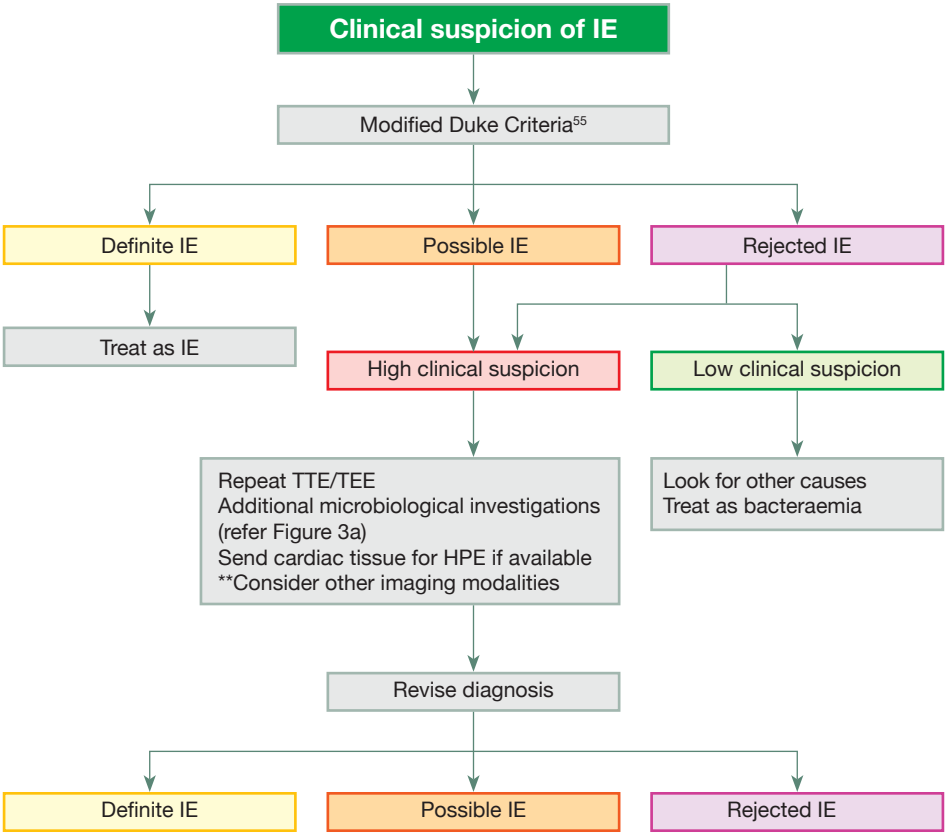
In cases where clinical suspicion is high but the application of the Duke criteria yields "possible IE", some other investigations that can be pursued include:

- Repeat TTE/TEE and proceed with advanced microbiological testing.
- Cardiac CT to look for periannular extension.
- Cerebral MRI to look for silent embolic events.
- SPECT/CT and ^{18}F-FDG PET/CT especially for the assessment of prosthetic valve endocarditis.

KEY MESSAGE:

1. The modified Duke criteria are used as a guide to diagnose definite, possible and rejected IE.
2. For patients with possible or rejected IE in whom there is a high clinical suspicion of IE, it is advisable to consider further microbiological testing or other imaging modalities to guide in the diagnosis.
3. Clinicians should treat each individual patient accordingly.

Figure 3c: The use of modified Duke criteria in diagnosing IE



**Other imaging modalities:

- Cardiac CT (detect pseudoaneurysms, abscesses and fistulae) especially in patients with prosthetic valves/ conduits (major criteria).[47,48]
- Screen for silent septic emboli:
  - > CT/MRA brain: infarct/mycotic aneurysm (detection of cerebral lesions on MRI in patients with no neurological symptoms or signs adds 1 minor Duke criteria).
  - > CTPA (pulmonary infarcts/abscesses/ mycotic aneurysm) in right-sided IE.
- CT abdomen: splenic infarct.
- ^{18}F-FDG PET/CT and radiolabelled leucocyte SPECT/CT to detect silent metastatic infectious lesion/peripheral embolism.

^{18}F-FDG: fluorine-18 (F-18) fluorodeoxyglucose (FDG); CT: computed tomography; CTPA: CT pulmonary angiogram; IE: infective endocarditis; MRA: magnetic resonance angiogram; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single photon emission computerised tomography; TEE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

Adapted from Habib G, et al. Eur Heart J. 2015.

4.0 MANAGEMENT

4.1 Clinical management

The major goals of management of IE are:

- To eradicate the infectious agent from the endocardium.
- To address the complications of the infection, both intra and extracardiac.

The mainstay of treatment for IE is appropriate antimicrobial therapy. Factors which maximise treatment success include:

- Early diagnosis.
- Accurate microorganism identification.
- Reliable susceptibility testing.
- Prolonged intravenous administration of bactericidal antimicrobial therapy.
- Proper monitoring of potentially toxic regimens.
- Aggressive surgical management of correctable mechanical complications.

4.1.1 Monitoring

Whilst in the ward, general management steps include the monitoring of:

- Clinical condition:
  - Fever:
    - Fever usually resolves in a few days after commencement of appropriate antimicrobials.
    - However, fever may return after this initial period in 30% of cases.
    - If fever persists after 10 days of treatment, the patient should be evaluated for suppurative complications (e.g. abscess collections in the abdomen, lungs or intracardiac abscess).
  - The patient should be examined regularly for symptoms and signs of the following:
    - Heart failure: symptoms should be treated with standard medical therapy and its severity regularly assessed. Heart failure may persist despite microbiological resolution.
    - Embolic events.
    - Ongoing sepsis.
    - Neurological sequelae.

- ECG:
  - Should be done daily to monitor heart rhythm and to look for conduction defects. This is especially important in cases of prosthetic valve IE or native valve IE as they are at higher risk for extension of infection to the conduction pathways which can occur very abruptly.
  - Conduction defects may be a sign of perivalvular extension of infection especially in cases involving the aortic valve.

- Blood investigations:
  - General investigations:
    - Regular levels of inflammatory markers e.g. CRP and ESR (daily in the acute period and at least twice weekly thereafter once the patient is more stable).
    - Regular FBC for total white cell count, haemoglobin and platelet count (thrombocytopaenia).
    - Blood urea and electrolytes for signs of acute renal failure. Renal failure is a complication of IE and haemodialysis may be required.
    - Liver function tests.
    - Coagulation profile in patients on anticoagulation.

- Blood cultures:
  - Should be taken 3-4 days after the commencement of treatment to document the eradication of bacteraemia.
  - If the blood cultures remain positive despite adequate levels of appropriate antimicrobials, metastatic infection should be looked for.

- Echocardiography (refer Figure 3b):
  - TTE should be repeated if there is any change to the patient's clinical condition.
  - During the course of management of IE, assess for:
    - Haemodynamics and/or cause of heart failure.
    - Causes of uncontrolled infection: paravalvular abscess, pseudoaneurysms or fistulae (using TEE).
    - Echocardiographic features for risk of embolisation (refer Section 4.1.2.3).
    - Monitor vegetation:
      - Resolution of IE: vegetations gradually reduce in size, decrease in mobility and increase in echogenicity. In the long-term, these vegetations may not disappear or even change in size, even with clinical treatment success.
      - Risk of embolisation: vegetations increase in size[60,61] and mobility.
    - Monitor for rarer complications: e.g. purulent pericarditis (presence of fluid in the pericardial space), coronary obstruction (regional wall motion abnormality corresponding to coronary artery distribution) and myocarditis (general hypokinesia).
  - In uncomplicated cases, a baseline, pre-discharge TTE should be performed.

- Antimicrobial peak and trough levels should be done as appropriate. Patients should be assessed for clinical features of antimicrobial toxicity.

4.1.2 Complications

It is important to recognise the common and serious complications of IE, as cardiac surgery should be considered in circumstances involving such complications. The main complications of IE are:

- Heart failure.
- Persistent infection and perivalvular extension.
- Systemic embolism.
- Neurological complications.

All IE patients who develop cardiac complications should be referred to a SC (a centre with cardiology and cardiothoracic surgery services; refer Section 4.1.4) as most would need more advanced imaging, surgical intervention and cardiac intensive services.

4.1.2.1 Heart failure

Heart failure is the most common complication of IE, which occurs in up to half of all cases.[62] It is the most important predictor of mortality. In most cases of IE, heart failure is usually caused by valvular dysfunction and not myocardial failure.[63] Heart failure is more commonly associated with aortic valve dysfunction compared to mitral valve dysfunction.[64] Less commonly, intracardiac fistulae may also cause heart failure.[65] The clinical presentation of heart failure includes dyspnoea, pulmonary oedema and cardiogenic shock.

The management of heart failure in infective endocarditis

A. Imaging and monitoring in heart failure

Echocardiography (TTE or TEE) is important in the evaluation of:

- Acute valve regurgitation: if symptoms or signs of heart failure occur, an echocardiogram should be performed immediately to diagnose possible acute valve regurgitation, which carries a very high mortality. In acute regurgitation, the size of the chamber may be normal or only slightly enlarged. Ejection fraction may be normal. There may be findings of:
  - > Extensive destruction of the valve leaflets.
  - > Massive regurgitation.
  - > Abscess or pseudoaneurysms.

However in cases of chronic valve regurgitation with superimposed IE, the size of the cardiac chamber may be enlarged with impaired systolic function.

- Valve perforation.
- Secondary mitral lesions.
- Aneurysms/fistula (are best assessed using TEE).[43]
- Haemodynamic consequences of valvular dysfunction:
  - > Measurement of pulmonary artery pressure.
  - > Detection of pericardial effusion.
  - > Assessment and monitoring of left ventricular systolic function.[43]

B. Heart failure marker

- N-terminal pro brain-type natriuretic peptide (NT-proBNP) is useful in diagnosing heart failure and effectiveness of medical therapy.[66]

C. Medical management (refer to 3rd edition of Management of Heart Failure CPG 2014, Section 7.1 available at http://www.moh.gov.my/penerbitan/CPG)

- Pharmacotherapy:
  - > Diuretics (e.g. furosemide).
  - > Intravenous diuretics are indicated for patients with symptoms of acute pulmonary oedema or fluid overload (raised jugular venous pressure; JVP and ankle oedema).
    - > Angiotensin converting enzyme (ACE) inhibitors.
    - > Beta-blockers:
      - » Although beta-blockade in acute heart failure may cause harm and beta-blockers should also not be used in aortic regurgitation as this will increase diastolic time and regurgitation volume.

D. Surgical management (refer Chapter 5.0)

- Indication and timing:
  - > All cases of IE with acute heart failure should be stabilised with medical management and referred for consideration of surgery.
  - > Although surgery is urgent, the timing should be agreed with the surgical team in order to optimise the patient's condition to minimise surgical risk.

4.1.2.2 Persistent infection and perivalvular extension

If after 7-10 days of antimicrobial therapy, there is persistent fever and positive blood cultures, assess for the following possibilities and manage accordingly:

- Inadequate or inappropriate antimicrobial therapy.
- Resistant microorganisms.
- Complications: perivalvular extensions and extracardiac septic embolisation.
- Thrombophlebitis/infected intravenous lines.

In cases of both suspected persistent infection and perivalvular extension, the following should be considered:

- Regular (e.g. daily) ECG to monitor for conduction abnormalities e.g. AV block.
- Perform a TEE in cases of persistent fever especially in those with prosthetic valves, aortic valve IE and *S. aureus* infection, or new AV block.
- Perform an ECG-gated cardiac CT scan to assess for aortic root abscess or perivalvular extension in cases when TEE facilities are not available.

4.1.2.3 Systemic embolism

The risk of systemic embolism is very high in IE (20-50%) and life-threatening complications are often related to the migration of cardiac vegetations. The risk is highest during the first days following the initiation of antimicrobial therapy and rapidly decreases subsequent to that.[61,67] Frequent sites for embolisation in left-sided IE are the brain and spleen whilst pulmonary embolism frequently occurs in native right-sided and pacemaker lead IE.[68] Stroke is a major complication and is associated with increased morbidity and mortality.[68]

Factors associated with an increased risk of embolism are:

- Vegetation size > 10 mm (higher risk if > 15 mm).[69]
- Mobility of vegetations.[69]
- Location of the vegetation on the anterior mitral valve leaflet.
- Increase in the size of the vegetation under antimicrobial therapy.[60]
- *S. aureus*[60] and *Streptococcus bovis*[70] infection.
- Fungal endocarditis.
- Previous embolism.[61]
- Multivalvular IE.[71]
- Biological markers (e.g. elevated CRP).[72]

Embolisation may occur before diagnosis, usually within the first 2-4 weeks of therapy or after antimicrobial therapy.[68] Late embolisation can occur up to 15-30 weeks after diagnosis usually due to poor response to antimicrobial treatment. In order to predict the risk of embolic events, several features can be assessed with the use of echocardiography. They are usually related to the size, mobility and the location of the vegetation.[60,68]

Distal emboli may lead to metastatic infection or abscesses.[63] Emboli may also involve other systemic organs such as the liver, kidneys and abdominal mesenteric vessels.[63] Osteomyelitis is estimated to occur in 2-6% of cases of IE and is more common in intravenous (IV) drug abusers.[73] ^{18}F-FDG PET/CT imaging in IE has been useful in detecting peripheral embolic and metastatic infectious events in some cases where other diagnostic imaging has not identified foci.[54]

4.1.2.4 Neurological complications

IE can have profound and devastating neurological consequences. Neurological complications can occur before or during the diagnosis of IE, but they can also occur later in the clinical course of IE. Symptomatic neurological events develop in 25-40% of patients with IE.[4,46,74]

Most neurological complications occur early in the course of IE and they are most common in left-sided IE. The most common complications are ischaemic and haemorrhagic complications.

Diagnosis of neurological complications

It is important to make the diagnosis of neurological complications early, as well as to assess the severity of the complication. Intracerebral events are diagnosed by history-taking, clinical examination, and by imaging modalities. Imaging modalities commonly used for the assessment of intracerebral events include:

- CT scan, with or without contrast agents (most commonly performed).
- MRI, with or without gadolinium enhancement (better detection in patients with focal neurological lesions and may also detect lesions in patients without symptoms e.g. microbleeds). In addition to normal sequences, diffusion-weighted magnetic resonance imaging (DWI)/T2-weighted (T2W) gradient-echo (GRE) sequences are important to show asymptomatic infarcts or small microbleeds respectively.
- Cerebral angiography is advisable when there is strong clinical suspicion of mycotic aneurysm despite negative findings on non-invasive imaging modalities.

Imaging investigations should be done as soon as clinical features appear, preferably within 24 hours. The presence of neurological complications, its type and severity is important as it will impact the optimal management of IE. It is of particular importance to be specific when **describing and grading** the neurological complications of IE (refer Table 4.1).

Table 4.1: Description of neurological complications

Neurologic complication	Epidemiology	Clinical manifestation in IE	Management	Implications for cardiac surgery if indicated
Ischaemic	Clinically present in 20-40% of patients with IE. Asymptomatic ischaemia can be found in an additional 30-40% of patients with IE. Can be divided into: • Small ischaemic complications such as TIA or minor infarction affecting < 30% of a brain lobe or clinically silent infarcts. • Moderate-severe ischaemic complication such as multiple cerebral embolisms or a single embolism affecting ≥ 30% of a brain lobe.	Focal deficits, encephalopathy and seizures.	Avoid IV tissue plasminogen activator (tPA) or streptokinase, antiplatelet agents and warfarin.[75-77] Decision to withhold anticoagulation should be individualised and dependent on the multidisciplinary team (IE team).	As the evidence is not yet strong enough to make a uniform recommendation, these decisions should be individualised in consultation with all members of the IE team. Clinically silent or small lesions should not delay cardiac surgery. Larger infarcts may warrant a delay (refer Chapter 5.0).

Neurologic complication	Epidemiology	Clinical manifestation in IE	Management	Implications for cardiac surgery if indicated
Haemorrhagic	Present in 4-27% of patients with IE. These include: • Primary intracerebral haemorrhage. • Haemorrhagic infarction (transformation). • Subarachnoid haemorrhage. • Microhae-morrhage is present in up to 57% of patients with IE.	Focal deficits, headache, encephalopathy and seizure.	Native valve: avoid all antiplatelets and anticoagulants. Prosthetic valves: stop anticoagulation with close monitoring and evaluation of the patient's clinical condition for at least 2 weeks.[78] Consider magnetic resonance angiogram (MRA) in this group of patients and refer for Neurology consult (for best timing to recommence the anticoagulation). Consider conversion to heparin in anticipation of surgical intervention. As the evidence is not yet strong enough to make a uniform recommen-dation, these decisions should be individualised in consultation with all members of the specialist team.	Postpone cardiac surgery for 4 weeks following clinically significant haemorrhage.[79,80]

Neurologic complication	Epidemiology	Clinical manifestation in IE	Management	Implications for cardiac surgery if indicated
Mycotic aneurysms	Present in at least 2-4% of patients with IE.	Headaches, seizures, focal deficits, encephalopathy, opthalmoplegia and rarely proptosis.	Antimicrobials and serial imaging for stable, small, unruptured aneurysms. Endovascular repair of large or enlarging unruptured aneurysms, if suitable. Open surgical clipping for large or enlarging unruptured aneurysms not amenable to endovascular repair or in areas where surgical anastomoses may spare function. Any anticoagulation should be stopped and the decision to restart should be made in consultation with all members of the IE team.	Postpone cardiac surgery for 1-2 weeks following aneurysmal repair.
Cerebral abscess	Present in 1-7% of patients with IE.	Focal deficits, headache, encephalopathy, unresolved sepsis and seizures.	Antimicrobials alone for small or multifocal abscesses. Surgical drainage for abscesses that are large or do not respond to antimicrobials. Neurosurgical intervention as appropriate for hydrocephalus or significant mass effect.	Typically will not interfere with surgical planning. Prioritise neurosurgical intervention in the setting of hydrocephalus or significant mass effect.

Neurologic complication	Epidemiology	Clinical manifestation in IE	Management	Implications for cardiac surgery if indicated
Meningitis	Present in 1-20% of patients with IE.	Headache, encephalopathy, seizures, neck/back pain, nuchal rigidity and photophobia.	At least 4 weeks of antimicrobials.	Typically will not interfere with surgical planning.

Adapted from Morris et al. Neurohospitalist. 2014.[81]

- Patients at highest risk of morbidity and mortality are those who had moderate-severe ischaemic strokes and intracranial haemorrhage.
- Antimicrobial therapy should be started as soon as possible as the rate of neurological complications reduces significantly after one week of treatment.
- Anticoagulation therapy (warfarin or heparin) should be reviewed and adjusted according to clinical status (e.g. *S. aureus* IE in the presence of a mechanical prosthetic valve).
- However, despite antimicrobial therapy, patients with large vegetations (> 10 mm) should be considered for early surgical intervention (refer Chapter 5.0).

Management of neurological complications

A. General Principles

Some general measures in the management of neurological complications:

- Antimicrobial therapy should be started as soon as diagnosis is made to reduce the development of complications in the first week.
- The duration of antimicrobial therapy will depend on the type of complication and microorganism involved (refer Section 4.2).
- In the event of any neurological complication, it is advisable to refer to a neurologist for consultation and further management.
- Referrals to a neurosurgeon and interventional radiologist may be needed in the event of an intracerebral bleed, mycotic aneurysm or brain abscess.

