Chapter 10

Wound and Postoperative Infections and Management

10.1 Wound Infections

10.1.1 General Classification

The operative wound is classified by the nature of the would whether it is clean or contaminated, the location of the wound, and the risk of infection as follows:

i) Clean wound:

Wound criteria: Elective, non-emergency, non-traumatic, and primarily closed.

No acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts are not entered. Infection risk (< 2%).

ii) Clean-contaminated wound:

Wound criteria: Urgent or emergency case that is otherwise clean, minor break in technique, elective opening of respiratory, gastrointestinal, biliary / genitourinary (GU) tract with minimal spillage. Infection risk (< 10%).

iii) Contaminated wound:

Wound criteria: Major break in technique; penetrating trauma < 4 hours old.

No purulent inflammation; gross spillage from gastrointestinal tract. Entry into biliary or GU tract in the presence of infected bile or urine. Chronic open wounds waiting to be grafted or covered. Infection risk (20%).

iv) Dirty wound:

Wound criteria: Penetrating trauma > 4 hours old, purulent inflammation (e.g., abscess), preoperative perforation of respiratory, gastrointestinal, biliary or genitourinary tract. Infection risk (40%).

10.1.2 Factors of Wound Infection

Several local wound factors and systemic factors are associated with an increased risk of infection as discussed below.

Systemic Factors:

Diabetes, corticosteroid use, obesity, extremes of age, malnutrition, recent surgery, massive transfusion, multiple (3 or more) preoperative co-morbid medical diagnoses.

Local Factors:

Foreign body, use of electrocautery, injection with epinephrine, wound drains, hair removal with razor, and previous irradiation of`the site.

10.1.3 Pathogens of Wound Infection

The following micro-organisms are the potential pathogens of the wound infection.

a) Gram-positive cocci:

Beta-hemolytic streptococci (Streptococcus pyogenes),* enterococci (Enterococcus faecalis), and staphylococci (Staphylococcus aureus/MRSA).*.

b) Gram-negative aerobic rods:

Pseudomonas aeruginosa*

c) Gram-negative facultative rods:

Enterobacter species, Escherichia coli, Klebsiella species, and Proteus species.

d) Anaerobic bacteria:

Bacteroides, and Clostridium species.

e) Fungi:

Yeasts (candida) and Aspergillus.

* Most common causative organisms associated with wound infections.

10.1.4 Recognition of Wound Infection

1) Signs of inflammatory process:

Wound erythema, pain, localized heat, cellulitus and edema of the wound.

2) Further criteria:

Abnormal smell, pain and/or tenderness at the time of dressing change.

Discolored, purulent, and viscous wound discharge.

Discoloration of tissues at the wound margins.

Friable and bleeding granulation tissue despite gentle handling of the wound (if non adhesive wound management materials are used).

Abscess and delayed healing not previously anticipated.

10.1.5 Diagnosis of Wound Infection

Simple following laboratory techniques would confirm the diagnosis of wound infection.

i) Wound swabbing:

It is the most common sampling method.

It identifies the causative organism (s) and possible sensitivities to antibiotics.

ii) Blood: Elevated white cell counts.

iii) Elevated serum C-reactive protein (CRP).

(CRP normally is not found in the serum).

iv) Quantitative analysis (e.g., wound biopsies):

Aids in recognition of an increased bacterial burden.

10.1.6 Treatment of Wound Infection

Objectives:

Have overall assessment and treat the patient, and not the infection alone. Reduce rather than eradicate the bacterial burden within the wound margins. Wound management with compounds containing silver or iodine ↓ the bacterial burden. Systemic antibiotics are essential for the management. Select most appropriate antibiotic based on culture and sensitivities. Topical antibiotics use is not justified for colonized or infected wounds. Systemic and topical antibiotics are not justified for chronic infected wounds.

Topical agents:

A. Iodine:

Iodine is used in two forms:

i) Cadexomer iodine - a polysaccharide starch containing 0.9% elemental iodine.

ii) Povidone iodine - an iodophor composed of elemental iodine and a synthetic polymer.

Indications: Wound cleansing, wound bed preparation, and prevention and management of wound infection.

B. Silver Compounds:

Silver interferes with electron transport of bacteria and inhibits bacterial multiplication. Dressings containing silver may be used but silver ions have to be able to enter a bacterial cell.

i) Silver sulphadiazene:

Safe broad-spectrum agent for topical use.

Silver is released slowly in concentrations that are selectively toxic to bacteria and fungi.

May be used in the management of acute and chronic wounds.

ii) Other silver products:

May sustain the interaction of silver with bacteria in the wound.

May be more effective in preventing/controlling local infection.

C. Further interventions:

These interventions reduce bacterial burden on the wound surface:

i) Autolytic or enzymatic debridement.

ii) Surgical debridement and maggot therapy.

iii) Topical negative pressure (TNP) or vacuum-assisted closure (VAC) is used in conjunction with secondary dressings as required.

10.2 Sternal (Mediastinal) Infection

It is the most common infection leading to significant morbidity and mortality (mortality ranges 0.15% to 8%) after open heart surgery.

10.2.1 Diagnosis of Deep Sternal Infection

Symptoms and Signs:

a) Wound discharge, fever, leukocytosis, and elevated C-reactive protein in the blood.

b) Evidence of bacterial growth (cultures of pus or soft tissue from the mediastinum):

1) Staphylococcus aureus, including MRSA is the most common pathogen.

2) Gram-negative organisms account for < 10% of wound pathogens.

Pseudomonas aeruginosa, Serratia marscens, and Enterobacter cloacae.

3) No organisms may be isolated (< 20%).

c) Sternal instability.

10.2.2 Management of Deep Sternal Infection and Operative Technique

A. If wound infection is clinically suspicious:

Do early wound exploration and drainage under local anesthesia, and send for bacterial and fungal cultures. Pack the wound with wet dressings for 2 to 3 days.

B. Give vancomycin IV until wound tissue culture and sensitivity tests are known. If the systemic signs of infection are under control with a diagnosis of deep sternal wound infection, do the following:

1. Reopen the sternotomy under general anesthesia.

2. Remove all sternal wires.

3. Debride sternal edges until healthy solid bone with briskly bleeding margins are found.

4. Resect the entire sternum if the bone is necrotic and soft with oozing pus.

5. Send for culture the subcutaneous tissue, mediastinal fluid, and sternal bone.

6. Irrigate the wound with antibiotic solution (500 mg of vancomycin in 1 L of normal saline).

7. Advance pectoralis major muscle (PMM) flaps as discussed below:

Use the left PMM flap to cover the lower mediastinum and the right PMM flap to cover the upper mediastinum. The flaps can be easily advanced to the midline without tension (see Figure 28).

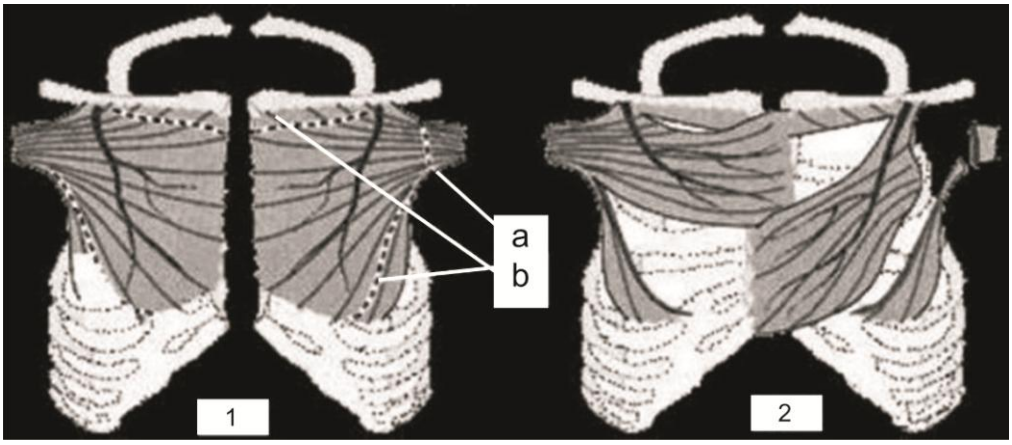

Figure 28 *Design of right and left pectroalis muscle flaps for treatment of deep sternal wound infection.1) a. Dashed lines represent division of clavilcular attachment and lower costal attachment of right and left muscles. Division of a lower costal attachment of pectoralis major muscle fibers may further require separation from external oblique muscular digitations to completely free the muscle flap b. Division of humeral insertion of the muscle to gain additional mobility of the muscle flap. 2) Left muscle is used to cover the lower sternal defect and right muscle is used to cover upper sternal defect after a thorough debridement of infected and necrotic sternum.*

Operative technique of PMM flaps:

Flaps are raised from medial to lateral side in the avascular plane.

Dissection plane is beneath the PMM using minimal diathermy.

Dissect superiorly to the level of the clavicles, and laterally as far as the anterior axillary line.

Left PMM flap: Split the clavicular and sternal segments.

Divide the tendon insertion from the humerus for sternocostal component of the muscle flap. Preserve thoraco-acromial pedicles of artery and nerve.

Right PMM flap: Split the clavicular and sternal segments.

May not need division of the tendon insertion from the humerus

Thoracoacromial pedicles of artery and nerve are preserved.

Approximate and fix both PMM flaps to the edge of the defective chest wall using a non absorbable polypropylene suture.

Insert a closed suction drain above and under the muscle flaps before closure.

Irrigation catheter may be inserted for antibiotic irrigation postoperatively.

The skin is closed with interrupted nylon sutures.

8. Choice and duration of antibiotic therapy in sternal infection:

Determine the choice of antimicrobial coverage by culture and sensitivity results.

Duration of treatment is for 4 weeks if WBC counts and C-reactive protein concentrations are normalized.

Duration is for 6-8 weeks if WBC counts and C-reactive protein concentrations are not normalized or with positive blood cultures.

10.2.3 Clinical Notes on Deep Sternal Infection

Mortality of sternal infection post-cardiotomy ranges 0.15% to 8%.

Risk factors for sternal infection:

Children with asplenia syndrome and the child who has undergone cardiac transplantation.

Association with the use of ß-adrenergic drugs: A 20-fold increase in the risk in adults requiring ß-adrenergic drugs post cardiac surgery.

Obstructive pulmonary problems: Mechanical strain on the sternotomy incision creates sternal instability and dehiscence. Dehiscence leads to seeding of infection.