B. Management of ischaemic and haemorrhagic complications

Ischaemic stroke and haemorrhagic events are associated with higher mortality. Therefore, it is crucial to anticipate the potential risk in patients with predisposing factors for embolisation (refer Section 4.1.2.3), make a rapid diagnosis and initiate appropriate antimicrobials as soon as possible to prevent a first or recurrent neurological event.[80]

C. Management of mycotic aneurysms

An aneurysm is a focal arterial dilatation involving all three layers of the arterial wall. Anuerysmal degeneration secondary to bacteraemia or septic embolisation is called a mycotic aneurysm. They are thin walled, friable and rupture easily resulting in intracranial haemorrhage. Cerebral mycotic aneurysms are a rare and deadly type of aneurysm that have no definitive treatment guidelines and represent 0.7-5.4% of all cerebral aneurysms. The mortality rate after rupture could reach as high as 80%.[82] The diagnosis of mycotic aneurysm is made by magnetic resonance angiography (MRA) or cerebral angiography.

The evolution of mycotic aneurysms is unpredictable even after antimicrobial therapy and variable outcomes have been reported.[83] Predictive factors for aneurysmal rupture have not been ascertained up to date.

The treatment of mycotic aneurysms should be tailored according to response to antimicrobial therapy, location of aneurysm and clinical status of the patient. They can be treated surgically, endovascularly or by watchful waiting. Cerebral mycotic aneurysms should be treated by a multidisciplinary team in a tertiary centre. This team consists of cardiologists, neurosurgeons, interventional neuroradiologists, neurologists and intensivists. In addition, this centre must have facilities and expertise to manage cerebral mycotic aneurysm patients. There are many factors which determine the choice of management, either open surgery or endovascular management. However, the most important are the following:[82]

- The morphology and location of the aneurysm.
- Whether it is possible to sacrifice the parent artery.
- Whether the patient needs or has received valve replacement surgery.
- The patient's overall status.

Decisions by the multidisciplinary team should be followed after discussion with the patient and family members.

If cardiac surgery is needed in the presence of a mycotic aneurysm, pre-operative endovascular intervention may be considered. Endovascular intervention involves occluding the aneurysm with a coil or other occluder materials (such as autologous clots or polyvinyl alcohol microparticles) and can be done safely with good outcomes in centres with available expertise.[83]

The role for routine MRA or cerebral angiography in all patients with left-sided IE is unknown as is the role of prophylactic coiling of all asymptomatic mycotic aneurysms.

D. Management of brain abscess, meningitis or encephalitis.

In the event of these complications, consultation from a neurologist and ID specialist should be sought.

Recommendations

In the management of complications in IE:

1. Surgery should be considered in patients with acute heart failure due to mechanical complications (refer Chapter 5.0). [I/B]
2. Further imaging should be considered in patients with persistent infection or high-risk for systemic embolisation. [IIa/C]
3. A multidisciplinary team inclusive of a neurologist with or without a neurosurgeon is recommended in the management of patients with IE and neurological complications. [I/C]
4. If cardiac surgery is indicated in the presence of cerebral mycotic aneurysm, pre-operative endovascular or neurosurgical intervention may be considered. [IIb/C]

4.1.3 Issues with anticoagulation

Cerebral injuries occur in 20-40% of patients during the active course of IE.[84] These include ischaemic stroke, TIA or intracerebral haemorrhage. The management of ischaemic stroke due to IE is different to ischaemic strokes from non-infective causes with regards to anticoagulation.

Anticoagulation in the setting of IE raises concerns of intracerebral haemorrhage, an often fatal event. Cerebral haemorrhage in endocarditis occurs through one of three mechanisms:

- Acute pyogenic arteritis secondary to uncontrolled infection.
- Haemorrhagic transformation of embolic infarcts.
- Rupture of dilated mycotic aneurysms.

Antiplatelet therapy

The potential role of antiplatelet therapy such as aspirin to reduce cerebrovascular events in IE has been investigated.

- Aspirin has not been shown to be of clear benefit as an adjunctive treatment in reducing mortality or morbidity in IE[75,85] and initiation of aspirin as treatment for IE is not recommended.
- In patients who were on aspirin long-term prior to the diagnosis of IE, it may be continued if there are no bleeding complications.[86]
- The role of other antiplatelet agents such as clopidogrel has not yet been extensively investigated.

Anticoagulation with warfarin

Cerebral haemorrhage is a major determinant of poor clinical outcome in IE.

A. Native valve infective endocarditis

- No evidence of a cerebrovascular ischaemic or haemorrhagic event.
  - > Warfarin may be continued for those who are on anticoagulation with warfarin for non-valvular indications (e.g. atrial fibrillation and deep vein thrombosis).[87]

- Presence of a cerebrovascular ischaemic or haemorrhagic event.
  - > Warfarin should be stopped to prevent haemorrhagic transformation (in the case of ischaemic stroke) or expansion of the haemorrhagic event.[88]
  - > Warfarin may be recommenced 2-3 weeks after the event or until the period of sepsis is over.[89]
  - > The role of low molecular weight heparin (LMWH) and new oral anticoagulants (NOAC) in this context is not known. It is advisable to stop all forms of anticoagulation such as NOAC or LMWH in the event of an ischaemic stroke or intracerebral haemorrhage in IE patients.[81]

B. Mechanical prosthetic valve infective endocarditis

Patients with mechanical prosthetic valves require anticoagulation with warfarin because of the risk of thromboembolic complications. Mechanical prosthetic valve IE (MPVIE) carries a higher mortality and poorer prognosis compared to native valve IE (NVE).[90,91] In MPVIE, the risks of cerebral haemorrhage with continued anticoagulation need to be weighed against the risk of thromboembolic complications from the mechanical prosthesis if anticoagulation is stopped.

The thromboembolic risk is higher with certain features such as:[92]

- Prosthetic mitral valves rather than aortic valves.
- Non-bileaflet valves.
- Early post-operative period (< 3 months) rather than late post-operative period.
- Presence of atrial fibrillation.
- Left ventricular dysfunction.
- Left atrial dilatation.
- Previous thromboembolic events.
- Hypercoagulable conditions (e.g. pregnancy).

In the event that a major ischaemic cerebral event occurs in MPVIE, it is reasonable to:

- Stop warfarin for at least 2-3 weeks during the period of highest risk for haemorrhagic transformation.
- Unfractionated heparin may be used from the 2nd week after stopping warfarin under close monitoring to reduce the thromboembolic complications from the mechanical valve prosthesis.
- Patients with[77,80] MPVIE due to *S. aureus* have been shown to be at much higher risk for cerebral haemorrhage. In these cases, even if there is no neurological complication, once diagnosis of IE is made warfarin can be stopped and substituted with unfractionated heparin for 2 weeks.

In the event of intracranial bleeding occurring in MPVIE:

- Anticoagulation should be stopped.
- Anticoagulation should be avoided during the first 2 weeks as the risk of further bleeding and expansion of the intracerebral haemorrhage is highest during this period.
- It is reasonable in most cases to restart anticoagulation with caution using unfractionated heparin after 2 weeks as the risk of further intracranial bleeding is low after 2 weeks, while the risk of thromboembolic complications in mechanical prosthetic valves without anticoagulation increases.[89,93]
- In cases where the risk of further intracranial bleeding after 2 weeks is judged to be high by the neurosurgical team, this must be balanced with the risk of thromboembolic complications from the mechanical prosthetic valve without anticoagulation, and a consensus decision made by the team.
- In those patients with MPVIE who may require imminent surgery it is advisable to discontinue warfarin at the time of diagnosis until the management plan is elucidated.
- If surgery is not indicated and the patient is deemed stable without contraindications or neurologic complications, warfarin can be restarted with caution.[94]

Restarting anticoagulation should be done very cautiously starting with intravenous unfractionated heparin guided by activated partial thromboplastin time (aPTT) monitoring and subsequently with dose adjusted warfarin. The role of LMWH in this context is not known. There are currently no guidelines on the use of NOAC for mechanical prosthetic valves. A Phase II trial on dabigatran in mechanical valves was terminated early due to excess bleeding in the dabigatran arm.

Recommendations

On the use of anticoagulants in IE patients with neurological complications:

1. In the event of intracranial bleeding, anticoagulation should be stopped. [I/B]
2. In MPVIE complicated by a major ischaemic cerebral event, it is reasonable to stop anticoagulation with warfarin for 2-3 weeks and cautiously substitute with intravenous unfractionated heparin after 2 weeks. [IIa/C]
3. In MPVIE due to *S. aureus*, it may be reasonable to stop warfarin and substitute with unfractionated heparin for 2 weeks, even with no neurological complication. [IIa/C]
4. In the event of intracranial bleeding, it is reasonable to stop warfarin for 2 weeks and anticoagulate with unfractionated heparin after 2 weeks in most cases. [IIa/C]

4.1.4 Referral for specialist care

IE is an unusual disease for a few reasons:

- The clinical manifestation, predisposing risk factors and epidemiology of IE can be very variable.
- Despite being relatively rare, it has significant morbidity and mortality.
- Ideal management of IE requires multiple, highly specialised expertise in one centre which is often not widely available. These include but are not limited to: echocardiologists, ID specialists, cardiac surgeons, interventional radiologists, neurologists, neurosurgeons and microbiologists.

To ensure a good outcome and to prevent complications, it is important to establish an accurate diagnosis early and institute appropriate treatment. It is recommended to have a multidisciplinary team approach in the management of patients with IE especially those with high-risk features. Where indicated, these patients may need additional subspecialty consultation or referral to a specialist centre. A **Specialist Centre (SC)** is defined here as a hospital with cardiothoracic, cardiac imaging and specialised cardiology services (refer Appendix 7).

Referral to a SC is recommended in the following situations (refer Table 4.2):

- Strong clinical suspicion of IE but TTE negative.
  - > Requires TEE and/or other imaging modalities to diagnose IE and to monitor for complications.
- Patients with high predisposing risks.
  - > Prosthetic valves or material (e.g. conduit IE, prosthetic shunts and intracardiac devices).
  - > Transcatheter valve implantation (e.g. transcatheter aortic valve implantation; TAVI and pulmonary valve implantation; PVI).
  - > CIED infections.
  - > CHD.
- Patients with indications for cardiac surgery (refer Section 5.1).
- Patients with cardiac complications.
  - > Valvular dysfunction especially of the left-sided valves.
  - > Cardiac abscess (confirmed or suspected).
  - > Congestive heart failure.
  - > Metastatic infection.

Specific situations that may need other non-cardiac consultations:

- ID and microbiology:
  - > BCNIE.
  - > Persistent infection that is not responding to treatment.
- Neurology/neurosurgery:
  - > Patients with neurological complications.
- Haematology:
  - > Patients who are on anticoagulation with coagulopathies and haemorrhagic complications.

Patients with non-complicated IE can be managed in a centre with internal medicine specialists. These are patients with:

- Mild-moderate abnormality of cardiac valvular function with no heart failure.
- Native valves only.
- Not more than mild ischaemic neurological complications (involving < 30% of a lobe).

However, in the event that complications arise they should be referred to a SC.

Table 4.2: Specific clinical situations needing referrals/specialised consultation

Complicated IE (requires transfer to a SC if possible or constant consultation with a SC)	Non-complicated IE (manage in centre with internal medicine specialists but refer to SC in the event complications arise)
• Heart failure • Perivalvular extensions • Embolic complication • Neurological complication** • Metastatic or uncontrolled infection# • CHD • Prosthetic valve • CIED • Transcatheter implantable valves or devices	• Mild-moderate abnormality of cardiac valvular function with no heart failure • Native valves only • Not more than mild ischaemic neurological complications (involving < 30% of a lobe)
Additional consultation with non-cardiac subspecialties: **neurology/neurosurgery; #ID and microbiology.	

A Specialist Centre (SC) is defined as a centre with cardiothoracic, cardiac imaging and specialised cardiology services.

Patients with high predisposing risk for complications, with indications for cardiac surgery and with cardiac complications should ideally be referred to a SC.

Recommendations

For referral of IE patients for specialist care:

1. IE should be preferably managed by a multidisciplinary team with the necessary expertise in endocarditis management. [IIa/B]
2. Patients with complicated IE should be considered for referral to a SC. [IIa/C]

4.1.5 Pre-discharge management

All patients who have experienced an episode of IE remain at high-risk for recurrent infection indefinitely (refer Appendix 1). Those with significant valvular regurgitation and/or cardiac lesions who have completed successful antimicrobial therapy may require eventual cardiac surgery. The assessment for timing of surgical intervention can be guided by the clinical status and serial echocardiographic evaluation.

Therefore, prior to discharge, patients who have had appropriate and effective medical treatment and surgery (if necessary) should undergo the following:

- Detailed physical assessment to document the clinical status (blood pressure, heart rate and rhythm should be documented).
- Laboratory investigations e.g. inflammatory markers, FBC and serology (improving trend/resolution of infection).
- Echocardiography to establish a new baseline (most often TTE is adequate).
- Evaluation of toxicity resulting from prolonged antimicrobial use such as renal function, ototoxicity and diarrhoea (refer Section 4.2).
- Counselling or rehabilitation for IVDU.
- Education and counselling on:
  - > Recognition of relapsing infection e.g. fever, chills, rigors and the need for blood cultures BEFORE starting any antimicrobials (even oral ones).
  - > Heart failure signs and symptoms in case of mechanical deterioration of cardiac function.
  - > Good oral hygiene and when indicated, antimicrobial prophylaxis prior to dental procedures (refer Chapter 8).

Recommendations

For pre-discharge assessment of IE patients:

1. Pre-discharge echocardiogram is recommended to establish a new baseline. [IIa/C]
2. Education to patients on recognising relapses, complications and oral hygiene is recommended. [IIa/C]

4.2 Antimicrobial therapy: principles and methods

4.2.1 General principles

General principles for the treatment of IE include:

- Parenteral antimicrobials in high dose to sustain antibacterial concentrations for treatment success.
- Bactericidal antimicrobials are necessary for effective treatment.
- Adequate duration is required to prevent relapses.

4.2.2 Suggested regimes for treatment of native or prosthetic valve infective endocarditis

The choice of antimicrobials will depend on the type of microorganism isolated and whether it is a native or a prosthetic valve IE. These are presented in the tables below. All doses quoted are for patients with normal renal function. For dosing adjustment in patients with renal impairment refer to Appendices 8 and 9.

4.2.2.1 *Streptococcus viridans*

Table 4.3: Endocarditis due to penicillin-susceptible viridans group streptococci (VGS) and *S. gallolyticus (bovis)*[95-98]

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Penicillin-susceptible VGS and *S. gallolyticus (bovis)* (MIC ≤ 0.125 µg/ml) – native and prosthetic valve				
Benzyl penicillin (Crystalline penicillin)	3MU** every 4 to 6 hourly or 12-18 MU/day as a continuous infusion **MU = mega unit; 600 mg = 1 MU	200,000 -300,000 units/ kg/day IV in 4-6 equally divided doses (up to 12-18 MU daily)	4 (native) 6 (prosthetic)	
Ampicillin	2 g IV 4 hourly	300 mg/kg/day IV in 4-6 equally divided doses		
Ceftriaxone	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)		
Vancomycin[b,c]	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/ day)	4 (native) 6 (prosthetic)	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity.

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Relatively resistant to penicillin VGS and *S. gallolyticus (bovis)* (MIC > 0.125 to 2 µg/ml) – native valve endocarditis				
Benzyl penicillin (Crystalline penicillin) **OR**	4 MU** 4 hourly or 24 MU/day as continuous infusion **MU = megaunit; 600 mg = 1 MU	200,000 - 300,000 units/kg/day IV in 4-6 equally divided doses (up to 12-18 MU daily)	4 (native) 6 (prosthetic)	Cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type
Ceftriaxone **PLUS**	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	2 (native) 6 (prosthetic)	
(Low dose) Gentamicin[4]	3 mg/kg/day IV once daily	1 mg/kg IV 8 hourly		See notes below on how to monitor for gentamicin toxicity
Vancomycin[b,c] **PLUS**	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 3 equally divided doses (maximum 2g/day)	4 (native) 6 (prosthetic)	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity
(Low dose) Gentamicin[d]	3 mg/kg/day IV once daily	1 mg/kg IV 8 hourly	2 (native) 6 (prosthetic)	See notes below on how to monitor for gentamicin toxicity

a. Paediatric doses should not exceed the max of normal adult dose.
b. Vancomycin: aim for serum trough level of 10-15 mg/l.
c. Vancomycin dose should be adjusted in patients with renal impairment. Refer Appendices 8 and 9 for dosing recommendations.
d. For patients on gentamicin:
- Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity.
- When given in a single daily dose give infusion over 30 minutes. Aim for pre-dose (trough) serum level of < 1 mg/l.
- Consider biweekly clinical screening for ototoxicity:
  > Check baseline visual acuity using a Snellen pocket card.
  > To screen for ototoxicity, have patient shake head and reread the card.
  > Consider formal audiology test if patient loses 2 lines of visual acuity.

Recommendations

For antimicrobials in *Streptococcus viridans* infection:

1. For penicillin susceptible (MIC ≤ 0.125 µg/ml) *streptococcus viridans*, monotherapy with benzyl penicillin, ampicillin or ceftriaxone is adequate. [IIa/B] Duration of therapy is for 4 weeks for NVE and 6 weeks for prosthetic valve endocarditis (PVE). [IIa/C]
2. For penicillin relatively resistant (MIC > 0.125 to 2 µg/ml) *streptococcus viridans*, gentamicin has to be added to the regime. [IIa/B] Duration of gentamicin is for 2 weeks for NVE and 6 weeks for PVE. [IIa/C]

4.2.2.2 Nutritionally variant streptococci

Table 4.4: *Abiotrophia defective* and *Granulicatella* species (both formerly known as nutritionally variant streptococci; NVS)[99, 100]

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Ampicillin **OR** **Benzyl penicillin (Crystalline penicillin)** **PLUS** **(Low dose) Gentamicin[d]**	2 g IV 4 hourly 4 MU** IV 4 hourly or 24 MU/day as a continuous infusion). **MU = megaunit; 600 mg = 1 MU 1 mg/kg IV 8 hourly	300 mg/kg/day IV in 4-6 equally divided doses 300,000 units/kg/day IV in 4-6 equally divided doses 1 mg/kg IV 8 hourly	6 2	Follow susceptibility test results, if available See notes below on how to monitor for gentamicin toxicity
Ceftriaxone **PLUS** **(Low dose) Gentamicin[d]**	2 g IV once daily 1 mg/kg IV 8 hourly	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day) 1 mg/kg IV 8 hourly	6 2	Ceftriaxone is preferred if clinically not responding with penicillin
Vancomycin[b,c]	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/day)	6	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity

a. Paediatric doses should not exceed the max of normal adult dose.
b. Vancomycin: aim for serum trough level of 10-15 mg/l.
c. Vancomycin dose should be adjusted in patients with renal impairment. Refer Appendices 8 and 9 for dosing recommendations.
d. For patients on gentamicin:
   - Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity.
   - Aim for pre-dose (through) serum level of < 1 mg/l.
   - Consider biweekly clinical screening for ototoxicity:
     > Check baseline visual acuity using a Snellen pocket card.
     > To screen for ototoxicity, have patient shake head and reread the card.
     > Consider formal audiology test if patient loses 2 lines of visual acuity.