Management strategies of sternal infection:

The management of sternal infection is controversial and varies from simple debridement with antibiotic irrigation and sternal closure to liberal use of omentum, PMM, and rectus abdominus muscle flaps (latter are used, especially in adults). Extensive surgical debridement, and early sternal reconstruction with either omentum, PMM, or rectus abdominus muscle flaps yields good results in majority.

Early recognition of sternal infection and early and aggressive debridement of all infected material is essential, plus systemic antibiotic treatment for control of sepsis. The management algorithm in suspected sternal infection is shown in figure 29.

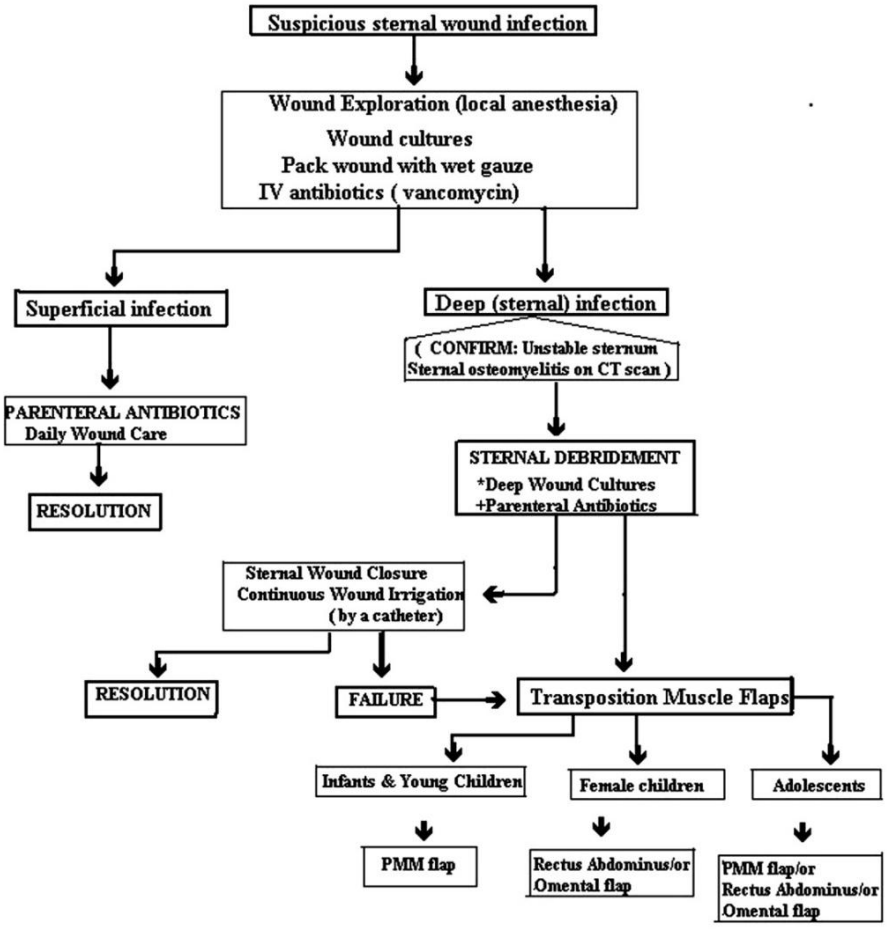

Figure 29 *Management algorithm for a suspicious sternal wound infection in children. IV=intravenous, PMM=Pectoralis major muscle, * Wound cultures consist of debrided sternal tissue and infected mediastinal tissue, **Parenteral antibiotics are chosen based on results of deep wound cultures.*

If adequate debridement is done, reconstruction should be done at same sitting or 2 days later. Prolonged open dressing and growth of granulation is not necessary. The latter strategy is time consuming and has not demonstrated good results.

Important points in selection of muscle flaps or omentum for coverage:

1. The ability of muscle flaps and omental flaps to control and eliminate sepsis is well documented.

2. Choice of a flap is dependent on surgeon's preference, patient age, size, gender, and presence of percutaneous enterostomies.

3. Use of rectus abdominis muscle and omental flap requires additional abdominal incisions that increase postoperative pain and may compromise respiratory functions.

4. Harvesting of the rectus abdominis muscle creates a risk of herniation or a diffuse bulging through the defect.

5. Laparotomy to harvest the omentum may cause fibrous adhesions and possibly small bowel obstruction.

6. Pectoralis major muscle (PMM) is readily accessible and has an excellent blood supply, i.e., thoracoacromial artery, segmental pedicles from the internal thoracic artery branches of the lateral thoracic, and intercostals arteries.

7. Potential risk for disturbance of breast development with use of PMM flaps in females.

High Points in use of PMM Flaps:

1. PMM is delicate with indistinct tissue planes in children, especially in infants and neonates.

2. Vascular pedicle is much smaller and less resilient to stretching.

3. Sternum and ribs are highly cartilaginous and offer a poor defense against contamination.

4. Debridement should be conservative to preserve future growth, but should remove all non viable and infected tissue.

5. In patients with palliative surgery (i.e., shunts) tissue hypoxia and resultant polycythemia may impair wound healing, and graft viability.

6. Reentry should be considered for staged or corrective operations.

7. PMM flap techniques are easy, promotes wound healing, facilitates additional operations, produces minimal growth, and developmental problems.

10.3 Pneumonias in the Intensive Care Unit

These pneumonias are classified as:

1. Postoperative pneumonia.

2. Ventilator-associated pneumonia.

3. Pneumonia in unventilated moderately or critically ill hospitalized inpatients.

Postoperative pneumonias is one of the most common hospital-acquired pneumonias.

10.3.1 Causative Organisms

1. Staphylococcus aureus (methicillin-sensitive and resistant MRSA strains).

2. Pseudomonas aeruginosa.

3. Enteric gram-negative bacteria (i.e., Enterobacter species, Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Proteus species, and Acinetobacter species).

10.3.2 Predisposing Factors

1. Prior Antibiotic treatment:

Increases the likelihood of polymicrobial infection. The methicillin-resistant S. aureus and pseudomonas infections are common.

2. Duration of hospitalization influences the etiological organism:

4 to 7 days stay: S. aureus, Pneumococcus, and Haemophilus influenzae are the most commonly implicated.

> 7 days and increasing duration of intubation: Enteric gram-negative organisms are common.

3. High-dose corticosteroids:

↑ Risk of Legionella and pseudomonas infections.

10.3.3 Symptoms and Signs

1. Non- intubated patients:

Same as those for community-acquired pneumonia.

2. Intubated patients:

Fever and ↑ respiratory and/or heart rate, ↑ purulent secretions, or changes in respiratory parameters with worsening hypoxemia.

Leukocytosis with a new infiltrate on a chest x-ray taken for evaluation of new symptoms or signs are highly suggestive of postoperative pneumonia.

Nevertheless, no specific symptom, sign, or x-ray finding is sensitive for the diagnosis of pneumonia.

10.3.4 Diagnosis

1) Exclusion: Exclude other (non-infectious) causes of pulmonary deterioration, such as:

Acute respiratory distress syndrome (ARDS), pneumothorax, and pulmonary edema.

2) Gram stain and culture of endotracheal aspirates: It's value is controversial, as specimens are contaminated with colonizers as well as pathogens. Positive culture may or may not indicate infection.

3) Bronchoscopic sampling of lower airway secretions:

Quantitative culture may yield more reliable results, but this approach on outcomes (diagnosis and treatment) are controversial.

4) Bronchoalveolar lavage fluid: Measurement of inflammatory mediators (i.e., concentration of soluble triggering receptors expressed on myeloid cells) has a future role in the diagnosis.

10.3.5 Treatment

Initial antimicrobial therapy:

Should cover both resistant gram-negative and gram-positive organisms.

Multiple regimens exist, but chose the regimen that suits the patient.

Antimicrobial Therapy Options:

1) Carbapenem (imipenem-cilastatin): 7 mg/kg (adult 500 mg) IV q. 6 h. /or

Meropenem: 15 to 30 mg/kg (adult 1 to 2 g) IV q. 8 h.

2) Monobactam (aztreonam): 15 to 30 mg/kg (adult 1 to 2 g) IV q. 8 h. / or

Ticarcillin (antipseudomonal β-lactam): 45 mg/kg (adult 3 g) IV with or without clavulanic acid q. 4 h.

3) Piperacillin: 45 mg/kg (adult 3 g) IV with or without tazobactam q. 4 to 6 h.

4) Ceftazidime: 30 mg/kg (adult 2 g) IV q. 8 h / or

Cefepime: 15 to 30 mg/kg (adult 1 to 2 g) IV q. 12 h. given either alone or combined with an aminoglycoside:

Gentamicin / tobramycin 1.7 mg/kg IV q. 8 h. or 5 to 6 mg/kg once a day /or

Amikacin 5 mg/kg IV q. 8 h. and/or

Vancomycin 15 mg/kg IV (adult 1 g) q. 12 h.

Linezolid may be used for MRSA in patients who cannot take vancomycin.

Daptomycin should not be used for pulmonary infections.

10.4 Invasive Fungal Infection (Candidiasis)

Synonyms: "Disseminated candidiasis", "systemic candidiasis," and "hematogenous candidiasis".

Candida spp. can invade and cause disease in virtually any organ of the body.

10.4.1 Risk Factors

Granulocytopenia, colonization with candida, severity of illness, prior surgery, solid-organ transplantation, bone marrow transplantation, type/duration of chemotherapy and graft-versus-host disease.

Risk factors in neonates: Gestational age, low Apgar score, prolonged ICU stay, shock, use of H_2 blockers, and intubation.

10.4.2 Clinical Mnifestations

Very often completely are non-specific or manifest the following:

1. Fever and Sepsis Syndrome:

Fever is often the only clinical clue of on a high risk patient. Progressive sepsis with multi-organ failure in surgical patients may indicate invasive candidiasis.

Persistent unexplained fever and sepsis not responding to broad spectrum antibiotics is typical for acute forms of invasive candidiasis, and recognize the need for empirical antifungal therapy in neonates, non-neutropenic, and selected non-neutropenic patients.

2. Cutaneous Lesions:

Macronodular rash isolated to extremities, abdomen, or covering the entire body occurs in 15% of neutropenic patients with invasive candidiasis.

Biopsy of lesions show small oval blastopores with buds and pseudohyphae in deeper layers of skin, and dermis. (Heroin addicts show a rash consisting of papules, pustules, nodules, and folliculitis.)