Recommendations

For antimicrobials in NVS infection:

NVS are fastidious and slow growing making it technically difficult to determine antimicrobial susceptibility. Combination treatment of penicillin, ampicillin or ceftriaxone with gentamicin for at least the first 2 weeks, followed by continuation of chosen antimicrobial without gentamicin for 6 weeks is recommended. [II/B]

4.2.2.3 *Staphylococcus aureus* and *Coagulase-negative staphylococcus* (CoNS)

Table 4.5: Native valve endocarditis due to *S. aureus* (right-sided)[101-105]

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Methicillin-susceptible staphylococci (MSSA) – left-sided				
Cloxacillin	12 g/day IV in 4-6 equally divided doses	200-300 mg/kg/day IV in 4-6 equally divided doses	4- 6	
Methicillin-susceptible staphylococci (MSSA) – right-sided; tricuspid valve				
Cloxacillin	12 g/day IV in 4-6 equally divided doses	200-300 mg/kg/day IV in 4-6 equally divided doses	2-4; see comments	2 weeks regime is sufficient provided the patient fulfils all the following criteria: • MSSA • Good response to treatment • Absence of metastatic sites of infection or empyema • Absence of cardiac and extracardiac complications • Absence of associated prosthetic valve or left-sided valve infection • < 20 mm vegetation • Absence of severe immuno-suppression (< 200 CD4 cells/ml) with or without acquired immune deficiency syndrome (AIDS)

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Regimens for β-lactam allergic patients – both left-sided and right-sided				
Cefazolin	2 g IV 8 hourly	100 mg/kg/day IV in 3 equally divided doses	4-6	Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin. Cefazolin has inadequate blood-brain barrier penetrability. In cases of brain abscesses complicating MSSA IE, watch out for treatment failure.
Vancomycin[b,c]	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range)	4-6	Loading dose of 25-30 mg/ kg (actual body weight) may be considered for seriously ill patients. Vancomycin is inferior to cloxacillin for treatment of MSSA. Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity
Methicillin-Resistant Staphylococci (MRSA) – left-sided and right-sided				
Vancomycin[b,c]	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range)	4-6	Loading dose of 25-30 mg/ kg (actual body weight) may be considered for seriously ill patients
Daptomycin	10 mg/kg IV daily	10 mg/kg IV daily	4-6	Daptomycin is superior to vancomycin for MRSA bacteraemia with vancomycin MIC > 1 mg/l

Table 4.6: Staphylococcal endocarditis in the presence of a prosthetic valve or other prosthetic material

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Methicillin-susceptible staphylococci (MSSA)				
Cloxacillin **PLUS**	2 g IV 4 hourly	200-300 mg/ kg/day IV in 4-6 equally divided doses	≥ 6	Allergy to penicillin but not immediate- type hypersensitivity use cefazolin or vancomycin Immediate-type hypersensitivity to penicillin use vancomycin **Rifampicin has better penetration. However to avoid the development of resistance, it should be started after 3-5 days of effective initial cloxacillin therapy and/or once the bacteraemia has been cleared.
Rifampicin **PLUS**	300-450 mg PO 12 hourly**	20 mg/kg/day PO in 3 divided doses	≥ 6	
(Low dose) Gentamicin[d]	1 mg/kg IV 8 hourly	1 mg/kg IV 8 hourly	2	
Methicillin-Resistant Staphylococci (MRSA)				
Vancomycin[b,c] **PLUS**	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range)	≥ 6	For adults, loading dose of 25-30 mg/kg (actual body weight) may be considered for seriously ill patients. **Rifampicin has better penetration. However to avoid the development of resistance, it should be started after 3-5 days of effective initial vancomycin therapy and/or once the bacteraemia has been cleared.
Rifampicin **PLUS**	300-450 mg PO 12 hourly**	20 mg/kg/day PO in 3 divided doses	≥ 6	
(Low dose) Gentamicin[d]	1 mg/kg IV 8 hourly	1 mg/kg IV 8 hourly	2	

a. Paediatric doses should not exceed the max of normal adult dose.
b. Vancomycin: aim for serum trough level of 15-20 mg/l.
c. Vancomycin dose should be adjusted in patients with renal impairment. Refer Appendices 8 and 9 for dosing recommendations.
d. For patients on gentamicin:
   - Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity.
   - Aim for pre-dose (trough) serum level of < 1 mg/l.
   - Consider biweekly clinical screening for ototoxicity:
     > Check baseline visual acuity using a Snellen pocket card.
     > To screen for ototoxicity, have patient shake head and reread the card.
     > Consider formal audiology test if patient loses 2 lines of visual acuity.

Recommendations

For antimicrobials in *S. aureus* and CoNS infections:

1. Addition of gentamicin for native valve staphylococcus endocarditis is not recommended. [III/B]
2. Addition of gentamicin and rifampicin is recommended for PVE. [I/C]

4.2.2.4 *Enterococcus* species

Table 4.7: Endocarditis due to *enterococcus*-native and prosthetic valve[106]

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Fully penicillin-susceptible strains (penicillin MIC ≤ 8 mg/l)				
Ampicillin **PLUS** **(Low dose) Gentamicin[d]**	2 g IV 4 hourly 1 mg/kg IV 8 hourly	200-300 mg/kg/day IV in 4-6 equally divided doses 1 mg/kg IV 8 hourly	4 or 6 depending on duration of symptoms and type of valve; see comments 2 or 6 depending on duration of symptoms and type of valve; see comments	Duration of symptoms < 3 months and native valve: Ampicillin duration - 4 weeks Gentamicin duration - 2 weeks Duration of symptoms > 3 months or prosthetic valves: Ampicillin duration - 6 weeks Gentamicin duration - 6 weeks See notes below on how to monitor for gentamicin toxicity For patients who develop renal impairment or ototoxicity secondary to gentamicin switch to ampicillin/ceftriaxone regime
Ampicillin **PLUS** **Ceftriaxone**	2 g IV 4 hourly 2 g IV 12 hourly	200-300 mg/kg/day IV in 4-6 equally divided doses 100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	6	Preferred in patients with renal impairment (≤ 50 ml/min) or elderly Ceftriaxone should not be used alone for *enterococcus* infection, as they are intrinsically resistant This combination is not active against *E. faecium*

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Sensitive to penicillin and vancomycin but high level resistance to gentamicin (MIC > 500 mg/l)				
Ampicillin **PLUS** **Ceftriaxone**	2 g IV 4 hourly 2 g IV 12 hourly	300 mg/kg/day IV in 4-6 equally divided doses 100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	6	Ceftriaxone should not be used alone for *enterococcus* infection, as they are intrinsically resistant This combination is not active against *E. faecium*
Resistant to penicillin and susceptible to aminoglycosides and vancomycin				
Vancomycin[b,c] **PLUS** **(Low dose) Gentamicin**[d]	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose 1 mg/kg IV 8 hourly	40 mg/kg/day IV in 3 divided doses (maximum 2 g/day unless unable to achieve therapeutic range) 1 mg/kg IV 8 hourly	6 6	

a. Paediatric doses should not exceed the max of normal adult dose.
b. Vancomycin: aim for serum trough level of 10-20 mg/l.
c. Vancomycin dose should be adjusted in patients with renal impairment. Refer Appendices 8 and 9 for dosing recommendations.
d. For patients on gentamicin:
- Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity.
- Aim for pre-dose (trough) serum level of < 1 mg/l.
- Consider biweekly clinical screening for ototoxicity:
  - > Check baseline visual acuity using a Snellen pocket card.
  - > To screen for ototoxicity, have patient shake head and reread the card.
  - > Consider formal audiology test if patient loses 2 lines of visual acuity.

Recommendations

For antimicrobials in *enterococcus* infection:

1. In native valve *enterococcus* endocarditis, the duration of ampicillin and gentamicin is dependent on the duration of symptoms before treatment initiation. [IIa/C]
2. Combination therapy with ceftriaxone and ampicillin is recommended for patients with gentamicin high-level resistance, the elderly and those with renal impairment. [IIa/B]

4.2.2.5 HACEK microorganisms

Table 4.8: Therapy for endocarditis due to HACEK microorganisms *(Haemophilus parainfluenza, Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella kingae)* both native and prosthetic valve

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric		
Ceftriaxone **OR**	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	4 (native) 6 (prosthetic)	HACEK-group bacilli produce beta-lactamases; definitive treatment should be adjusted based on the cultures
Ampicillin + Sulbactam **OR** **Ciprofloxacin**	3 g IV 6 hourly 400 mg IV 12 hourly or 500 mg PO 12 hourly	200-300 mg/kg/day IV in 4-6 equally divided doses (ampicillin component)	4 (native) 6 (prosthetic) 4 (native) 6 (prosthetic)	May be an option if isolate is susceptible If unable to tolerate cephalosporin and ampicillin therapy fluoroquinolones generally not recommended for patients < 18 years old

Recommendations

For antimicrobials in HACEK group of microorganism infection:

1. Ceftriaxone monotherapy is recommended for endocarditis due to HACEK microorganisms. [IIa/B]
2. Alternative drugs such as ampicillin/sulbactam or ciprofloxacin may be used provided the isolate is susceptible. [IIa/C]

4.2.2.6 *Candida*

Table 4.9: Therapy for *Candida* endocarditis (native and prosthetic valve)[107]

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric		
Amphotericin B deoxycholate **OR** **Lipid formulation Amphotericin B** **with or without Flucytosine**	0.6-1.0 mg/kg IV once daily 3-5 mg/kg IV once daily 25 mg/kg PO 6 hourly	1.0 mg/kg IV once daily 3-5 mg/kg IV once daily 100-150 mg/kg PO in 4 equally divided doses	At least 6 weeks after surgery At least 6 weeks after surgery	Step down therapy: fluconazole 400-800 mg (6-12 mg/kg) orally daily for susceptible microorganism in stable patients with negative blood cultures (clearance of *Candida* from blood stream) For synergistic effect Causes dose related marrow toxicity Avoid using in patients with renal failure
Micafungin **Caspofungin** **Anidulafungin**	150 mg IV daily 150 mg IV daily 200 mg IV daily		At least 6 weeks after surgery	Step down therapy: fluconazole 400 -800 mg (6-12 mg/kg) orally daily for susceptible microorganism in stable patients with negative blood cultures (clearance of *Candida* from blood stream)

- Valve replacement is mandatory. Continue therapy for 6 weeks after replacement or longer in patient with perivalvular abscess.
- The duration of therapy will depend on patient response and surgical intervention.
- For patients who cannot undergo valve replacement, long-term suppression with fluconazole at a dosage of 400-800 mg (6-12 mg/kg) daily is recommended.
- For PVE, the recommendations above apply, and suppressive therapy should be lifelong if valve replacement is not possible.

Recommendations

For management of *Candida* infection:

Valve surgery combined with antifungal therapy is required for adequate treatment of *Candida* endocarditis. [I/B]

4.2.2.7 Non-HACEK Gram-negative microorganisms

This includes microorganisms such as *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella*. The choice of antimicrobials for these microorganisms depends on antimicrobial susceptibility pattern. Commonly combination therapy with β-lactam (column A) and aminoglycosides or fluoroquinolones (column B) are used (refer Table 4.10). Medical therapy often needs to be combined with cardiac surgery. The duration of therapy is 6 weeks.

Table 4.10: Antimicrobial choices for pseudomonas endocarditis (6 weeks duration) in adults^

Column A	Column B
Anti Pseudomonal β-lactams	**Aminoglycosides**
Ceftazidime 2 g IV 8 hourly	Gentamicin 5-7 mg/kg IV daily
Cefepime 2 g IV 8 hourly	Amikacin 15 mg/kg IV daily
Piperacillin-tazobactam 4.5 g IV 6 hourly	OR
	Flouroquinolones**
	Ciprofloxacin 400 mg IV 8 hourly
	Levofloxacin 750 mg IV daily
**Flouroquinolones can be switched to appropriate oral dose if patient can tolerate oral medications. ^As there are very limited data on treating these infections in the paediatric population, a Paediatric ID specialist consult is recommended for an appropriate treatment plan.	

Adapted from Reyes MP, et al. Medicine (Baltimore). 2009.[108]

Recommendations

For antimicrobials in non-HACEK group of microorganism infections:

In non-HACEK Gram-negative IE a combination therapy with a β-lactam and aminoglycoside or fluoroquinolone are used. [IIa/C]

4.2.2.8 Other microorganisms

Table 4.11: Therapy for other microorganisms (adults)**

Pathogen	Antimicrobial	Dosage and route	Duration of therapy
***Brucella* spp.**[109]	Doxycycline **PLUS** Rifampicin **ADD** Streptomycin (For first 2-3 weeks only) **OR** Gentamicin	100 mg PO 12 hourly 300-600 mg PO daily 1 g IM daily 5 mg/kg IV daily	3-6 months
***C. burnetii* (agent of Q fever)**[110]	Doxycycline **PLUS** Hydroxychloroquine	100 mg PO 12 hourly 600 mg PO daily or 200 mg PO 8 hourly	18-24 months based on clinical and serological response
***Bartonella* spp.**[111,112]	Doxycycline **PLUS** Gentamicin	100 mg PO 12 hourly 3 mg/kg IV daily	2 weeks

**As there are very limited data on treating these infections in the paediatric population, a Paediatric ID specialist consult is recommended for an appropriate treatment plan.

4.2.3 Empirical therapy

The initial empirical regime for endocarditis will depend on the following factors (refer Figure 4a):

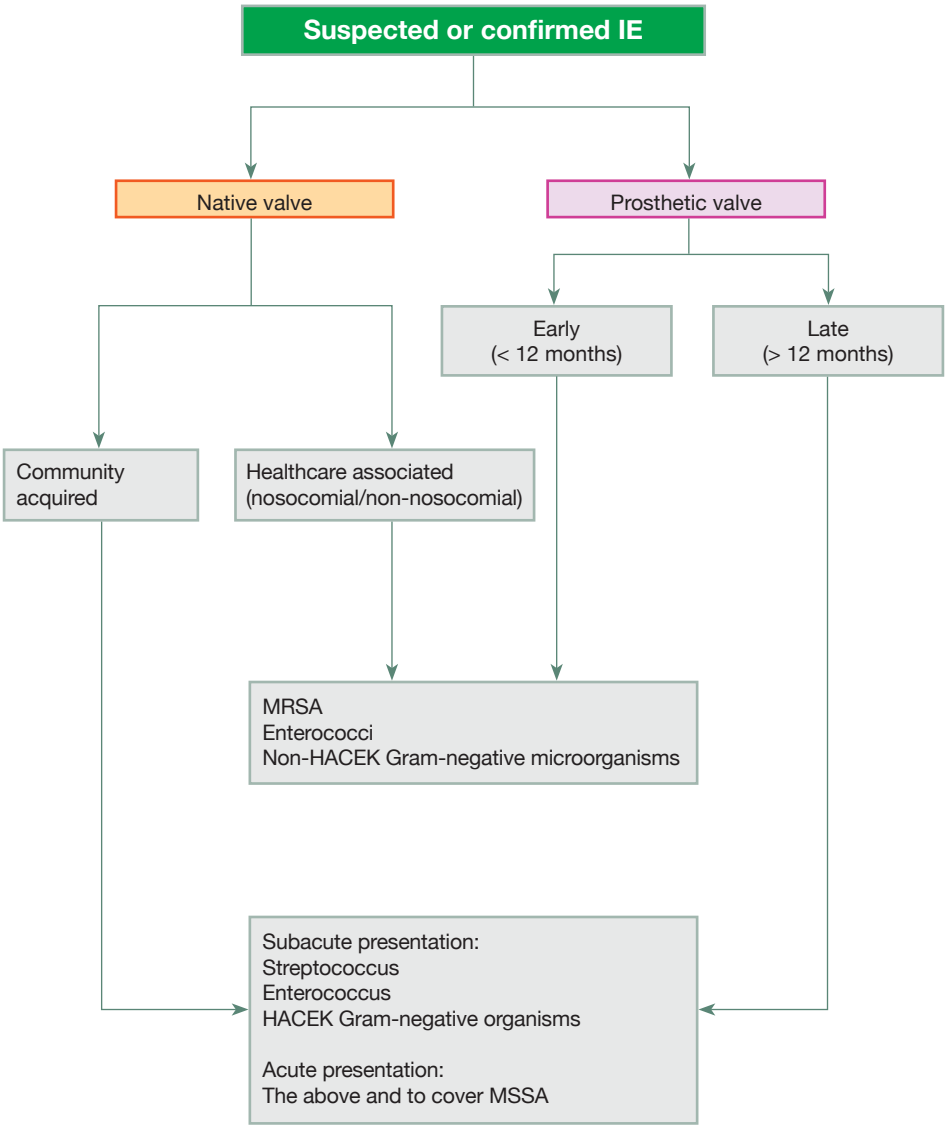
- Involvement of native or prosthetic valves.
- Duration following prosthetic surgery; early vs. late PVE (refer Appendix 1).
- Community acquired or healthcare associated (refer Appendix 1).
- Presence of risk factors for multidrug resistant microorganisms e.g. previous antimicrobial use or colonisations (extended-spectrum β-lactamases; ESBL producing microorganisms, *Pseudomonas* and MRSA).
- Risk factors/clinical clues for fastidious or intracellular pathogens (refer Table 3.2).
- Acute or subacute presentation.

Patients with subacute presentation are more likely to be infected with less virulent microorganisms such as VGS, enterococci, HACEK Gram-negative or NVS.

Patients may present acutely due to:

- Infection with more virulent microorganisms such *S. aureus* and non-HACEK Gram-negatives.
- Infection with less-virulent microorganisms such as VGS, enterococci and HACEK Gram-negatives due to prolonged illness or immunocompromised status.

Figure 4a: Antimicrobial coverage required for initial empirical treatment



Proposed antimicrobial regimens for initial empirical treatment of infective endocarditis (before pathogen identification) are presented in the table below.

Table 4.12: Therapy for initial empirical treatment of IE in acute severely ill patients

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Community-acquired native valves or late prosthetic valves (≥ 12 months post-surgery) endocarditis				
Ampicillin **PLUS** **(Low dose) Gentamicin[d]** **PLUS/MINUS** **Cloxacillin****	12 g/day IV in 4-6 equally divided doses 3 mg/kg/day IV once daily 12 g/day IV in 4-6 equally divided doses	200-300 mg/kg/day IV in 4-6 equally divided doses 1 mg/kg IV 8 hourly 200 mg/kg/day IV in 4-6 equally divided doses		**For patients with suspected *S. aureus* infections (such as IVDU or patients with prosthesis) and acute presentation
Vancomycin[b,c] **PLUS** **(Low dose) Gentamicin[d]**	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose 3 mg/kg/day IV once daily	40 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/day unless unable to achieve therapeutic range) 1 mg/kg IV 8 hourly		For patients who are allergic to β-lactam antimicrobials

Antimicrobial	Dosage and route		Duration of therapy (weeks)	Comments
	Adult	Paediatric[a]		
Early PVE (< 12 months post-surgery) or nosocomial and non-nosocomial healthcare associated endocarditis				
Vancomycin[b,c] **PLUS**	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/day unless unable to achieve therapeutic range)		**Rifampicin is only recommended for PVE and it should be started 3-5 days later than vancomycin and gentamicin
(Low dose) Gentamicin[d] **PLUS/MINUS**	3 mg/kg/day IV once daily	1 mg/kg IV 8 hourly		^Cefepime is indicated if local epidemiology suggests for non-HACEK Gram- negative rod infections (such as *Pseudomonas*)
Rifampicin** **PLUS/MINUS**	300-450 mg PO 12 hourly	20 mg/kg/day divided every 8 hourly (maximum dose: 900 mg/day)		
Cefepime^	2 g IV 8 hourly	50 mg/kg IV 8 hourly		

a. Paediatric doses should not exceed the max of normal adult dose.
b. Vancomycin: aim for serum trough level of 15-20 mg/l .
c. Vancomycin dose should be adjusted in patients with renal impairment. Refer Appendices 8 and 9 for dosing guide.
d. For patients on gentamicin:
- Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity.
- Aim for pre-dose (trough) serum level of < 1 mg/l.
- Consider biweekly clinical screening for ototoxicity:
  > Check baseline visual acuity using a Snellen pocket card.
  > To screen for ototoxicity, have patient shake head and reread the card.
  > Consider formal audiology test if patient loses 2 lines of visual acuity.