3. Retinal Lesions:

Majority of patients have nonspecific retinal lesions, and appear similar to diabetic/hypertensive retinopathy in documented candidemia. Retinal examination has limited value as a diagnostic tool in high risk patients for invasive candidiasis, but with negative blood cultures for Candida species. So testing is not needed.

10.4.3 Laboratory Diagnosis

Invasive disease should be distinguished from colonization.

Knowledge of the pathogenetic mechanisms leading to invasion is informative.

A. PCR-based method:

Potential tool for a diagnosis of systemic invasive candidiasis.

Detect and identify fungi directly from human venous blood.

Species-specific hybridization probes are used, and PCR amplicons were analyzed.

Between 2 to 10 fungal cells/mL of spiked blood samples could be detected.

Correctly identifies Candida albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis

B. Microbiology:

1) Gram stain:

Gram-positive 4-6 micrometer, thin-walled, ovoid yeasts with budding and pseudohyphae, but the stain is not always positive.

2) Tissue Culture:

Biopsy specimens, aspirates, or surface culture:

Requires only 1 to 3 days for growth of C. albicans, C. parapsilosis and C. tropicalis. It takes slightly longer for C. krusei and C. glabrata on any standard medium. The colonies are smooth, creamy, and glistening, but some species produce coarser colonies.

3) Blood culture (BC):

Recovering candida from blood is a key for diagnosis of invasive candidiasis.

BC is positive in < 50% of autopsy-proven invasive candidiasis.

The lysis-centrifugation method is sensitive and positive in 58% of invasive infection, and estimates number of colonies of candida per mL of blood.

Other techniques: BacTEC high-blood-volume fungal media (HBV-FM) and the BacT/Alert system has equal sensitivity.

4) Urine culture:

Candiduria is common in the hospitalized patients with urinary catheters (colonization). It is difficult to decide if candiduria is clinically relevant, and absolute colony count or the presence of WBC's in urine is not consistently helpful to diagnose invasive infection.

Asymptomatic candiduria in the low-risk patient is of no clinical relevance, and the presence of colonization in a high risk patient increases the risk of invasive candidiasis, but it alone is rarely diagnostic.

5) Surgical wound or drainage or peritoneal fluid:

Isolation of candida from these sources is not diagnostic of localized infection as candida is frequently recovered from these sites in surgical patients. But entertain the possibility of candidal peritonitis if candida is isolated from the peritoneal fluid.

6) Sputum or bronchoalveolar lavage:

Candida species are normal commensals of the human mucous membranes and the mouth. Specimens from the airways (respiratory tract of severely ill) are frequently contaminated with candida. Isolation of candida in the sputum has only a loose association with documented pneumonia as clinically relevant candidal pneumonia is quite rare.

7) CSF Fluid:

Positive culture is due to CNS candidiasis and and more so, in neonatal candidiasis. Positive cultures are rare in adults, and contamination should be entertained.

C. Serology and biomarkers:

Many numbers of tests are able to detect the presence of invasive candidiasis.

But none of the tests has been shown to have clinical applicability as 1) candida species are normal commensals, 2) serological tests become positive only after the diagnosis is strongly suggested by other data.

1) Antibodies for candida: Seen late in the course of disease, and has limited use in immune suppressed patients.

2) Antigens: Mannan: Sensitivity ~70%, short serum half-life. It is complicated measurement technique.

3) D-Glucan: Cross reactivity with multiple fungi and appears sensitive.

4) Candida enolase: Low sensitivity and specificity. Testing of multiple serum samples increase sensitivity.

5) Glycoprotein: Sensitivity and specificity varies, generally < 60%. Testing of multiple serum samples increases sensitivity. Colonization produces positive results.

6) Metabolites: D-arabinitol / L-arabinitol

Values of urine D-arabinitol/L-arabinitol ratio in a suspected infection in a neutropenic patient:

↑ levels are not commonly associated with candidemia during course of the infection, and the test is of no use in guiding the initiation of antifungal therapy. ↑ D-arabinitol/L-arabinitol ratio is seen in the late phase of infection.

Pneumonia is the most common manifestation of invasive candidiasis, and 53% patients have ↑ D-arabinitol/L-arabinitol ratio, and was associated with a mortality of 67%. Patients who died had higher D-arabinitol/L-arabinitol ratio than the survivors. Detection of ↑ D-arabinitol/L-arabinitol ratio during empirical Rx with amphotercin-B is associated with poor prognosis.

D. Histopathology:

Multiple small abscesses (1 to 5 mm) are noted in the parenchyma of affected organs, and neutrophils form circumscribed acute abscesses. Intracapillary yeasts (round, 5 to 7 microns) with budding and pseudohyphae suggests acute infection.

Classic granuloma formation with giant cells suggests chronic infection.

Candida are observed using the methenamine-silver staining and periodic acid-Schiff's stain.

10.4.4 Therapy of Invasive Candidiasis

Classification of antifungal agents for treatment of Candidiasis:

i) Azoles: These inhibit the synthesis of ergosterol by blocking 14-alpha-demethylase.

E.g., fluconazole.

ii) Allylamines and non-azole ergosterol biosynthesis inhibitors: These lead to reduced ergosterol biosynthesis and related to the azole antifungal agents.