4.2.3.1 Empirical antimicrobial therapy for infective endocarditis in intravenous drug users

S. aureus is the most common cause of IE among IVDUs. However fungal and Gram-negative bacilli such as *Pseudomonas aeruginosa* can also cause IE in this population. Tricuspid valve involvement is the most common. Septic pulmonary emboli and pneumonia are common complications of tricuspid valve involvement and does not alter the duration of treatment (refer Section 4.2.2.3; Table 4.5 & 4.6).

4.2.4 Outpatient parenteral antimicrobial therapy for infective endocarditis

In carefully selected patients, outpatient parenteral antimicrobial therapy (OPAT) can be a safe and effective means of completing therapy for IE. Patients require minimum 2 weeks of inpatient therapy before being considered for OPAT. Beyond 2 weeks of treatment consider OPAT service if patient is:

- Medically stable.
- Has no heart failure.
- Has no neurological signs.
- Has no renal impairment.
- Has no high-risk cardiac features on echocardiogram (refer Section 3.3.1; Table 3.4).

The hospital must have established OPAT services with trained staff and protocols. Patients need to be reviewed daily by a trained nurse and by a doctor once/twice a week. Some important parameters that should be reviewed are presented in Appendix 10.

5.0
SURGICAL INTERVENTION

5.1 Indications

Surgical intervention is indicated in the following cases of IE:[113-116]

- Severe valvular incompetence, haemodynamic instability or heart failure.
- Uncontrolled sepsis and paravalvular extension of infection.
- Fungal or multiresistant endocarditis.
- Large vegetations (> 10 mm for left-sided IE) and recurrent systemic embolisation.

A. Severe valvular incompetence, heart failure or haemodynamic instability

Valvular regurgitation in NVE occurs as a result of:

- Leaflet perforation.
- Rupture of the leaflet supporting apparatus.
- Interference of the vegetative mass with leaflet closure.
- Intracardiac and extracardiac fistulas.
- Valve obstruction of prosthetic valves by very large vegetations (rare).

When acute and severe, heart failure and haemodynamic instability ensues. Surgery in these situations is life saving and has been shown to improve survival.[114]

B. Persistent infection, uncontrolled sepsis and paravalvular extension of infection

Surgery is indicated when:

- Fever or positive blood cultures persist despite appropriate antimicrobial treatment after 5-7 days.
- Extracardiac causes have been excluded.

Paravalvular extension of IE is the most frequent cause of uncontrolled infection and is associated with a poor prognosis. Most of these patients undergo surgery with a very high hospital mortality of up to 41%.[117]

Abscesses are more common in native aortic valve endocarditis compared to mitral or tricuspid valve endocarditis and typically occur in the weakest part of the annulus near the membranous septum and AV node.[118]

- Heart blocks are therefore a sign of abscess formation.
- Acute coronary syndromes can also occur.
- Abscesses are more common in PVE as the annulus rather than the prosthetic valve is usually the primary source of the infection.[119]
- These abscesses may progress to fistulous tracts creating intracardiac or pericardial shunts.[117]

C. Fungal or multiresistant endocarditis

Surgery is indicated in IE caused by the following microorganisms/infection:

- Fungal IE:
  - > Responds poorly to medical treatment.
  - > Reported mortality of up to 70%.[120,121]
  - > Even with surgery, survival remains poor.
- Multiresistant microorganisms.
- Non-HACEK Gram-negative bacteria.
- *S. aureus* infection, if a favourable early response to antimicrobials is not achieved.

D. Very large vegetations (> 10 mm) or previous systemic embolism

Surgery should be considered for vegetations > 10 mm in size particularly when other risk factors for embolisation are present. These include:[36,61,71,115]

- Mobile vegetation.
- Increase in vegetation size despite treatment.
- Vegetation on the mitral valve (particularly the anterior leaflet).
- *S. aureus*, fungal and HACEK endocarditis.
- Previous systemic embolism.

Recommendations

Surgical intervention in IE is indicated for:

1. Severe valvular incompetence, heart failure or haemodynamic instability. [I/B]
2. Persistent infection, uncontrolled sepsis or paravalvular extension of infection. [I/B]
3. Fungal or multiresistant endocarditis. [I/B]
4. Very large vegetations (> 10 mm) or previous systemic embolism. [I/B]

5.2 Timing of surgery

In general, when there is an established indication for surgery as discussed in Section 5.1 above, surgical intervention should be undertaken as soon as practically possible after completion of surgical workup.

Early surgical intervention in these patients:

- Improves survival.[113,122,123]
- Prevents the risk of progressive heart failure, cardiogenic shock and multiorgan failure.[124]
- Decreases the progression of infection causing further structural damage with abscess formation.
- Reduces systemic embolism of the vegetations.[116]
- Increases the likelihood of valve repair rather than replacement due to lesser destruction of the native valve.[125]

The improved results with early surgery is seen in those with heart failure or paravalvular complications. However in practice, surgery is often delayed in endocarditis due to:

- High operative risk.
- Possible risk of the newly implanted prosthetic valve getting infected.

A recent meta-analysis involving 8,141 patients demonstrated that early surgery within 2 weeks of diagnosis improved both early mortality and long-term survival compared with non-early surgery.[126] In patients with cardiogenic shock, surgery should be undertaken much earlier, within 24 hours of diagnosis.[127] However, it may be reasonable to delay surgery for 48 hours in a patient with septic shock to allow a period of stabilisation and better control of the sepsis with intravenous antimicrobials as cardiac surgery with cardiopulmonary bypass in the presence of septic shock carries an excessively high operative mortality.[125,127]

In selected patients, surgery can be carried out on an elective or semi-elective basis in the subacute or healed phase of endocarditis where the operative risk and the risk of infection of the implanted valve prosthesis is lower.[68,128] This is applicable for the following patients:

- Pre-existing chronic valvular regurgitation who are haemodynamically stable.
- Vegetation is < 10 mm in size.
- Well-controlled sepsis.

A multidisciplinary team approach, comprising cardiologists, cardiac surgeons and ID specialists is recommended when deciding on the indication and optimal timing for surgical intervention. This approach has lowered overall morbidity and mortality for IE. Patients with an indication for surgical intervention should be transferred to a SC at the earliest opportunity where such a multidisciplinary approach can be offered.

5.2.1 Preventing systemic embolism

Most emboli occur before the diagnosis of endocarditis and in the first 2 weeks thereafter; the embolic rate decreases significantly after 2-3 weeks of antimicrobial therapy.[17,61,67,129] There is emerging evidence for urgent surgery in preventing embolic events in those with large vegetations > 10 mm.[130]

A randomised controlled trial of 76 patients with left-sided NVE comparing early versus late surgery in IE with large vegetations (> 10 mm) reported a lower composite rate of hospital deaths, embolic events and recurrent endocarditis at 6 months with early surgery within 48 hours (3% versus 23%). The difference was largely due to a reduction in embolic events with early surgery.[116] Surgery undertaken for the prevention of systemic embolism should be performed urgently during the first few days following initiation of antimicrobial therapy, as the risk of embolism is highest at this time.

Recommendations

Timing of surgery	Clinical condition
The timing of surgical intervention in IE patients depends on the clinical condition of the patient.	
Emergency (within 24 hours)	Cardiogenic shock from severe valve dysfunction. [I/C]
Urgent (within 3-4 days)	Pulmonary oedema but not in cardiogenic shock. [I/B] Very large vegetations (> 10 mm). [I/B] Paravalvular abscess or heart block. [I/C]
Early (within 1-2 weeks)	Fungal, *S. aureus* or other highly resistant microorganisms. [I/C] Persistent infection. [IIa/B] Persistent or enlarging vegetations despite antimicrobials. [IIa/B] Recurrent emboli. [I/B]
Semi-elective (after 2 weeks of antimicrobial cover)	PVE and relapsing infection. [I/B]
Elective (after 6 weeks of antimicrobial therapy)	Well-tolerated chronic severe valvular regurgitation with controlled infection. [I/C]

5.3 Surgery in specific conditions

5.3.1 Cerebral infarction or haemorrhage

Up to 80% of patients with left-sided endocarditis have cerebral embolism detected by MRI. However, the majority of these are subclinical and clinical stroke is diagnosed in only 25-29%.[48,131]

The risk of significant neurologic complications occurring as a result of cardiac surgery performed early after a significant cerebral infarction is high:

- Approximately 20% in the first 3 days.
- 20-50% between 4 and 14 days.
- 6-10% between 15 and 28 days.
- < 1% after 28 days.

Hospital mortality is also dependent on the time of cardiac surgical intervention after a cerebral infarction; 66% when surgery is performed within 24 hours of a stroke, and gradually decreasing every week to 7% when surgery is performed more than 4 weeks after a stroke.[132] The risk of clinical deterioration is independently associated with stroke severity.

The recommended timing for valve surgery **if indicated**, following a cerebrovascular event is as follows:

- Without delay:
  - > In the presence of subclinical cerebral emboli or small cerebral infarcts without severe neurological damage.
  - > Absence of cerebral haemorrhage.
- Delayed for at least 2 weeks:
  - > In the presence of major ischaemic strokes, if more urgent surgery is indicated e.g. due to congestive heart failure, progressive decline in cardiac function or uncontrolled infection.
  - > Absence of cerebral haemorrhage.
  - > Areas of brain infarction are small.

- Delayed for at least 4 weeks:
  - > In the presence of major ischaemic strokes.
  - > In the presence of major intracranial haemorrhage (> 2 cm in diameter):
    - » This reduces the risk of cerebral haemorrhage during cardiac surgery on cardiopulmonary bypass with systemic heparinisation.[79]
    - » In one study, hospital mortality was 75% when performed within 4 weeks of a haemorrhagic stroke compared to 40% when surgery was performed after 4 weeks.[80]

Recommendations

Surgical indication for patients with cerebral infarction or haemorrhage:

1. In the presence of subclinical cerebral emboli or infarcts without haemorrhage, surgery can be undertaken without delay when indicated. [IIb/B]
2. In the presence of major ischaemic strokes or intracranial haemorrhage, surgery may be delayed for at least 4 weeks. [IIa/B]
3. In the presence of major ischaemic strokes without coma or intracranial haemorrhage, surgery can be performed after 2 weeks if urgent surgery is indicated e.g. due to congestive heart failure, deteriorating cardiac function or uncontrolled infection. [IIa/B]

5.3.2 Right-sided endocarditis

Right-sided IE accounts for 5-10% of all cases of IE mostly involving the tricuspid valve, while isolated pulmonary valve involvement is rare. Right-sided IE resolves with conservative treatment in most cases and surgery is not commonly performed. The insertion of a prosthetic valve is generally avoided as much as possible in these cases as the majority of these patients are IVDUs and the risk of subsequent infection of an implanted valve prosthesis is high with continued intravenous drug use.

5.3.2.1 Indications for surgery

Surgery is indicated in the following situations:

- Persistent infection due to difficult to eradicate microorganisms not responding to antimicrobial therapy beyond 2 weeks.[133]
- Persistent vegetation size > 20 mm and recurrent septic pulmonary emboli despite appropriate antimicrobials.[134,135]
- Massive or worsening tricuspid regurgitation causing right heart failure unresponsive to medical therapy.
- Failure or complications of percutaneous removal of infected pacing wires.

S.aureus infections are often complicated with large vegetations, aggressive valve destruction and embolic manifestations resulting in an increased risk of mortality. In a recent meta-analysis, medical therapy of staphylococcal endocarditis was associated with higher mortality than combined medical/surgical therapy especially if multiresistant type of microorganism is present.

Recommendations

Surgical indication for right-sided IE:

1. Persistent infection despite 2 weeks of appropriate antimicrobial therapy. [IIa/C]
2. Persistent vegetation size > 20 mm and recurrent septic pulmonary emboli despite appropriate antimicrobials. [IIa/C]
3. Massive or worsening tricuspid regurgitation causing right heart failure unresponsive to medical therapy. [IIa/C]
4. Failure or complications of percutaneous removal of infected pacing wires. [IIa/C]

5.3.3 Prosthetic valve endocarditis

In addition to the indications for surgery in NVE mentioned above, surgery in PVE is also recommended for:

- Staphylococcal endocarditis.
- Severe prosthetic valve dysfunction or dehiscence.

Only about half of patients with PVE undergo surgery, more commonly in those with early PVE i.e. occurring in the first year after valve surgery. The risk of recurrent PVE after surgery for PVE is significant and further surgery is required in up to 18% of these patients.[136,137]

Most patients treated conservatively have uncomplicated non-staphylococcal and non-fungal late PVE. However, these patients require careful follow-up because of the risk of late events.[138] Unlike in NVE, early surgery in PVE has not been shown to improve survival except in those with the highest risk.[18,139]

Recommendations

Indications for surgery are:

1. As in NVE (refer Section 5.1).
2. Staphylococcal endocarditis. [I/C]
3. Severe prosthetic valve dysfunction or dehiscence. [I/C]

5.4 Principles of surgery

The surgical principles in IE are well established.

Pre-operative assessment and management would include:

- Investigating and treating the primary source responsible for the endocarditis.
- Treatment of extracardiac sepsis such as splenic and paravertebral abscesses either by splenectomy[140] or percutaneous drainage to avoid infection of the new valve.
- Investigating and managing cerebrovascular events for those at risk.
- Dental consultation.

Pre-operative workup should therefore include imaging of the brain, chest, abdomen and pelvis, and maxillofacial area.

5.0 SURGICAL INTERVENTION

Some important surgical strategies are:

- Wherever possible valve repair rather than replacement is preferred. Valve repair:
  - > Improves in-hospital and long-term survival.
  - > Has better preservation of ventricular function.
  - > Eliminates the risk of prosthetic valve-related complications compared with valve replacement.
  - > Decreases the risk of infection of the newly implanted prosthetic valve.[79,141]
- Complete removal and radical debridement of all infected and necrotic material, leaving only healthy tissue, which will hold suture.
- To avoid excessive manipulation of the heart prior to going on cardiopulmonary bypass to prevent embolisation of the vegetations.
- Reconstruction using autologous or bovine pericardium, or dacron, if necessary, avoiding prosthetic material if possible.[79,125,142]
- Vegetations/cardiac tissue sent for Gram stain, cultures and for HPE (refer Sections 3.2.2 & 3.2.3, and Appendix 5).
- The choice of valve prosthesis type is based on the usual considerations when deciding between a mechanical or bioprosthetic valve i.e. age, life expectancy, co-morbidities and compliance with anticoagulation therapy. There is no difference in the risk of infection between mechanical or bioprosthetic valves.[79,142,143]
- Bioprosthetic valve replacement rather than mechanical valve replacement should be considered in the presence of mycotic cerebral aneurysms identified by imaging studies pre-operatively to avoid the need for anticoagulation post-operatively.
- Post-operative anticoagulation management should be reviewed and managed accordingly in those with cerebrovascular complications.
- Antimicrobials should be continued to complete a total course of 6 weeks in most cases.

KEY MESSAGE:

MRA of the brain may be considered before cardiac surgery in patients without neurological complications who are at high-risk of developing mycotic aneurysm to aid with the surgical strategy.

5.4.1 Aortic valve

Due to the increased risk of embolisation, CT guided coronary angiography instead of conventional catheter based coronary angiography is recommended to assess for the presence of perivalvular extensions.

In the presence of periannular abscess, it may be necessary to reconstruct the aortic annulus using autologous or bovine pericardium, or dacron. In most cases, it is possible to suture a valve prosthesis onto the reconstructed annulus.

An aortic root replacement with a homograft or stentless root is a good option when aortic root replacement is necessary.[79,144]

5.4.2 Mitral valve

Whenever possible, repair rather than replacement of destroyed mitral valves should be undertaken. Successful repair of the mitral valve in IE is often possible with the right expertise, which may require repair of the leaflet perforation or augmentation with pericardial patch and use of artificial neochordae.

However, complete and radical debridement of all infected tissue remains the key principle and should not be compromised to repair the mitral valve. If mitral valve replacement is necessary, complete preservation of the subvalvular apparatus should be performed.

5.4.3 Tricuspid valve

Whenever possible, repair rather than replacement of destroyed tricuspid valves is preferable. When valve repair is not possible and replacement is necessary, the choice of prosthesis should follow the same algorithm as in patients without endocarditis. In IVDUs, it may be reasonable to use a bioprosthetic valve if there is concern about compliance with anticoagulation medication.[79]

5.4.4 Periannular extension

Where abscess cavities are present, these must be drained, necrotic tissue excised and any fistulous tracts closed where appropriate. These patients often require temporary or permanent pacing.

Recommendations

Surgical principles in IE:

1. Complete removal and radical debridement of all infected and necrotic material, leaving only healthy tissue, which will hold suture, is recommended. [I/C]
2. Valve repair when possible is preferred rather than replacement. [IIa/C]
3. The choice of valve prosthesis type should be based on the standard considerations when deciding between a mechanical or bioprosthetic valve (e.g. age and childbearing females). [I/C]

5.5 Surgery for infective endocarditis in congenital heart disease

5.5.1 Indications for surgery

Although no paediatric specific surgical guidelines for acute IE exist, established American Heart Association (AHA) adult guidelines have been endorsed by the American Academy of Paediatrics (AAP).[145]

The determinant factors of surgical therapy for **active IE** in the paediatric population are mentioned in Table 5.1.