E.g., terbinafine acts by inhibiting squalene epoxidase.

iii) Antimetabolites: These are DNA substrate analogs that leads to incorrect DNA synthesis, e.g., flucytosine.

iv) Glucan synthesis inhibitors: These inhibit the enzyme necessary for production of glucan, a key component of the fungal cell wall, and these produce significant antifungal effects, e.g., caspofungin.

v) Polyenes: These binds the fungal cell membrane, causing the fungus to leak electrolytes, e.g., amphotericin B.

vi) Miscellaneous systemic agents: These agents disrupt the mitotic spindle.

E.g., griseofulvin.

Choice of an antifungal agent:

The drug should act promptly and effectively as hematogenous candidiasis has a mortality of 40%. Therapy should be available in a parenteral form for administration. Amphotericin B is a highly effective and its lipid-associated forms are less toxic and effective, but all preparations result in a certain degree of unavoidable toxicity.

Fluconazole (parenteral): It is an alternative therapy for invasive candidiasis.

Itraconazole (parenteral): It is an additional choice, but the anti-candida spectrum is same as fluconazole.

Flucytosine: It has an excellent activity against candida, but the dose is adjusted for renal dysfunction and challenging to use with difficulty in quickly obtaining serum levels.

Glucan synthesis inhibitors: These drugs, combined with their low toxicity, provide broad anti-candida activity and an alternate choice for amphotericin B.

Common therapeutic choice:

Amphotericin B is the broadest spectrum therapy currently available.

Dose: 0.5-1.0 mg/kg/day for amphotericin B deoxycholate.

3 mg/kg/day for lipid preparations of amphotericin B.

C. glabrata and C. krusei have higher MICs to amphotericin B, so maximal doses are used. Due to the frequent prior use of azoles in neutropenic patients, amphotericin B is preferred.

10.5 Bacterial Sepsis and Therapy

Definition of Sepsis: Patient has symptomatic bacteremia, with or without organ dysfunction as a result of overwhelming infection with active multiplication of bacteria in the bloodstream.

10.5.1 Pathophysiology

Due to sustained bacteremia, circulating bacterial products mediated by cytokine release produces various clinical effects on the host:

Impaired pulmonary, hepatic, or renal function results from excessive cytokine release. The cytokines (previously termed endotoxins) play major role in the septic process.

Sources of infection:

A. Intravenous (IV) line infections:

If other sources of sepsis are eliminated, strongly suspect IV line sepsis, especially, if IV line has been in for a prolonged period (more than a week).

Central IV lines are commonly associated with bacteremia or sepsis.

Peripheral venous lines and arterial lines are rare cause of bacteremia.

B. Intra-abdominal, thoracic, pulmonary, pelvic or urinary tract source:

Positive history or physical examination is elicited for antecedent conditions predisposing to pneumonia, intestinal or hollow viscus inflammation, perforation or abscess, pyelonephritis, congenital abnormal collecting system, and previous surgery.

C. Increased risk group:

These are patients with diabetes, systemic lupus erythematosus (SLE), those on steroids, or those with absent splenic function.

10.5.2 Symptoms, Signs, and Diagnosis

Fever and impaired mental status if hypoperfusion is present.

Physical examination:

Increased breathing rate (results in respiratory alkalosis) warm or cold skin depending on the adequacy of organ perfusion.

Systematic examination may suggest a potential source, i.e.,

Infected IV site (only 50% of central IV-line infections show evidence of infection), abdominal tenderness, costovertebral angle (CVA) tenderness etc, pleural effusion/pericardial effusion, or unimpressive examination with absent physical findings.

Exclude pseudosepsis before starting extensive workup and empiric antibiotic therapy.

Signs and Symptoms of Pseudosepsis and Recognition:

Fever, chills, leukocytosis with a left shift, increased cardiac output, and ↓ peripheral vascular resistance with or without hypotension. One should differentiate these clinical findings resulting from true sepsis (see *Table 10.1).*

Table 10.1 *Clinical differentiation of sepsis and pseudo-sepsis.*

Pseudo sepsis	**Sepsis**
No bacteremia	Bacteremia from thoracic, GI, GU, pelvic, and IV source
102 ℉	102 ℉ / or more
Tachycardia	Hypothermia
Respiratory alkalosis	Mental status changes
Hypotension	Hypotension
No definite source of infection	Identifiable infectious / process/source
(--) blood culture	Positive buffy coat smear or (+) blood cultre
↑CO and↓ Peripheral vascular resistance	LV dilatation

CO = cardiac output, GI = gastrointestinal, GU = genitourinary, IV = intravenous, LV = left ventricle, (--) = negative, (+) = positive.

Diagnostic Investigations:

i) Blood cultures:

The negative blood culture results are mandatory to rule out pseudosepsis.

The cultures might suggest the underlying disease process:

Bacteroides fragilis → colonic or pelvic source.

Klebsiella species or Enterococci → frequent in gallbladder or urinary tract infection (UTI) than intra abdominal source.

ii) CBC count:

Leukocytosis with variable degrees of a left shift present in numerous conditions. It is a nonspecific diagnostic finding.

iii) Gram stain & Culture:

A. Perform the following cultures:

1) Urine, including urinalysis if urosepsis is suspected.

2) Drainage site, i.e., chest drain, intrapleural fluid, etc, from suspected sites.