Table 5.1: Determinant factors for surgical therapy

During active IE	
Complications of IE	**Vegetation**
• Congestive cardiac failure • Valvular complications such as progressive valve dysfunction, perivalvular extension (fistula and abscess) and valve perforations/ rupture • Persistent infection despite optimal antimicrobial therapy • Unstable prosthesis • History of embolisation depending on size and site of vegetation (refer Sections 5.1 & 5.2) > ≥ 1 embolic event during 1st 2 weeks of antimicrobial therapy > > 2 embolic events during or after the antimicrobial therapy • New heart block	• Anterior valve vegetation • Vegetation size > 10 mm • Increasing vegetation size despite 4 weeks of antimicrobials • Persistent vegetation after systemic embolisation • Microorganisms > Fungal IE > Staphylococcal infection
Following completion of treatment in uncomplicated and haemodynamically stable patients	
• In the presence of prosthetic material/conduits	
• In unrepaired left-to-right shunts (e.g. ventricular septal defect; VSD and patent ductus arteriosus; PDA) or obstructive lesions (e.g. infundibular stenosis and coarctation of aorta; CoA)	

5.5.2 Timing of surgery

Early intervention in children with heart failure or *S.aureus* infection can be safely performed in children with low post-operative mortality and accepted medium to long-term outcome. Nomura and colleagues[146] demonstrated that surgical intervention during the active phase of infection might be a necessary adjunct to antimicrobial therapy in certain subgroups. Cardiac surgery performed within 1 week of diagnosis of a cerebrovascular accident (CVA) due to septic embolisation was safe.[147] Early surgical involvement in children with staphylococcal infection might have an advantageous role in their treatment by minimising the risk of embolisation and abscess formation, achieve native valve repair and potentially reverse the cause of ventricular dysfunction.[148]

KEY MESSAGE:

Timing of surgery	Preferable clinical condition
For native and prosthetic valve endocarditis, the timing for intervention is similar to that of adults.	
Early (within 1-2 weeks)	• Unrepaired congenital heart lesions with haemodynamic instability • Infected pacemakers/CIED • Infected conduits with conduit failure causing haemodynamic instability • Infected conduit or intracardiac patches with enlarging vegetations despite antimicrobial therapy and recurrent embolisation • Infected intracardiac patches with dehiscence • Heart block secondary to IE
Semi-elective (after 2 weeks of antimicrobial cover)	• Unrepaired CHD with persistent infection • Infected conduit, devices, stents and intracardiac patches with persistent infection • Fungal, *S. aureus* or other highly resistant microorganisms
Elective surgery (after 6 weeks of antimicrobial therapy)	• Infected conduit, devices, stents and intracardiac patches with controlled infection and haemodynamic stability • Unrepaired CHD with controlled infection and haemodynamic stability

5.5.3 Surgical techniques

Surgical techniques are similar as in the adult patients with IE (refer Sections 5.1-5.4). However there are some important principles to consider in the paediatric or CHD population.

- Preserving the native valve is important in children.
- Early intervention favours the preservation of the native annulus.
- Surgery aims at valve repair rather than replacement:
  - > Mitral valve debridement and repair using Carpentier techniques offer excellent survival, freedom from re-operation and late function status.[147]
  - > If aortic valve replacement is required, the Ross operation is effective for patients with annular or root abscesses.[145]
- Endocarditis involving the VSD patch should undergo replacement of the patch.
- Right ventricular to pulmonary artery conduit have to be replaced to prevent abscess formation and pulmonary embolisation.

The surgical mortality for IE in the group of CHD has been reported between 10-15%. Mortality is higher in premature infants and in the presence of fungal endocarditis.[149] Prophylactic surgery to prevent a primary embolic event is not recommended given the lack of proven benefit and long-term risks of valve replacement in childhood.[145]

Recommendations

Principles of surgical intervention in the paediatric CHD patients:

1. Degree of illness not be considered a limitation to surgical intervention, because the alternative, to delay or defer surgery, can have dire consequences. [I/B]
2. Surgery may be considered for patients with relapsing PVE even if valvular function remains intact after prolonged medical therapy. [II/B]

6.0
OUTCOME AND FOLLOW-UP

Following adequate antimicrobial therapy with/without surgery, resolution of the infection occurs in most patients with IE. However close monitoring with clinical examination and echocardiography is encouraged especially during the first year post-IE.

The subsequent frequency of follow-up will depend on the following:

- Clinical status of patient on discharge.
- Residual valvular dysfunction (regurgitation).
- Presence and severity of intra and extracardiac complications e.g. heart failure and neurological deficits.

Patients post-IE that require referrals back to a cardiac centre during follow-up include those who:

- Develop relapse and reinfection.
- Require advanced imaging to further quantitate valvular and cardiac structural insult.
- Require surgical intervention.

Surveillance with clinical and echocardiogram evaluation is recommended to monitor for:

- Relapses or reinfection of IE (refer Appendix 1):
  - > If patient presents with febrile illness, it is crucial to take 3 sets of blood cultures before starting empirical antimicrobials.
- Worsening clinical status and progression of heart failure:
  - > This may be due to on-going infection or progression of the valve dysfunction.
- Severity and progression of the valvular regurgitation with regards to deciding the timing of surgical intervention:
  - > For those patients with stable valvular heart disease, recommendation for valve surgery should follow the established guidelines for management of valvular heart disease.[1]
- Delayed antimicrobial toxicity e.g. vestibular or audio toxicity (refer Section 4.2) and *Clostridium difficile* colitis (diarrhoea).
- In those with IE associated with CHD, referral for surgical repair of uncorrected CHD and residual lesions are recommended.

Other important areas to re-emphasise during follow-up are:

- Oral care and dental hygiene (refer Chapter 8).
- Rehabilitation for high-risk behaviour (e.g. IVDU).
- Good skin hygiene.
- Body piercing and tattoos should be discouraged.

Relapse and reinfection (refer Appendix 1) are rare (2-6%).[150-152] Patient education is important regarding subsequent febrile illness and prompt medical assessment should be emphasised. Physicians should have a high clinical suspicion regarding relapse or reinfection in such cases. A high rate of relapse is associated with:[150-152]

- *S. aureus*, *enterococcus* and Gram-negative microorganisms such as *Pseudomonas aeruginosa*.
- IVDU especially with pre-treatment symptoms of more than three months duration.
- Previous episode of IE.
- Presence of prosthetic material and CHD.

6.0 OUTCOME AND FOLLOW-UP

Factors associated with an increased rate of relapse include:[16]

- Inadequate antimicrobial treatment (duration, dose and resistant microorganism).
- Polymicrobial infection in IVDU.
- Empirical antimicrobial treatment in BCNIE.
- Periannular extension.
- Persistent metastatic foci of infection (abscess).
- Prosthetic valve IE.
- Chronic dialysis.

In the case of relapse or reinfection, appropriate antimicrobial therapy is given similar to patients with primary IE, which is up to 42 days.

KEY MESSAGE:

1. On follow-up, patients should be monitored for recurrences of IE, evaluation of side effects from medical therapy and development of complications e.g. heart failure, and the timing and indication for elective surgery.
2. For those patients with valve regurgitation, regular monitoring with echocardiography is needed, following the established guidelines for management of valvular heart disease.
3. Education on preventive measures e.g. good oral and skin hygiene, and rehabilitation of high-risk behaviours should be provided.
4. Risk of relapse is higher in those with inadequate initial antimicrobial therapy, previous history of IE, prosthetic valves, unrepaired CHD, IVDU and *S. aureus* IE.

7.0 SPECIFIC SITUATIONS

7.1 Infective endocarditis in congenital heart disease

Advances in imaging, congenital heart surgery and intensive care have changed the spectrum of IE in paediatrics and CHD. More paediatric patients with CHD are surviving to adulthood.[153-155]

Surgery may eliminate the risk of IE in patients with simple shunts with no residual lesions. However, in complex congenital lesions, due to the use of prosthetic material, palliative shunts and long-term sequelae of the post-operative course, the risk of IE is increased.[156-158] The risk of IE in patients with CHD increases with age. The cumulative incidence of post-operative IE in adults with CHD ranges between 1% and 6% at 10 and 25 years follow-up respectively, and varies based on the different heart defects.[157] Cumulative incidence of IE post-aortic valve stenosis repair at 25 years was however, unusually high at about 13%.[157] Based on a prediction model of IE risk in adults with CHD, the cumulative observed risk of IE is 2.4% at 40 years old and 4.7% at 60 years of age.[159] In developing countries, IE complicates unrepaired CHD, cyanotic heart defects and those who have had palliative procedures.[160-163]

7.1.1 Epidemiology

Most available data are from single large centres, based on in-patient findings. A population based review of the Quebec CHD Database from 1988 to 2010 reported that the cumulative incidence of IE from birth to 18 years was 6.1 first cases per 1,000 children which corresponded to an incidence rate of 4.1 per 10,000 person-years,[164] which is lower than the overall incidence of IE in adults with CHD, reported as 11 per 10,000 person-years.[159] In a Japanese survey of hospitalised patients from 66 institutions (1997-2001), the prevalence of IE in CHD was 0.42%.[165]

The mean age of IE in children with CHD was 8.4 years (range 10 days-17 years) and in the adult patient with CHD it ranged between 16.8-32.5 years.[160,165,166] There was a male preponderance (1.5:1).[159,165,167] IE in CHD occurred more commonly on the right side and was highest up to 6 months post-intervention.[165,167,168]

Gram-positive cocci are the common aetiological agents of IE in children; VGS is most common followed by *S. aureus* especially in those patients with indwelling catheters and prosthetic material.[158]

7.1.2 Mortality

IE in patients with CHD has significant morbidity and mortality. The overall in-patient mortality for IE in children and adults with CHD were 9.4-11% and 6-7.2% respectively.[165,166,168] Late mortality was 7.7%.[167]

Risk factors for in-hospital mortality in CHD were:[149,161,169]

- Vegetation size ≥ 20 mm.
- Age < 1 year.
- Presence of heart failure at diagnosis.
- *S. aureus* as a causative microorganism.
- Aortic valve involvement.
- Nosocomial/healthcare associated endocarditis.

Surgical intervention in selected cases decreased the in-hospital mortality.[149] However, as surgery was performed in those who were more ill and/or had complications, the mortality of surgery during active IE was high, ranging from 11-14%.[165,167]

Predisposing risk factors for IE in CHD are:[164,168]

- Complex cyanotic CHD.
  - > Unrepaired and/or palliated (e.g. aorto pulmonary shunts).
- Repaired CHD with prosthetic material including conduits, bioprosthetic homograft and/or CIED.[156]
- Repaired CHD with residual lesions (refer Table 7.1).[157]
- Within 6 months following cardiac surgery or transcatheter device interventions.[170]
- VSD with associated valve or outflow tract anomalies (aortic regurgitation, left ventricle to right atrial shunt, subaortic ridge and infundibular stenosis).[157,159,171]
- Age of < 3 years.[164]

7.1.3 Lesion specific incidence of infective endocarditis in congenital heart disease

Identifying patients who are at risk of IE allows for earlier diagnosis and treatment as well as instituting infection prevention measures. Review of a population based registry of all Oregon residents less than 19 years old who underwent surgery for 12 major CHD over a period of more than 30 years showed that the cumulative risk of post-operative IE varied depending on the cardiac defect.[157] The cumulative incidence of post-operative IE based on different heart defects is shown in Table 7.1.

Table 7.1: Cumulative incidence of post-operative IE based on CHD lesions

Type of repaired CHD	Cumulative incidence of IE at years post-intervention
High to moderate risk	
Valvular AS	13.3% at 25 years
	20.6%* at 30 years
Pulmonary atresia and VSD	6.4%+ at 15 years
VSD	4.1%✱ at 30 years
d-TGA	4.0% at 20 years
Primum ASD	2.8% at 20 years
CoA	3.5% at 30 years
Complete AVSD	1.1% at 15 years
TOF repair	1.3% at 30 years
Low risk	
Secundum ASD	0.0%◗
PS	0.0%
PDA	0.0%

* The risk of IE in the aortic valve was noted to be higher in post-interventional or prosthetic valve compared to native valve with a 10-year incidence of 26% and 5% respectively. In the cohort with aortic valve stenosis, risk of IE increased over time after surgery, with a cumulative incidence of 13.3% at 25 years.
+ For patients with pulmonary atresia and VSD the risk depended on the residual right ventricle to pulmonary artery conduit stenosis.
✱ IE in repaired/unrepaired VSD was higher when associated with valve anomalies or outflow tract obstructions (aortic valve regurgitation and left ventricle to right atrial shunt). The estimated lifetime risk of IE in unrepaired VSD was higher in the adult with CHD (9.7-12%).[157] There was no documented IE in repaired VSD without other associated lesions.
◗ The risk of IE in secundum ASD is negligible. This risk increases in the presence of mitral valve anomalies (mitral regurgitation from a cleft or prolapsed mitral valve).

AS: aortic stenosis; VSD: ventricular septal defect; d-TGA: dextro-transposition of the great arteries; ASD: atrial septal defect; CoA: coarctation of the aorta; AVSD: atrioventricular septal defects; TOF: tetralogy of Fallot; PS: pulmonary valve stenosis; PDA: patent ductus arteriosus.

Adapted from Morris CD, et al. JAMA. 1998.[157]

For patients with CHD followed up to 18 years from birth, the cumulative risk of IE per 1,000 patient-years was noted to be highest in:[164]

- Cyanotic CHD.
- Atrioventricular septal defect (AVSD).
- Left-sided lesions (aortic and mitral stenosis/regurgitation and coarctation of aorta; CoA).
- Right-sided lesions (Ebstein anomaly, tricuspid or pulmonary valve anomalies).

7.1.4 Management of infective endocarditis in congenital heart disease

The diagnostic and management principles of IE in CHD do not defer from the general principles (refer Chapters 3,4 & 5). The management is mainly appropriate antimicrobial treatment based on the respective microorganism. Surgery is limited to those with failure of medical treatment, complications and prosthetic material IE (refer Section 5.5). These patients preferably should be referred to a centre with the expertise to diagnose (imaging and microbiological diagnosis) and manage (medically and surgically) the IE as well as its complications.

However some specific considerations are suggested below:

- TTE is adequate for most patients. However TEE should be considered in those with poor transthoracic echocardiography window, prosthetic material and in those who have high clinical suspicion but normal TTE findings.
- In the context of complex CHD with or without prior surgical interventions, cardiac MRI and cardiac CT are also powerful tools to assist in diagnosis.
- Following completion of IE treatment, patients with residual lesions or uncorrected intracardiac shunts should be referred for surgical repair.
- Good oral and skin hygiene is crucial, and antimicrobial prophylaxis is limited to high-risk lesions and following selective procedures (refer Chapter 8).

Recommendation

Management of adult paediatric CHD IE patients:

Referral to tertiary centres with expertise in CHD imaging, surgery and intensive care is advisable. [IIa/C]

7.2 Infective endocarditis in paediatric patients

Frequency of IE in paediatric population is increasing due to:[158,164,172]

- Improved survival in children with CHD.
- Hospitalised neonates.

Rheumatic heart disease is currently not a common cause of IE in children except in some developing countries.[160-163,173] In a multicentre report, the annual incidence rate of paediatric IE in the USA was reported to be between 0.05-0.16 per 1,000 hospital admissions from 2003-2010.[167] Review of children hospitalised with IE from Healthcare Cost and Utilization Project Kids' Inpatient Databases (KID) from 2000 and 2003 in the USA showed a bimodal pattern of admission, with peaks in infancy (31 days-11 months of age) and late teenage period (17-20 years of age).[174]

IE in paediatric patients occurred in three groups of patients:

- Children with CHD (refer Section 7.1).
- Children with acquired valvular heart disease.
- Neonates with normal heart structures.

7.2.1 Infective endocarditis in neonates with normal heart structures

Diagnosis of IE in the first month of life has been reported to be about 7.3-18%[175] of total paediatric IE cases. This is due to the prolonged use of indwelling central venous catheters in the management of neonates and infants with complex medical problems in intensive care units.[158,174,176] The mortality was highest in the premature infant (31%) and those with *S. aureus* IE.[174] The left-sided cardiac structures were usually affected. Common microorganisms were *S. aureus*, *Coagulase negative staphylococcus strains*, Gram-negative bacterial species and *Candida* spp.

Predisposing risk factors include:[175,176]

- Immunosuppressed patients such as premature babies, oncology patients on chemotherapy, chronic diseases on prolonged steroid therapy and post-transplant on immunosuppressive drugs.
- Intravenous therapy within 4 weeks before the onset of endocarditis.
- Previous invasive procedure (cardiac surgery, cardiac catheterisation and non-cardiac invasive procedure) within 8 weeks before IE onset.
- Presence of an indwelling central venous catheter 1 week before onset of symptoms of IE.

7.2.2 Clinical presentation

Diagnosis of IE may be difficult as the clinical manifestations may be non-specific and undistinguishable from septicaemia.[175] The presentation may be indolent with non-specific signs or, acute and fulminant.

The classical extracardiac manifestations (Osler's nodes, Janeway lesions and splinter haemorrhage) are not common in children. More commonly seen are clinical manifestations of septic emboli to the abdomen, brain and lungs (refer Table 7.2). Complications of IE are similar to the adult patient e.g. congestive heart failure, embolic phenomenon, heart block and valve dehiscence.[175]

Table 7.2: Common symptoms and signs in paediatric IE

Non-specific symptoms of sepsis	• Fever • Poor feeding • Reduced activity • Vomiting and/or diarrhoea • Weakness • Weight loss • Arthralgia • Recurrent fever for > 4 weeks
Signs	• General: > Tachypnoea > Tachycardia > Respiratory distress > Pallor • Cardiac: > Signs of congestive heart failure > New or changing murmur • Septic emboli: > Abdomen: splenomegaly > Neurological: seizure, hemiparesis and meningitis > Bone: osteomyelitis > Lungs: pneumonia
Laboratory parameters	• Thrombocytopenia • Neutrophilia/neutropenia • Raised CRP and ESR

7.2.3 Management of paediatric infective endocarditis

7.2.3.1 Diagnosing infective endocarditis in paediatric patients

As in adults, the diagnosis of IE in children is made based on the modified Duke criteria.[56,177,178] Since the presentation in children can be non-specific, a high clinical suspicion is necessary especially in those with predisposing risk factors. A thorough history, physical examination and investigations (imaging, blood cultures, microbiological tests and HPE) should be done to make the diagnosis (refer Chapter 3.0).

S. Aureus bacteraemia is one of the major criteria in the modified Duke criteria irrespective of the cause and is the most common pathogenesis of bacteraemia in the presence of central venous catheters.[56] Removal of the central venous catheters in those with prolonged bacteraemia is advised before the diagnosis of IE.[179] The associated use of hyperalimentation and high glucose concentrations with central venous catheter has contributed to the increase in *Candida* spp. IE in neonates. BCNIE although less common, can also occur. It is usually due to either previous antimicrobial treatment or fastidious microorganisms. The diagnosis and management of BCNIE is similar to the adult and is described in Chapters 3 and 4.

TTE is more sensitive (97%) in young patients (weight < 60 kg) compared to adult patients in detecting endocarditis. However for those patients who are obese, have prosthetic grafts, valves and conduits, chest deformities, and in those with hyperinflated lungs or compromised respiratory function, TEE serves as an important adjunct (refer Section 3.3).[180]

7.2.3.2 Treatment of infective endocarditis in paediatric patients

The management of IE in paediatric patients and IE in CHD is predominantly by medical treatment and the choice of antimicrobials will depend on the microorganism cultured (refer Section 4.2). It is important to use appropriate dosing based on weight especially in the neonate. It is recommended to remove or change all long-standing central venous catheters if present.

KEY MESSAGE:

1. IE in CHD is increased in post-operative/intervention patients with prosthetic material, devices and residual lesions.
2. TEE in paediatric patients is recommended for those with poor transthoracic echocardiographic windows and those with high-risk of developing complications (abscesses and paravalvular leakage/dehiscence) and those with prosthetic valve/conduit/material endocarditis. [IIa/B]
3. Antimicrobial prophylaxis and infection prevention measures are recommended in patients with high-risk of developing IE (refer Chapter 8).
4. Consider other imaging modalities such as cardiac MRI or cardiac CT in CHD.

7.3 Infective endocarditis in transcatheter valve implantations

7.3.1 Transcatheter pulmonary valve implantation

Transcatheter (percutaneous) pulmonary valve implantation (TPVI) as an alternative to open-heart surgery for right ventricular outflow tract (RVOT) valve implantation was first described in 2000 by Bonhoeffer *et al*.[181] Similar to surgical valve series, the incidence of early PVE has been reported to be ≤ 1%.[182]

IE in TPVI is a clinical diagnosis and requires a high index of suspicion, as patients may present with non-specific symptoms. Patient characteristics, timing and presentation of TPVI IE are quite complex.[183]

Early PVE is defined as occurring within the first 12 months after valve implantation/replacement.

- High index of suspicion is required.
- In addition to Duke criteria, any degree of increase of RVOT gradient (unexplained by a structural complication such as stent fracture), valvular involvement and new onset of pulmonary regurgitation should raise a high suspicion of IE.[183]

Possible risk factors:[183,184]

- Male.
- Dental treatment.
- Septic skin wound.
- Reactivation of previously treated fungal infection.
- Previous history of medically treated IE.
- Multiple stents in RVOT.
- Distorted RVOT anatomy.
- Contegra conduit and Melody valve are at higher risk compared to homograft.

Buber *et al*. proposed life long pre-procedural prophylactic antimicrobials for TPVI patients, with either a history of previous IE or a complex RVOT anatomy.[185] Fever (80%) and heart failure (22%) were the most common initial symptoms of PVE in the transcatheter valve replacement group (aortic and pulmonary valve).

7.3.1.1 Management plan

- If TPVI endocarditis is suspected, the patient should be referred to a SC.
  - > Medical management:[182]
    - » Antimicrobial treatment for at least 6 weeks, based on the causative microorganism (usually *S. aureus* in TPV).
  - > Surgical intervention:
    - » The in-hospital mortality rate associated with episode of PVE was 7.1%.
    - » Surgical ex-plantation of the infected conduit valve is recommended considering the younger population of patients in TPVI.[182]
- Post-discharge follow-up
  - > Due to complexity of patient with TPVI IE, follow-up should be at a SC (refer Section 4.1.4).

Recommendations

For the management of TPVI IE in children:

1. In addition to Duke criteria, any degree of increase of RVOT gradient (unexplained by a structural complication such as stent fracture), valvular involvement and new onset of pulmonary regurgitation should raise a high suspicion of IE. [IIa/B]
2. Antimicrobial prophylaxis is recommended prior to invasive procedures in TPVI patients. [IIa/C]

7.3.2 Transcatheter aortic valve implantation/transcatheter aortic valve replacement

Transcatheter aortic valve implantation/replacement (TAVI/TAVR) is an important therapeutic option for the treatment of aortic valve stenosis in patients with high operative risk. Although infrequent, one important complication of TAVI is IE. IE for TAVI is classified according to the modified Duke criteria.[186] Patients with high clinical suspicion of TAVI related PVE should be referred to specialist centres (refer Section 4.1.4). In patients who have had TAVI and who develop prolonged fever, valve murmur or new valvular regurgitation, a TTE should be performed. Since images may be suboptimal due to acoustic shadows, a TEE should also be considered in order to obtain clearer views of the prosthetic valve.

In the major PARTNER (Placement of Aortic Transcatheter Valves) trial, PVE occurred at a similar rate in the surgical and transcatheter groups (1.5% and 1.0% respectively, $p = 0.61$).[187] Two varieties of valves; the Edwards SAPIEN (Edwards Lifesciences Inc., Irvine, CA, USA) and Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA) have had reported cases of PVE.[188]

In IE with TAVI, patients have had positive blood cultures with a microbiological profile typical to that previously documented in surgical bioprosthetic PVE; *Enterococcus* spp.,CoNS, *S. aureus* and *Streptococcus* spp.[188] The incidence of PVE may also be increased by patient risk factors such as diabetes mellitus, oral hygiene and adherence to antimicrobial prophylaxis for dental procedures.[188]

Antimicrobial prophylaxis for TAVI patients is recommended as in Chapter 8.0. For TAVI related PVE, the first line of treatment is targeted antimicrobial therapy. While conventional indications for operative intervention in the setting of PVE may be less applicable to high-risk TAVI cohorts, surgical treatment remains an option to be discussed in the context of complications related to IE.[188]

Recommendations

Management of patients with TAVI IE:

1. Patients with high clinical suspicion TAVI related PVE should be referred to SC. [IIa/C]
2. Targeted antimicrobial therapy remains the first line of treatment for TAVI related PVE. [IIa/B]

7.4 Infective endocarditis in cardiac implantable electronic devices

CIED IE is serious and is associated with high mortality.[189] The precise incidence of CIED IE is uncertain and varies widely between published series.[190,191] Nonetheless, rates are set to rise due to a wider range of cardiac devices available in the market, and with increased implantation in the older population.[191,192]

Factors associated with a greater risk of CIED IE include:

- Immunosuppression (corticosteroids use, diabetes and renal failure).
- Oral anticoagulation use.
- Co-existing illness (ageing population).
- Periprocedural factors such as failure to use appropriate periprocedural antimicrobial prophylaxis.
- Device revision/replacement.
- Amount of indwelling hardware.
- Operator experience.
- Microbiology of bloodstream infection (*S. aureus*).

Clinical presentation is often vague and non-specific and thus a high index of clinical suspicion is mandated.[193] CIED IE must always be considered in the presence of unexplained fever in a patient with a CIED. Patients who develop fever or blood stream infection with no obvious source, should be referred back to the primary centre responsible for the implantation. Patients should be educated regarding these risks.

Echocardiography and blood cultures (refer Sections 3.2 & 3.3) are the mainstay for the diagnosis of CIED IE. TTE may identify lead vegetation and tricuspid valve involvement. However, a negative TTE does not rule out CIED IE, hence it is recommended to proceed to a TEE examination. TEE is more sensitive and specific to TTE for diagnosis of lead-related endocarditis.

Considering their complementary role, it is preferable to perform both investigations in cases of suspected CIED IE, as a TTE at time of diagnosis may be used as baseline for additional studies during the course of the illness. In cases where the clinical suspicion is still high but cardiac imaging with TTE and TEE yields no evidence of endocarditis (false negative) other imaging modality such as radiolabelled leucocyte scintigraphy and ^{18}F-FDG PET/CT scanning may prove useful.[194-196] Repeated TEE is not necessary after completion of treatment.

Recommendations

For the management of patients with CIED IE:

1. Before initiation of antimicrobial therapy, 3 or more sets of blood cultures should be taken. [I/C]
2. Patients with suspected CIED IE regardless of positive or negative blood cultures, and independent of TTE findings require TEE to evaluate the infection. [I/C]
3. In patients with suspected CIED IE with positive blood cultures and negative echocardiographic findings, ^{18}F-FDG PET/CT can be done. [IIb/C]

Staphylococcus (especially CoNS) account for 60-80% of CIED IE in most reported series.[197,198] Methicillin resistance among staphylococci varies among studies.[198,199] Polymicrobial infection sometimes involves more than one species of CoNS, *Corynebacterium* spp. and *Propionibacterium acnes*.[198,200,201] Gram-negative bacilli and *Candida* spp. are rarely identified as pathogens in CIED IE.[198,200]

At least 4-6 weeks of antimicrobials are recommended for CIED IE. In the presence of lead vegetation on echocardiography, urgent referral back to the primary implantation centre should be considered at this time point, if not done so *at priori*. Complete hardware removal is advocated and if required, a temporary device is implanted until the infection is resolved.[189,202] Careful assessment of new implantation strategy must be considered prior to removal in patients whom are "device-dependent". Blood cultures should be obtained within 24 hours after hardware removal for evidence of microorganism clearance from bloodstream. When a new device implantation is necessary, it should be done on the contra-lateral side to avoid new device infection.

Recommendations

When extraction and reimplantation of CIED is considered in CIED IE:

1. In definite CIED IE as well as isolated pocket infections, antimicrobials before and after extraction and removal of device and leads are recommended. [I/C]
2. When no other apparent source of infection is detected, complete removal of devices should be considered. [IIa/C]
3. Reassessment for the need of reimplantation is recommended after device extraction. [I/C]
4. Postponement of reimplantation for a few days or weeks during antimicrobial therapy is recommended if possible. [IIa/C]
5. In pacemaker-dependent patients who require antimicrobials before reimplantation, a "temporary" ipsilateral device can be considered. [IIb/C]
6. Temporary pacing is not routinely recommended. [III/C]

7.5 Infective endocarditis in pregnancy

IE during pregnancy is rare. All pregnant patients who are diagnosed with IE should be referred to a SC for assessment. A multidisciplinary team that includes a cardiologist, ID physician, obstetrician, obstetric anaesthetist and neonatologist should be involved in the management of the IE and the pregnancy from the onset of the diagnosis. The management care plan should include:

- General management of IE (i.e. similar to non-pregnant patient).
- Timing and indication for cardiac intervention e.g. surgery where indicated. Indications for surgery are as the non-pregnant patients (refer Chapter 5). However, unlike non-pregnant patients, cardiac surgery should be delayed wherever possible till post-delivery.
- A detailed pregnancy and delivery care plan.

The management of IE in pregnancy is addressed in the Heart Disease in Pregnancy CPG (2016) (refer to its 2nd edition Section 4.10 which is available at *https://www.malaysianheart.org/?p=cpg&a=1107*)

Cardiac patients at risk (of IE) must be given advice during pre-pregnancy counselling sessions on the need for good skin and oral hygiene to minimise the risk of IE. These patients must be referred for professional oral hygiene care throughout their pregnancy.

KEY MESSAGE:

All pregnant women who have IE in pregnancy should be referred to a SC with the appropriate expertise for the management of the IE and pregnancy.

8.0 ANTIMICROBIAL PROPHYLAXIS FOR INFECTIVE ENDOCARDITIS

8.1 Introduction

IE after interventional dental or other procedures is uncommon.[203] For this reason, the use of antimicrobial prophylaxis is only recommended for cardiac patients associated with the highest risk of IE (the European Society of Cardiology; ESC, AHA and National Antibiotic Guidelines).[16,204,205] Many bacterial species are known to cause IE, but in recent years staphylococci, commonly associated with health-care contact and invasive procedures, have overtaken streptococci as the most common cause of IE.[148] As for antimicrobial prophylaxis, the National Institute of Clinical Excellence (NICE) issued the CG64 in 2008[206] that effectively did not recommend antimicrobial prophylaxis against IE for people undergoing dental procedures (or other non-dental procedures) in the United Kingdom (UK). In the ensuing years, whilst there was a very significant fall in antimicrobial prophylaxis prescribing, there was also a significant increase in the incidence of IE. In 2016, NICE reviewed the evidence and concluded that there was no requirement to change the existing CG64 guidance and emphasised that antimicrobial prophylaxis against IE is not recommended routinely for people undergoing dental, gastrointestinal tract, genitourinary and respiratory tract procedures. Additionally, these guidelines emphasised prevention rather than prophylaxis to reduce the incidence of IE.

It is however, the consensus view of this writing committee that antimicrobial prophylaxis is administered to all patients at high-risk for IE including those with established rheumatic heart disease who are undergoing invasive dental and surgical procedures.

8.2 Cardiac conditions associated with the highest risk of infective endocarditis

Patients with cardiac conditions listed in Table 8.1 are considered as being at increased risk of developing IE and are indicated for antimicrobial prophylaxis.

Table 8.1: Cardiac conditions with increased risk of IE

- Prosthetic cardiac valves or prosthetic material used for cardiac valve repair
- Native valvular heart disease including established rheumatic heart disease
- Previous IE
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired CHD with prosthetic material or devices, for first 6 months after the procedure
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialisation)
- Cardiac transplantation recipients who develop cardiac valvulopathy

Adapted from European Society of Cardiology, American Heart Association and Cardiac Society of Australia and New Zealand infective endocarditis guidelines.[16,204,207]

Recommendation

Patients who require antimicrobial prophylaxis:

Antimicrobial prophylaxis must be indicated for patients with the highest risk of IE and/or highest risk of adverse outcome from IE. [IIa/B]

8.3 Antimicrobial prophylaxis for specific procedures

Antimicrobial prophylaxis to prevent IE is indicated in high-risk cardiac patients prior to selected dental and non-dental procedures.

Any procedure where antimicrobial prophylaxis is indicated for surgical reasons, the pre-procedural antimicrobial prophylaxis is normally adequate as IE prophylaxis in high-risk cardiac cases. In procedures where pre-procedural antimicrobial prophylaxis is not routinely given, cardiac patients considered as high-risk should receive antimicrobial prophylaxis prior to procedures expected to produce bacteraemia as discussed in Section 8.3.2.

8.3.1 Dental procedures

The estimated incidence of IE is about 1 per 150,000 dental procedures with antimicrobials prophylaxis and 1 per 46,000 for procedures unprotected by antimicrobials.[208] For patients considered as high-risk (Table 8.1), antimicrobial prophylaxis is recommended for invasive dental procedures that involve manipulation of the gingival or periapical region of the teeth or oral mucosa. Routine antimicrobial prophylaxis is not recommended for all patients undergoing dental procedures. Table 8.2 provides a list of dental procedures where antimicrobial prophylaxis for endocarditis may or may not be required for cardiac patients.

Table 8.2: Dental procedures and recommendations for prophylaxis of endocarditis

Prophylaxis always required	Prophylaxis required in some circumstances	Prophylaxis not required
• Extractions • Periodontal procedures including surgery, subgingival scaling and root planning • Replanting avulsed teeth • Other surgical procedures (e.g. implant placement and apicectomy)	Consider prophylaxis for the following procedures if multiple procedures are being conducted, the procedure is prolonged or periodontal disease is present: • Full periodontal probing for patients with periodontitis • Intraligamentary and intraosseous local anaesthetic injection • Supragingival calculus removal or cleaning • Rubber dam placement with clamps (where there is risk of damaging gingiva) • Restorative matrix band/strip placement • Endodontics beyond the apical foramen • Placement of orthodontic bands or interdental wedges • Subgingival placement of retraction cords, antimicrobial fibres or antimicrobial strips	• Oral examination • Infiltration and block local anaesthetic injection • Restorative dentistry • Supragingival rubber dam clamping and placement of rubber dam • Intracanal endodontic procedures • Removal of sutures • Impressions and construction of dentures • Orthodontic bracket placement and adjustment of fixed appliances • Application of gels • Intraoral radiographs • Supragingival plaque removal

Adapted from Therapeutic Guidelines: antibiotic version 13 and Therapeutic Guidelines: oral and dental version 1. 2008.[209]

8.3.2 Non-dental procedures

8.3.2.1 Respiratory tract procedures

Antimicrobial prophylaxis is recommended for patients with increased risk of IE (Table 8.1) who undergo an invasive respiratory tract procedure that involve incision or biopsy of the respiratory mucosa.[209,210] For procedures involving an established respiratory tract infection, the antimicrobial must be active against the causative microorganisms in addition to VGS.[210]

8.3.2.2 Gastrointestinal and genitourinary procedures

Routine pre-procedural antimicrobial prophylaxis is no longer recommended for patients undergoing genitourinary or gastrointestinal tract procedures. However, for high-risk cardiac patients who have an established gastrointestinal or genitourinary infection, or for those who receive antimicrobial therapy for surgical reasons, the antimicrobial regimen should include an agent active against enterococci, such as ampicillin or vancomycin.[16,210]

8.3.2.3 Other procedures

Antimicrobial prophylaxis is required for high-risk cardiac patients undergoing these procedures:[211]

- Incision and drainage of local abscess in the brain, skin and subcutaneous tissue (e.g. boils and carbuncles), eye (e.g. dacryocystitis), epidura, lung, orbital area, perirectal area, liver (e.g. pyogenic liver), tooth and surgical procedures through infected skin.
- Percutaneous endoscopic gastrostomy.

Recommendation

The indications for antimicrobial prophylaxis in high-risk patients:

High-risk procedures are usually those that cause bleeding or tissue damage. VGS is the most common cause of endocarditis after dental or upper respiratory procedures. [IIa/B]

8.4 Antimicrobial regimes for infective endocarditis prophylaxis

The most common pathogen for oral and respiratory tract procedures related endocarditis is alpha-haemolytic streptococci. Antimicrobial regimens for endocarditis prophylaxis are generally directed towards VGS.[16,212]

Table 8.3: Antimicrobial prophylaxis for invasive dental procedures

Single dose administered 30 to 60 minutes before the procedure				
Situation	Antimicrobial	Adults	Children	Reference
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin	2 g orally or IV	50 mg/kg orally or IV	ESC 2015[16] AHA 2007[212]
Allergic to penicillin or ampicillin	Clindamycin	600 mg orally or IV	20 mg/kg orally or IV	ESC 2015[16] AHA 2007[212]

- Alternatively, cephalexin 2 g IV for adults or 50 mg/kg IV for children, cefazolin or ceftriaxone 1 g IV for adults or 50 mg/kg IV for children.
- Cephalosporins should not be used in patients with anaphylaxis, angioedema or urticaria after intake of penicillin or ampicillin due to cross-sensitivity.
- For genitourinary and gastrointestinal procedures antimicrobials should include an agent active against enterococci, such as ampicillin or vancomycin.

Recommendation

Timing of antimicrobial prophylaxis in high-risk patients:

IE antimicrobial prophylaxis (when indicated) is administered as a single dose 30-60 minutes before the procedure. [IIa/B]

8.5 Preventive measures

8.5.1 Periodontal and dental disease

Periodontal and dental diseases can increase the risk of bacteraemia. Maintenance of optimal oral hygiene may reduce the incidence of bacteraemia with daily activities such as tooth brushing, flossing or use of oral irrigators, and is considered more important than prophylactic antimicrobials for a dental procedure to reduce the risk of IE.[213,214] Cardiac patients should be reminded to practise good oral hygiene and have a dental evaluation twice a year. Patients must be informed about the hazards of tongue piercing as this procedure may increase the risk of IE and should be discouraged.[16,215]

8.5.2 Cardiac implantable devices or prosthesis implantation

IE risk is high in patients undergoing procedures that involve implanting prosthetic material/valves, CIED and transcatheter occluder devices/implantable valves. Maintenance, and good oral and skin hygiene (this includes discouraging body piercing and tattooing) are two of the most important aspects in the preventive measures of IE.[216] As it has been shown that the highest risk of developing IE in these patients is during the periprocedure stage, the following measures are recommended:

- Pre-operative screening and eradication of nasal and skin carriage of MRSA using local mupirocin and chlorhexidine, is recommended before elective cardiac surgery in order to treat carrier.[217,218]
- Treat and eliminate potential sources of sepsis at least 2 weeks prior to procedure/surgery.[219]
- Pre-procedure antimicrobial prophylaxis before cardiac surgery or transcatheter intervention.[220,221]

Recommendation

Preventive measures by high-risk patients are:

Cardiac patients must be advised on the importance of dental and cutaneous hygiene. [IIa/B]

9.0 IMPLEMENTING THE GUIDELINES AND RESOURCE IMPLICATIONS

The objective of this CPG is to enable the healthcare professionals who encounter IE patients in the local setting to diagnose this disease early and manage it effectively.