Paracentesis is done for gross ascites. Thoracentesis is performed for pleural effusion.

3) Central IV line: Remove the line and send the tip for a semi-quantitative culture.

IV line sepsis may be diagnosed if the following criteria are met:

a) Blood culture results are positive and demonstrates 15 or more colonies.

b) Catheter tip isolate matches the blood culture isolate.

B. Buffy coat smears (of white cells) from peripheral blood:

The buffy coat smear is stained with gram or acrdine orange. It is best and rapid test, and if it is positive, it shows morphology of the bacteria causing bacteremia. It helps to base empiric antimicrobial therapy.

iv) ECG and cardiac enzymes:

These tests are performed for diagnosis of an asymptomatic myocardial infarction or damage, unexplained fever, leukocytosis, and hypotension. Asymptomatic myocardial infarction is common in the elderly with a recent major surgery, and is frequent in diabetic and uremic conditions.

v) Imaging Studies:

1) Chest radiograph:

It rules out pneumonia / or may differentiate causes of pulmonary infiltrate due to pulmonary emboli, pulmonary hemorrhage, pleural effusion, ARDS, and heart failure. Acute respiratory distress syndrome (ARDS) on a chest x-ray suggests extrthoracic source of infection.

2) Ultrasound:

Abdomen: Suboptimal for the detection of abscesses or perforated hollow organs.

It is useful only if the biliary tract obstruction is suspected.

3) CT scan or MRI:

Abdomen: These are performed if intra-abdominal (non biliary) source of infection is suspected and delineates intrarenal and extrarenal pathology.

4) Gallium or indium scans:

These have no place in the initial workup of acutely ill septic patients.

vi) Invasive procedures for diagnosis:

a) Swan-Ganz catheter:

Swan-Ganz hemodynamic parameters re not to be used to diagnose sepsis.

1) Most septics have ↑ cardiac output and ↓ peripheral vascular resistance but converse is not true, i.e., cannot rule out sepsis (if normal or ↓ CO and ↑ or normal SVR). In Pseudosepsis Swan-Ganz readings are compatible with sepsis of non- IV, abdominal, or genitourinary (GU) source.

2) Swan-Ganz catheter data is used only to manage the fluid status. It may also assess left ventricular (LV) dysfunction in patients with acute myocardial infarction.

b) Biopsy and Histological findings:

There are no specific findings caused by sepsis in various organs.

10.5.3 Antimicrobial Therapy of Sepsis

It provides a coverage for the resident flora of the organ presumed to be the source of the sepsis.

Empiric regimens:

These are given until tissue culture and sensitivity tests are available.

No one drug/regimen is superior to another.

Alternative agents may be used alone or in a combination.

The following recommendations are only the general guidelines.

i) Monotherapy: It is a single drug treatment with one of the following:

Imipenem, meropenem, cefoperazone, ampicillin / sulbactam, and piperacillin/tazobactam.

ii) Combination Therapy: Either two or more drugs may be used in a combination treatment:

Clindamycin or metronidazole plus either levofloxacin, aztreonam, trimethoprim/sulfamethoxazole (TMP-SMZ), or an aminoglycoside.

1) Treatment of IV line sepsis:

Empiric therapy:

A. Infections due to methicillin-resistant Staphylococcus aureus (MRSA) is infrequent, so do not use vancomycin empirically for IV-line infections.

B. If coagulase-negative staphylococcus (Staphylococcus epidermidis) is recovered from the blood:

a) Treatment requires removal of the central line, but no vancomycin therapy as coagulase-negative staphylococcus is a low-virulent organism.

b) If the central-line cannot be removed: Use empiric suppressive vancomycin therapy, but minimize vancomycin use to prevent the emergence of Enterococcus faecium (a vancomycin-resistant Enterococcus (VRE).

i) Monotherapy:

Imipenem, meropenem, cefoperazone, or cefepime.

ii) Combination therapy:

Anti-staphylococcal penicillin, e.g., 1. nafcillin or linezolid plus 2. aztreonam, plus 3. aminoglycoside or a quinolone.

2) Biliary tract infections:

Empiric therapy:

The common biliary tract pathogens are Escherichia coli, Klebsiella, or Enterococcus faecalis.

Usually coverage is not needed for staphylococci and anaerobes, except in diabetics with emphysematous cholecystitis in which the infection is caused by anaerobes and / or Clostridium perfringens.

Monotherapy:

Imipenem, meropenem, piperacillin, or cefoperazone.

3) Intra-abdominal / pelvic infections:

Empiric therapy:

The lower abdomen/pelvic pathogens are aerobic gram-neg Coliform bacilli and Bacteroides fragilis.

The antibiotic coverage is not needed for enterococci as these are permissive/opportunistic pathogens. Potent anti-Bacteroids fragilis and aerobic gram-negative bacillary coverage is essential, in addition to surgical drainage or repair of intra-abdominal viscera.

i) Monotherapy:

Imipenem, meropenem, piperacillin/tazobactam, or ampicillin/sulbactam.

ii) Combination therapy:

Clindamycin or metronidazole plus either of the following drugs:

Aminoglycoside, aztreonam, or levofloxacin.

4) Urosepsis:

Empiric therapy:

The primary pathogens of urosepsis are gram-negative aerobic bacilli, e.g., Coliforms or Enterococcus faecalis (not E. faecium, or VRE).