Wide dissemination via soft copy (available from *http://www.moh.gov.my*, *http://www.acadmed.org.my*, *http://www.malaysianheart.org/*) will facilitate the implementation of this CPG. However, the limited knowledge in the effective management of the disease and the varied treatment practice among HCP may be its main barriers.

The successful implementation of this CPG would require:

- Continuous medical education (CME) and training on the most effective means of diagnosing IE in patients via regular seminars, lectures, CME meetings and case sharing. These would include:
  - > How to recognise findings in patients that should trigger high clinical suspicion of IE.
  - > How to effectively confirm the diagnosis of IE.
  - > How and when to institute appropriate antimicrobial therapy.
  - > When to refer patients to a SC for further management and cardiac surgery.
- Effort to set up an effective referral process in the different states from primary care centres to SC (refer Section 4.1.4).
- The availability of this CPG to all healthcare professionals from primary care centres to tertiary institutions offering speciality and subspecialty care through electronic websites.
- The availability of Quick Reference (QR) guides both through printed copies and electronic websites as an easy yet comprehensive tool for the prevention, diagnosis and management of IE.

The measurement of specific performance measures (refer Appendix 11) affords an effective method in tracking the success of the implementation of these guidelines. The committee does not foresee any additional cost implications. The imaging modalities, microbiological testing and surgery can be performed, and appropriate antimicrobial therapy initiated in tertiary Ministry of Health and Ministry of Education hospitals.

10.0 APPENDICES

Appendix 1: Classification and definition of infective endocarditis

<table>
<tr><th colspan="3">IE according to localisation of infection and presence or absence of intracardiac material</th></tr>
<tr><td colspan="3">• Left-sided native valve IE
• Left-sided PVE
> Early PVE < 1 year after valve surgery
> Late PVE > 1 year after valve surgery
• Right-sided native valve IE
• Device related IE</td></tr>
<tr><th colspan="3">IE according to the mode of acquisition</th></tr>
<tr><td rowspan="2">Healthcare associated IE</td><td>Nosocomial</td><td>Non-nosocomial</td></tr>
<tr><td>IE developing in a patient hospitalised > 48 hours prior to onset of signs and symptoms consistent with IE</td><td>Signs and symptoms of IE starting < 48 hours after admission in a patient with healthcare contact defined as:
• Home-based nursing or intravenous therapy, haemodialysis, or intravenous chemotherapy < 30 days before the onset of IE
• Hospitalisation in an acute care facility < 90 days before the onset of IE
• Resident in a nursing home or long-term care facility</td></tr>
<tr><td>Community acquired IE</td><td colspan="2">Signs and symptoms of IE starting < 48 hours after admission in a patient not fulfilling the criteria for healthcare associated infection</td></tr>
<tr><td>Intravenous drug abuse associated IE</td><td colspan="2">IE in an active injection drug user with no alternative source of infection</td></tr>
<tr><th colspan="3">Active IE (at least one of the below)</th></tr>
<tr><td colspan="3">Persistent fever and positive blood cultures</td></tr>
<tr><td colspan="3">Inflammatory morphology findings during surgery</td></tr>
<tr><td colspan="3">On antimicrobial therapy</td></tr>
<tr><td colspan="3">Evidence of active infection on HPE</td></tr>
</table>

Recurrence	
Relapse	Repeat episodes of IE caused by the same microorganism < 6 months after the initial episode
Reinfection	• IE infection with a different microorganism • A repeat episode of IE caused by the same microorganism > 6 months after the initial episode

Adapted from European Society of Cardiology infective endocarditis guidelines. 2009.

Appendix 2: Enterobacteriaceae

The family Enterobacteriaceae includes many genera that are Gram-negative rods. They are also known as enteric Gram-negative rods or enteric bacteria (enteric means pertaining to the intestines).

Enterobacteriaceae have the following characteristics:

- Gram-negative rods.
- Grow well on MacConkey agar and can be divided into lactose-fermenter or non-lactose fermenters.
- Grow aerobically and anaerobically (are facultative anaerobes).
- Ferment glucose, often with gas production.
- Catalase-positive, oxidase-negative and reduce nitrate to nitrite.

The following are some of the Enterobacteriaceae microorganisms that can cause IE:

- *Enterobacter aerogenes.*
- *Enterobacter cloacae.*
- *Escherichia coli.*
- *Klebsiella pneumoniae.*
- *Salmonella* spp.
- *Serratia liquefaciens.*
- *Serratia marcescens.*

Reference:

Jawetz, Melnick and Adelberg's Medical Microbiology. In: GF Brooks, JS Butel and AS Morse. New York; Lange Medical Books/Mc_Graw Hill 27th Ed.

Appendix 3: Blood culture collection

Strict aseptic technique should be used throughout the procedure.

1. Identify the site of venepuncture where blood is to be drawn.
2. Wash your hands using soap and water, then dry or apply an alcohol hand rub.
3. Put on a pair of sterile gloves.
4. Cleanse the site of the venepuncture with 70% isopropyl alcohol, allowing it to air dry.
5. Disinfect the skin of site on a circle approximately 5 cm in diameter with chlorhexidine gluconate in alcohol, rubbing vigorously for at least 30 seconds. Allow to air dry.
6. To prevent contamination, do not palpate the disinfected venepuncture site.
7. Perform venepuncture.
8. Draw blood using a sterile needle and syringe or a blood collection device.
9. Prior to use, examine the blood culture bottles for evidence of damage or deterioration (discoloration).
10. Check the expiry date printed on each blood culture bottle. Discard bottles that have expired.
11. Recommended volume of blood (OR follow manufacturer's instruction):
    a. Adult: 10 ml of blood into **each** culture bottle (aerobic/anaerobic bottles).
    b. Paediatric: 1-5 ml of blood in paediatric blood culture bottle.
12. Disinfect the rubber septum on the blood culture bottles with 70% isopropyl alcohol using fresh alcohol prep for each container. Allow bottle tops to dry to fully disinfect.
13. Using a transfer device or a fresh sterile needle, aseptically transfer the blood into the blood culture bottles as soon as possible.
14. If the amount of blood drawn is less than the recommended volume, the blood should be inoculated into the aerobic bottle first, since aerobic and facultative bacteria cause most bacteraemia. Any remaining blood should then be inoculated into the anaerobic bottle.
15. Invert the blood culture bottles gently several times to prevent clotting.
16. Label each bottle with the appropriate specimen label that contains the patient's name, ID number and, date and time of collection.
17. Send the blood culture bottles to the laboratory within 2-4 hours of collection.

Note:

1. *Blood cultures **should not be** obtained from indwelling intravascular access devices, e.g. intravascular catheters or ports, as it is associated with higher contamination rates.* When blood is obtained from a port or line, blood drawn via a peripheral vein should also be taken for meaningful interpretation.
2. *Blood culture bottles **should not be** refrigerated after they have been inoculated.*
3. *Do not leave the blood cultures at room temperature for more than 4 hours,* as it will delay or impede the detection of growth by the continuous-monitoring blood culture instrument.

References:

1. Principles and Procedures for Blood Cultures; Approved Guideline; CLSI document M47-A Vol. 27. No. 17.
2. BD BACTEC Package insert PP-105E 2001/01.
3. Blood culture: A key innovation for diagnosis of bloodstream infections. Biomerieux 2016.

Appendix 4: Directory of laboratories*

Table: Directory of main laboratories that provide serological testing of rare aetiological agents of infective endocarditis

Microorganisms	Serology IgG/IgM
***Brucella* spp.**	IMR HSB
Coxiella burnetti	IMR HSB
***Bartonella* spp.**	IMR
***Legionella* spp.**	HKL UMMC PPUKM

- PCR for *Brucella* is available in IMR.
- HPE of the **cardiac or valvular tissue, or emboli** is available upon request at State and major specialist hospitals with anatomic pathology services.

IMR: Institute of Medical Research; HSB: Hospital Sungai Buloh; HKL: Hospital Kuala Lumpur; UMMC: University Malaya Medical Centre; PPUKM: Pusat Perubatan Universiti Kebangsaan Malaysia.

***This list is not exhaustive and only include public institutions with the available facilities. For a full list of accredited laboratories, please refer to Standards Malaysia website (*www.jsm.gov.my*).**

Note:

1. Interpretation of serological results in these rare aetiological agents of IE can be difficult. **Please consult an ID physician to guide treatment in these cases.**
2. PCR amplification of 16SrDNA gene and sequencing for the identification of bacterial pathogen from **bacterial isolate** is provided at the Department of Medical Microbiology PPUM.

The main laboratories and the contact details are as follows:*

Institution/hospital	Name of laboratory and address	Contact number
Institute for Medical Research	Bacteriology Unit Institute for Medical Research Jalan Pahang 50588 Kuala Lumpur	03-26162666
Hospital Sungai Buloh	Microbiology Unit Department of Pathology Hospital Sungai Buloh 47000 Sungai Buloh, Selangor	03-61454333
Hospital Kuala Lumpur	Microbiology Unit Department of Pathology Hospital Kuala Lumpur Jalan Pahang 50586 Kuala Lumpur	03-26155590
University Malaya Medical Centre	Department of Medical Microbiology Pusat Perubatan Universiti Malaya Lembah Pantai 59100 Kuala Lumpur	03-79493039
Pusat Perubatan Universiti Kebangsaan Malaysia	Department of Medical Microbiology and Immunology Pusat Perubatan UKM Jalan Yaacob Latiff 56000 Kuala Lumpur	03-91455555
Pusat Pakar Perubatan UiTM	Anatomic Pathology Unit Centre for Pathology Diagnostics and Research Laboratories Pusat Pakar Perubatan UiTM Sungai Buloh Campus 47000 Sungai Buloh Selangor	03- 61265053

***This list is not exhaustive and only includes public institutions with the available facilities. For a full list of accredited laboratories, please refer to Standards Malaysia website (*www.jsm.gov.my*).**

Appendix 5: Guidelines on specimen collection

Instructions for specimen collection and transport for HPE of cardiac valvular/ tissue/emboli in the diagnosis of infective endocarditis.

A. Specimen collection

1. Place the cardiac specimen in a container containing 10% formalin with a volume of approximately 3-4 times tissue volume (30 ml minimum).
2. Do not remove or scrape any tissue (e.g. clots and fibrins) attached to the cardiac specimen.
3. Secure the sample container properly to avoid spillage.

Note:

If a cardiac specimen is also being collected for:

- Microbiological culture, place the specimen in a container with normal saline.
- HPE, place another specimen in a different container with formalin.

B. Labelling of specimen container(s)

1. Label the specimen container(s) with the patient's full name, a second patient identifier, and the source/anatomical site and type of the specimen.
2. The label should be placed/written on the container and not on the cap.
3. If there is more than one sample, place multiple specimens in separate containers.
4. Review the completeness and accuracy of the request form in comparison with the label on the specimen container, against the patient's ID prior to leaving the procedural site.

Appendix 6: Centres with PET and SPECT/CT WBC scan services*

PET scan	WBC SPECT/CT scan
Institut Kanser Negara	Hospital Kuala Lumpur
Pusat Pengimejan Diagnostik Nuclear, Universiti Putra Malaysia	Jabatan Pengimejan Molekul dan Perubatan Nuklear, Pusat Perubatan Universiti Kebangsaaan Malaysia
Jabatan Pengimejan Molekul dan Perubatan Nuklear, Pusat Perubatan Universiti Kebangsaaan Malaysia	Medical Physics Unit, University Malaya Medical Centre
Medical Physics Unit, University Malaya Medical Centre	
Penang General Hospital	

***This list is not exhaustive and only includes public institutions with the available facilities.**

Appendix 7: Centres with available cardiothoracic surgery services*

Johor
Hospital Sultanah Aminah, Johor Bahru
Kelantan
Hospital Universiti Sains Malaysia, Kubang Kerian
Hospital Raja Perempuan Zainab II, Kota Bahru
Lembah Klang (Klang Valley)
Hospital Serdang
Pusat Perubatan Pakar, Universiti Teknologi Mara (UiTM), Sungai Buloh
Hospital Universiti Kebangsaan Malaysia, Cheras
Pusat Perubatan Universiti Malaya, Kuala Lumpur
National Heart Institute (IJN), Kuala Lumpur
Pahang
Hospital Tengku Ampuan Afzan, Kuantan
Penang
Penang General Hospital
Sabah
Queen Elizabeth Hospital, Kota Kinabalu
Sarawak
Heart Centre, Kota Samarahan

***This list is not exhaustive and only includes public institutions with the available facilities.**

Appendix 8: Antimicrobial dosing in adults with renal impairment

Loading dose

The size of a loading dose (LD) is the product of the desired drug concentration in the blood and the volume of distribution. It is independent of drug clearance. Therefore, provided the desired drug concentration and volume of distribution are unchanged, the size of the loading dose does not require modification in patients with renal impairment. In cases where there is slight alteration in the volume of distribution, e.g. those with low serum protein or fluid overload, some clinicians may alter the loading dose of some drugs with narrow therapeutic index.[1]

Methods of dose reduction in renal impairment

Three common methods are used to maintain drug doses in patients with renal impairment:[1]

- Interval method (I):
  Maintain the size of the individual dose and increase the dose interval – used where the size of the dose and the attainment of peak blood concentrations are critical for drug efficacy.

- Dose method (D):
  Reduce the size of individual dose and maintain the same dose interval – used where the size of a dose and peak concentrations are not critical for drug activity.

- Combination method (D & I):
  Uses a combination of the 'Dose' and 'Interval' methods – used for narrow therapeutic index drugs where close control over blood concentrations should be maintained.

Estimating creatinine clearance in adults

Check renal function before prescribing any drug that requires dose modification in renal impairment, even if only mild impairment is likely.

Renal function and muscle mass both decline with age, hence elderly people may have normal serum creatinine despite reduced renal function. Calculation of creatinine clearance (CrCl) may be necessary to estimate renal function in this population especially when prescribing renally excreted drugs with a narrow therapeutic index.

The Cockcroft-Gault equation estimates CrCl in ml/minute and has been successfully used in the calculation of adults with renal impairment. Weight, age, gender and serum creatinine are required. The formula below should not be used to estimate CrCl in severe renal insufficiency, or with rapidly changing renal function.

Modified Cockcroft-Gault equation:

*If actual body weight (ABW) is < ideal body weight (IBW), use ABW; refer to table for IBW.

$$\text{CrCl (mL/min)} = \frac{(140 - \text{Age}) \times \text{IBW (kg)}^*}{\text{Serum Creatinine (µmol/l)}} \quad (\times 1.04 \text{ for females}) \text{ or } (\times 1.23 \text{ for males})$$

Ideal body weight table for adults

Height (inches)	Height (cm)	Female IBW (kg)	Male IBW (kg)	Height (inches)	Height (cm)	Female IBW (kg)	Male IBW (kg)
5' 0"	152 – 154	45.5 – 47.3	50.0 – 51.8	6' 0"	183 – 184	73.4 – 74.3	77.9 – 78.8
5' 1"	155 – 157	48.2 – 50.0	52.7 – 54.5	6' 1"	185 – 187	75.2 – 77.0	79.7 – 81.5
5' 2"	158 – 159	50.9 – 51.8	55.4 – 56.3	6' 2"	188 – 190	77.9 – 79.7	82.4 – 84.2
5' 3"	160 – 162	52.7 – 54.5	57.2 – 59.0	6' 3"	191 – 192	80.6 – 81.5	85.1 – 86.0
5' 4"	163 – 164	55.4 – 56.3	59.9 – 60.8	6' 4"	193 – 195	82.4 – 84.2	86.9 – 88.7
5' 5"	165 – 167	57.2 – 59.0	61.7 – 63.5	6' 5"	196 – 197	85.1 – 86.0	89.6 – 90.5
5' 6"	168 – 169	59.9 – 60.8	64.4 – 65.3	6' 6"	198 – 200	86.9 – 88.7	91.4 – 93.2
5' 7"	170 – 172	61.7 – 63.5	66.2 – 68.0	6' 7"	201 – 202	89.6 – 90.5	94.1 – 95.0
5' 8"	173 – 174	64.4 – 65.3	68.9 – 69.8	6' 8"	203 – 205	91.4 – 93.2	95.9 – 97.7
5' 9"	175 – 177	66.2 – 68.0	70.7 – 72.5	6' 9"	206 – 207	94.1 – 95.0	98.6 – 99.5
5' 10"	178 – 179	68.9 – 69.8	73.4 – 74.3	6' 10"	208 – 210	95.9 – 97.7	100.4 – 102.2
5' 11"	180 – 182	70.7 – 72.5	75.2 – 77.0	6' 11"	211	98.6	103.1

Note: All doses recommended are for the treatment of infective endocarditis only.

Antimicrobial doses in adults with renal impairment

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
AMINOGLYCOSIDES							
Gentamicin[2,3]	1 mg/kg 8 hourly	I	CrCl 40-59: 1 mg/kg 12 hourly	CrCl: 20-39: 1 mg/kg daily CrCl < 20: 1 mg/kg ONCE (check level in 24 hours and redose when serum level is < 1 mg/l (< 2 µmol/l)	1 mg/kg ONCE (check level in 24 hours and redose when serum level is < 1 mg/l (< 2 µmol/l)		• Monitor gentamicin level and renal function weekly. There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity. • When given in a single daily dose, give infusion over 30 minutes. Aim for pre-dose (trough) serum level of < 1 mg/l (< 2 µmol/l). • Trough levels should be checked to monitor for toxicity in patients with renal impairment.

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
CEPHALOSPORINS							
Cefazolin[2,4,5-7]	2 g IV 8 hourly	I	2 g IV 8 hourly	CrCl 35-54: 2 g IV ≥ 8 hourly CrCl 11-34: 1 g IV 12 hourly	1 g IV 18-24 hourly	HD: 500 mg then 1 g IV daily; give post-dialysis on dialysis days CAPD: 500 mg IV 12 hourly CVVH: LD 2 g then 2 g IV 12 hourly CVVHD/CVVHDF: LD 2 g then either 1 g IV 8 hourly or 2 g 12 hourly	
Cefepime [2,6-9]	2 g IV 8 hourly (max. dose)	D & I	2 g IV 8 hourly	CrCl 30-60: 2 g IV 12 hourly CrCl: 11-29: 2 g IV daily	1g IV daily	HD: 1g initially then 500 mg-1 g daily; give post-dialysis on dialysis days CAPD: 2 g IV 48 hourly CVVH: LD 2 g then 1-2 g 12 hourly CVVHD/CVVHDF: LD 2 g then either 1 g IV 8 hourly or 2 g 12 hourly	
Ceftriaxone[10,11]	2 g IV daily (max. 4 g/day)	-	2 g IV daily	2 g IV daily	2 g IV daily (max. 2 g/day)	HD: 2 g IV daily; give post-dialysis on dialysis days HDF/Highflux, CAPD: Dose as in CrCl < 10 CAVHD/CVVHD/ CVVHDF: 2 g IV 12 hourly to daily	

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
FLUOROQUINOLONES							
Ciprofloxacin[6,7,12,13]	500 mg PO 12 hourly	D	500 PO 12 hourly	50-75% of usual dose 12 hourly	250 mg PO 12 hourly	HD: 500 mg PO or 400 mg IV daily; give post-dialysis on dialysis days CAPD: max 500 mg PO or 400 mg IV daily CVVH/CAVHD/CVVHD/ CVVHDF: 500 mg PO 12 hourly or 400 mg IV 12 hourly[6]	
	400 mg IV 12 hourly		400 mg IV 12 hourly	50-75% of usual dose 12 hourly	200mg IV 12 hourly		
PENICILLINS							
Ampicillin[2,6,13,14]	12 g/day IV in 4-6 equally divided doses	I	12 g/day IV in 4-6 equally divided doses	2 g IV 6 to 12 hourly	2 g IV 12 to 24 hourly	HD: 2 g IV 12 to 24 hourly; give post-dialysis on dialysis days CAPD: 250 mg IV 12 hourly CVVH: LD of 2 g then 2 g 8 to 12 hourly CVVHD: LD of 2 g then 2 g 8 hourly CVVHDF: LD of 2 g then 2 g 6 to 8 hourly	

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
Ampicillin (AM) + Sulbactam (SB) (IV 2:1)[2,6,7,15,16]	3 g IV 6 hourly		3 g IV 6 hourly	CrCl 15-29: 3 g IV 12 hourly	CrCl < 15: 3 g IV daily	HD: 3 g 12 to 24 hourly; give post-dialysis on dialysis days CVVH: Initial 3 g then 3 g 8 to 12 hourly CVVHD: Initial 3 g then 3 g 8 hourly CVVHDF: Initial 3 g then 3 g 6 to 8 hourly	
Cloxacillin[17,18]	2 g IV 4 hourly	-	2 g IV 4 hourly	2 g IV 4 hourly	2 g IV 4 hourly	HD: Dosage adjustment not needed	
Benzyl Penicillin[2,6,7,13,19] **(Crystalline Penicillin)**	3-4 MU IV 4-6 hourly	D	100%	75% of normal dose	20-50% of normal dose (See comments)	HD: up to 2 MU 4 to 6 hourly; give post-dialysis on dialysis days or supplement with 500,000 units post-dialysis	Increased risk of neurotoxicity (seizures) in renal impairment
MISCELLANEOUS							
Daptomycin[6,7,20,21]	10 mg/kg IV daily	I	10 mg/kg IV daily	CrCl < 30: 10 mg/kg IV 48 hourly Dose adjustment is based on case reports		HD/PD: Dose as in CrCl < 30 (give post-dialysis on dialysis days) or normal dose after HD 3x/week	Monitor creatine phosphokinase (CPK)

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
Vancomycin[6,7,22]	15 mg/kg 12 hourly based on ABW; not to exceed 2 g/day unless serum levels are monitored	D & I	Start with 15-20 mg/kg 8-12 hourly	CrCl 20-49: start with 15-20 mg/kg daily	CrCl < 20: will need longer intervals; determine by serum concentration monitoring	HD: LD then either 500 mg-1 g or 5-10 mg/kg after each HD session based on serum concentrations. Measure pre-HD serum level before 3rd HD session. Consider redosing for vancomycin pre-HD levels as follows: • < 10 mg/l give 1000 mg • 10-25 mg/l give 500-750 mg • > 25 mg/l hold Consider redosing for vancomycin post-HD levels < 10-15 mg/l give 500-1000 mg PD (via PD fluid): 15-30 mg/l of PD fluid PD (systemic): LD of 1 g then 500 mg-1 g 48 to 72 hourly (monitor levels closely) CVVH: LD 15-25 mg/kg then either 1 g 48 hourly or 10-15 mg/kg 24 to 48 hourly	• In the critically ill patient with renal insufficiency, the initial LD (25-30 mg/kg) should not be reduced. Make subsequent dose adjustment based on renal function and trough serum concentrations. • Trough level monitoring: > Trough levels are most accurate and practical (unless ESRD on HD). > Trough levels should be obtained approximately 30 minutes of the next dose before the 4th dose. > Once weekly monitoring is recommended for patients with stable renal function.

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
						CVVHD: LD 15-25 mg/kg then either 1 g daily or 10-15 mg/kg daily CVVHDF: LD 15-25 mg/kg then either 1 g daily or 7.5-10 mg/kg 12 hourly Note: Consider redosing patients receiving CRRT for vancomycin concentrations < 10-15 mg/l	> More frequent monitoring is recommended for patients who are haemodynamically unstable and changing renal function.
Rifampicin[23,24]	300-450 mg PO 12 hourly	D	No dose adjustment	CrCl ≤ 50 ml/min: 50-100% of the full dose		HD: Normal dose with no supplement after dialysis PD: 50-100% of the full dose, with an extra 50-100% of the full dose after PD CRRT: Dose as in normal renal function	Rifampicin is not dialysed & excreted in CAPD fluid causing an orange/yellow colour
ANTIFUNGALS							
Amphotericin B deoxycholate[25]	0.6-1 mg/kg/day IV	I	Avoid; if essential use normal dose (see Comments) If renal dysfunction is due to drug, the daily total can be decreased by 50% or the dose can be given every other day.			HD/CRRT: If essential use normal dose	Amphotericin is nephrotoxic; monitor serum creatinine closely; lipid formulations are less nephrotoxic

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
Amphotericin B lipid complex[2,13,26]	3-5 mg/kg IV daily	-	3-5 mg/kg IV daily	3-5 mg/kg IV daily	3-5 mg/kg IV daily	HD/PD/CRRT: 3-5 mg/kg IV daily	Amphotericin may be nephrotoxic; monitor serum creatinine closely
Anidulafungin[27-29]	200 mg IV daily	-	200 mg IV daily	200 mg IV daily	200 mg IV daily	HD/PD/CRRT: Dose as in normal renal function	
Caspofungin[29-31]	150 mg IV daily	-	150 mg IV daily	150 mg IV daily	150 mg IV daily	HD/PD/CRRT: No supplemental or dose adjustment necessary	
Fluconazole[28,29,32,33]	400-800 mg (6-12 mg/kg) IV/ PO daily	D	Normal dose	LD of 400 mg then 50% of normal dose	LD of 400 mg then 50% of normal dose	HD: 100% of daily dose after each dialysis session: on non-dialysis days patient should receive a reduced dose according to CrCl PD: Dose as for CrCl < 10 CVVH: LD of 400-800 mg then 200-400 mg daily CVVHD/CVVHDF: Dose as in normal renal function	

Drug	Dose for normal renal function	Method	Adjustment for renal failure Estimated CrCl (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
			> 50-90	10-50	< 10		
Flucytosine[29,34]	25 mg/kg PO 6 hourly	I	25 mg/kg PO 6 hourly	CrCl 20-40: 12.5 mg/kg PO 6 hourly	CrCl 10-20: 6.25 mg/kg PO 6 hourly	HD: 25 mg/kg 48 to 72 hourly	
Micafungin[29,35]	150 mg IV daily	-	150 mg IV daily	150 mg IV daily	150 mg IV daily	HD: No supplemental or dose adjustment necessary	

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Appendix 9: Antimicrobial dosing in children with renal impairment

Estimating creatinine clearance in paediatrics

There are 2 methods to calculate CrCl in children. Available data suggest that the bias of Schwartz calculated glomerular filtration rate (eGFR) increases at lower levels of GFR. The Schwartz and Counahan-Barratt formulae can provide rapid and convenient estimates of GFR, although clinicians should be aware of their imprecision in this setting.[1]

Schwartz Method:[1,2]

$$\text{CrCl (ml/min)} = \frac{k^* \times \text{Height in cm}}{\text{Serum Creatinine (µmol/l)}}$$

*k is a constant that varies with age and gender (see the following table):[1]

Age	k value
Preterm infants	29.2
Full-term infants	39.8
Children 2-12 years old	48.6
Adolescent females 13-21 years old	48.6
Adolescent males 13-21 years old	61.9

Counahan-Barratt:[1,3]

$$\text{GFR (ml/min/1.73m}^2\text{)} = \frac{38 \times \text{Height in cm}}{\text{Serum Creatinine (µmol/l)}}$$

Ideal body weight table for paediatric and young adults[4]			
Infants aged 0-24 months old (mo)			
Age	0-6 mo	6-12 mo	12-24 mo
Infant boys	$WT_i = 0.733\ A_{mo} + 3.6$	$WT_i = 0.433\ A_{mo} + 5.4$	$WT_i = 0.183\ A_{mo} + 8.4$
Infant girls	$WT_i = 0.667\ A_{mo} + 3.4$	$WT_i = 0.400\ A_{mo} + 5.0$	$WT_i = 0.183\ A_{mo} + 7.6$
Children and young adults aged 2-20 years (yr)			
Age	2-10 yr	10-16 yr	16-20 yr
Boys	$WT_i = 2.25\ A_{yr} + 8.50$	$WT_i = 5.00\ A_{yr} + 19.0$	$WT_i = 2.25\ A_{yr} + 25$
Girls	$WT_i = 2.38\ A_{yr} + 7.25$	$WT_i = 3.17\ A_{yr} + 3.33$	$WT_i = A_{yr} + 38$

Note: All doses recommended are for the treatment of infective endocarditis only. *WT_i: ideal body weight (kg); A_{mo}: age in months; A_{yr}: age in years.

Antimicrobial doses in paediatrics with renal impairment

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
AMINOGLYCOSIDES								
Gentamicin[5-7]	Infants, children and adolescents	1 mg/kg IV 8 hourly	D & I	All ages, give first dose as above and await plasma level result before further dosing. If trough level is still high after 36 hours consider reducing dose. **Blood levels/TDM:** • Take level 6 hours before 3rd dose (6 hours before 2nd dose if renal function is unstable). Repeat daily until stable then every 3 doses. • Pre-dose ('trough') concentration > < 2 µmol/ml (< 1mcg/ml for paediatrics) > < 4 µmol/ml (< 2mcg/ml for NICU/ PICU) • Re-dose patient at 24 hours if trough level achieved (at 36 hours if on 36 hour dosing). If trough is high, recheck level 12 hours after that level was taken and re-dose after that if level now in range. Dosing adjustment is to avoid accumulation, but do not delay at the detriment of not treating the patient. • In very overweight or grossly oedematous patients, use lean body weight for calculating dose.				

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
CEPHALOSPORINS								
Cefazolin[8-11]	Infants, children and adolescents	100 mg/kg/**day** IV in 3 equally divided doses	D & I	GFR 40-70: Normal initial dose then 60% of total daily dose given in 2 equal doses	GFR 20-40: Normal initial dose then 25% of total daily dose given in 2 equal doses; GFR 5-20: Normal initial dose then 10% of total daily dose daily	25 mg/kg IV daily	HD/PD: 25 mg/kg IV daily CRRT: 25 mg/kg IV 8 hourly	
Cefepime[7,12,13]	Infants, children and adolescents	50 mg/kg IV 8 hourly (Max. single dose 2 g)	D & I	Normal dose	25-50 mg/kg IV 12 to 18 hourly	25-50 mg/kg IV daily	HD: LD of 25-50 mg/kg IV on Day 1 then 12.5-25 mg/kg IV daily; dose after HD or give supplemental same dose after HD session PD: Normal dose daily CRRT: Normal dose 12 hourly	

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
Ceftriaxone[5-7,10,12,13]	Infants, children and adolescents	100 mg/kg IV once daily	-	Normal dose	Normal dose	Max 50 mg/kg IV daily (max. 2 g daily)	HD/CAPD: 50 mg/kg IV daily (max. 2 g daily) On HD days scheduled doses should be administered after HD session CRRT: Normal dose	Ceftriaxone should not be administered to premature, acidotic, jaundiced neonates or those with impaired or reduced bilirubin binding.
PENICILLINS								
Ampicillin[7,10,14,15]	Infants, children and adolescents	200-300 mg/kg/**day** IV in 4-6 equally divided doses (max. 12 g/**day**)	I	Normal dose	GFR 10-30: Normal dose 6 to 12 hourly	Normal dose 12 hourly	HD: Normal dose 12 hourly; dose after HD or give supplemental same dose after HD session CVVH: Normal LD then normal dose 8 to 12 hourly CVVHD: Normal LD then normal dose 8 hourly CVVHDF: Normal LD then normal dose 6 to 8 hourly	

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
Ampicillin (AM) + Sulbactam (SB) (IV 2:1)[10,15-17]	Infants, children and adolescents < 40 kg	200-300 mg AM/kg/**day** IV in 4-6 equally divided doses	I	Normal dose	FR 15-29: Normal dose 12 hourly; GFR 5-14: Normal dose daily	Normal dose daily	Dose expressed as AM component HD: Normal dose 12 to 24 hourly; give after dialysis on dialysis days CVVH: Max dose as LD then normal dose 8 to 12 hourly CVVHD: Max dose as LD then normal dose 8 hourly CVVHDF: Max dose as LD then normal dose 6 to 8 hourly	
Cloxacillin[18]	Children and adolescents	200-300 mg/kg/**day** IV in 4-6 equally divided doses (max. 2 g/**dose**)	-	Normal dose	Normal dose	Normal dose	HD: Dosage adjustment not needed	

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
Benzyl Penicillin[6,10,19] (Crystalline Penicillin)	Infants, children and adolescents	200,000-300,000 units/kg/**day** IV in 4-6 equally divided doses	I	Normal dose	Normal dose 8 to 12 hourly	Normal dose 12 hourly	HD: Normal dose 8 to 12 hourly; give afer dialysis on dialysis days CAVH/CVVH/ CVVHD: Normal dose 8 to 12 hourly	
MISCELLANEOUS								
Daptomycin[10,20]	Children ≥ 2 years and adolescents	10 mg/kg IV daily	I	Normal dose	GFR 10-29: 67% of full dose daily	67% of full dose 48 hourly	HD/PD: 67% of full dose 48 hourly after dialysis	In paediatric patients, daptomycin is not routinely used as a 1st line therapy. Avoid using in < 12 months due to musculoskeletal, neuromuscular and nervous system adverse effects.

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
Vancomycin[6,10,21]	Infants, children and adolescents	40-60 mg/kg/**day** IV in 2-3 equally divided doses (Initial dose is based on actual body weight; subsequent dosing based on serum trough levels)	Doses should be reduced in renal failure according to blood levels • Trough level monitoring: > Only give subsequent doses when vancomycin level reaches trough target > Therapeutic level: Trough 7-10 umol/l (10-15 mg/l) or 10-14 umol/l (15-20 mg/l) > Trough levels should be obtained approximately 30 minutes of the next dose > Approx. time to steady state 1-2 days > Peak levels are not usually required				HD/CAPD: 10 mg/kg IV as needed per serum concentration monitoring CRRT: 10 mg/kg IV 12 to 24 hourly, monitoring serum concentration	
Rifampicin[10,22,23]	Children and adolescents	20 mg/kg/**day** PO in 3 divided doses (max. 900 mg/**day**)	D	Normal dose	Normal dose	Normal dose	HD/CAPD/CRRT: Normal dose	

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
ANTIFUNGALS								
Amphotericin B deoxycholate[22,24]	Infants, children and adolescents	After test dose 1 mg/kg IV daily	-	Avoid; use normal dose if only no alternative (see Comments) If renal dysfunction is due to drug, the total daily dose can be decreased by 50% or the dose can be given every other day			HD/PD/CRRT: If essential use normal dose	Amphotericin is nephrotoxic; monitor serum creatinine closely; lipid formulations are less nephrotoxic.
Amphotericin B lipid complex[22,25]	Infants, children and adolescents	3-5 mg/kg IV daily	-	No dosage adjustment required in pre-existing renal failure.			HD/PD/CRRT: Normal dose; consider standard amphotericin due to cost	Amphotericin is highly nephrotoxic; monitor serum creatinine closely.
Fluconazole[6,7,10,22,26]	Infants, children and adolescents	6-12 mg/kg PO/IV daily	D	Normal dose	Normal LD then 50% of normal dose daily	Normal LD then 50% of normal dose 48 hourly	HD: 100% of normal dose 3x/ week after HD session or 50% of normal dose every 48 hours; administer after dialysis on dialysis days PD: 50% of normal dose 48 hourly CRRT: 6 mg/kg/ dose daily	Refer to product information for more dosing details.

Drug	Age	Dose for normal renal function	Method	Adjustment for renal failure Estimated GFR (ml/min)			Dose in patients undergoing renal replacement therapies	Comments
				> 50-90	10-50	< 10		
Flucytosine[5,10,27]	Infants, children and adolescents	150 mg/kg/**day** PO in 4 equally divided doses	-	Normal dose	GFR 30-50: 25-37.5 mg/kg/dose 8 hourly GFR 10-29: 25-37.5 mg/kg/dose 12 hourly	GFR < 10: 25-37.5 mg/kg/dose daily	HD/PD: 25-37.5 mg/kg/dose daily CRRT: 25-37.5 mg/kg/dose 8 hourly	

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Appendix 10: Weekly OPAT review checklist (for doctors)

General review of the patient and clinical examination (specifically look for)	
Heart failure	
Embolic events	
Recurrence of fever or worsening of other septic parameters	
New neurological signs or symptoms	
Ask about side effects of antimicrobials such as rash	
To check compliance of patient/difficulties faced with vascular device	
To check branula/peripherally inserted central catheter (PICC) line for evidence of thrombophlebitis	
To check on control of co-morbidities such as diabetes and hypertension	
Baselines blood investigations such as FBC, CRP, RP and LFT	
Review the planned duration of antimicrobials	
To ensure antimicrobials are ordered up to next hospital appointment	
If required	
ECG	
Therapeutic drug monitoring	
INR	
Echocardiogram	

Appendix 11: Clinical indicators

Performance measures for this CPG is to monitor the implementation of these guidelines with the aim of achieving the following within 5 years.

Performance indicators	Yes	No	Target to achieve in 5 years
Decrease in the mortality caused by IE: $\frac{\textit{Number of deaths of IE patients due to IE or its complications over a given time frame}}{\textit{Total number of patients diagnosed with IE over the same time frame}} \times 100\%$			By 50%
Surgery performed within 24 hours for patients with emergency indication (as per the guidelines): $\frac{\textit{Number of IE patients requiring emergency surgery receiving surgery within 24 hours}}{\textit{Total number of IE patients requiring emergency surgery}} \times 100\%$			50%

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ACKNOWLEDGEMENT

The members of the CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION, DIAGNOSIS & MANAGEMENT OF INFECTIVE ENDOCARDITIS development committee would like to express their gratitude and appreciation to the following for their contribution:

- Panel of external (local and international) reviewers who reviewed and contributed their expert feedback on the draft copy.
- Technical Advisory Committee, Clinical Practice Guidelines, Ministry of Health, Malaysia for their valuable input and feedback.
- Dr. Mohd Aminuddin Mohd Yusof of the Health Technology Assessment unit of Ministry of Health, Malaysia for his guidance throughout the process.
- Mediconnexions Consulting Sdn Bhd for taking on the secretariat role.
- All those who have contributed directly or indirectly to the development of this CPG.

DISCLOSURE STATEMENT

The panel members have no potential conflict of interest to disclose. None hold shares in pharmaceutical firms or act as consultants to such firms.

SOURCES OF FUNDING

The development of the Clinical Practice Guidelines on the prevention, diagnosis and management of IE was supported in its entirety by the National Heart Association of Malaysia (NHAM) and was developed without the involvement of the pharmaceutical industry.

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