Rrare uropathogens such as Pseudomonas aeruginosa, Enterobacter, and Serratia are associated with urological instrumentation.

Therapy is determined by the causative organisms as mentioned below:

a) Aerobic gram-negative bacilli infection:

Monotherapy: Aztreonam, levofloxacin, 3rd or 4th generation cephalosporins, or aminoglycoside.

b) Enterococci (E. faecalis) infection:

Monotherapy: Ampicillin or vancomycin (in penicillin-allergic patient).

c) Urosepsis due to unknown pathogenic organisms:

i) Monotherapy: Piperacillin, imipenem, meropenem, levofloxacin, and aztreonam.

ii) Combination therapy: Aminoglycoside plus ampicillin.

5) Empiric therapy for other causes of sepsis:

a) Infection of Prosthetic devices or Acute bacterial endocarditis:

Infection is usually due to Staphylococcus aureus.

The antibiotic of choice is nafcillin or / anti-staphylococcal cephalosporin or / carbapenem or / linezolid or / clindamycin in combination with or without rifampin.

b) Pneumococcal or meningococcal sepsis:

The antibiotic of choice is penicillin G with a beta-lactam.

If meningococcal meningitis is associated with sepsis, the selected antibiotic should penetrate CSF.

6) Sepsis of unknown origin:

Common sources of sepsis: Distal gastrointestinal (GI) tract, GU tract / pelvis / IV-line site.

Organisms to be covered from GI/GU tract and pelvis:

Aerobic gram-negative bacilli (Coliforms), B. fragilis, and Enterococci (E. faecalis, not VRE).

i) Empiric monotherapy:

Meropenem, imipenem, cefoperazone, piperacillin/tazobactam, and sulbactam/ampicillin.

ii) Empiric combination therapy:

(1) Levofloxacin plus either clindamycin or metronidazole / or

(2) Aztreonam plus either clindamycin or metronidazole / or

(3) Cefepime plus either clindamycin or metronidazole / or

(4) Aminoglycoside plus either clindamycin or metronidazole.

10.5.4 Antimicrobial Agents for Treatment of Sepsis

1. Imipenem (Primaxin):

Indicated for multi-organism infections if other drugs do not provide coverage or contraindicated.

Pediatric < 12 years: Not established, suggest 15 mg/kg/dose IV q. 6 h.

Pediatric > 12 years and adult dose: 1 g IV q. 6 h.

Adjust dose in renal insufficiency.

Generally avoid use in children < 12 years; avoid use in those with CNS disorders/seizures.

2. Meropenem (Merrem):

Semisynthetic carbapenem antibiotic that inhibits bacterial cell wall synthesis.

Pediatric < 10 years: Not established, suggest 15 mg/kg/dose IV q. 8 h.

Pediatric > 10 years and adult dose: 1 g IV q. 8 h.

Adjust dose in renal impairment. If pseudomembranous colitis and thrombocytopenia occurs, discontinue the medication immediately.

3. Cefoperazone (Cefobid):

Beta-lactam antibiotic that inhibits bacterial cell wall synthesis.

It is a third-generation cephalosporin with antipseudomonal and antistaphylococcal activity. It is only cephalosporin with anti-enterococcal (E. faecalis) activity.

Active against Staphylococcus aureus (MRSA), aerobic gram-negative bacilli, E. faecalis, and Bacteroides fragilis.

Pediatric < 10 years: Not established, suggest 30 mg/kg/dose IV q. 12 hours.

Pediatric > 10 years and adult dose: 2 g IV q. 12 hours.

May increase in prothrombin time or INR; may need prophylactic administration of Vit K 10 mg IM q. 1 week to all ill patients receiving any beta-lactam antibiotic.

4. Levofloxacin:

It is a quinolone and exerts bactericidal effect by interfering with DNA gyrase in bacterial cells. It is highly active against gram-negative and gram-positive organisms.

Pediatric < 10 years: Not established, suggest 7.5 mg/kg/dose IV q. 24 hours.

Pediatric > 10 years and adults: 500 mg IV q. 24 hours.

Superinfections may occur with a prolonged or repeated therapy.

5. Moxifloxacin (Avelox):

It inhibits A-subunits of DNA gyrase, and inhibits bacterial DNA replication and transcription.

Pediatric < 18 years: Usually not recommended.

Pediatric > 18 years and adult: 400 mg PO/IV q. daily.

Contraindicated in documented hypersensitivity for the drug, and if the patient has known Q-T prolongation, administration concurrently with drugs that cause Q-T prolongation is not indicated. In a prolonged therapy, periodically evaluate renal, hepatic, and hematopoietic systems. Superinfections may occur with a prolonged or repeated antibiotic therapy. Fluoroquinolones may induce seizures, tendinitis or tendon rupture.

6. Piperacillin/tazobactam (Zosyn):

It is a semi synthetic extended-spectrum penicillin. It inhibits bacterial cell wall synthesis binding to specific penicillin binding proteins (PBPs), like most of the anti-pseudomonal penicillins. Tazobactam increases piperacillin activity against Staphylococcus aureus, Klebsiella, Enterobacter, and Serratia species, and it has greatest increase in activity against B. fragilis. Tazobactam does not increase anti-Pseudomonas aeruginosa activity of piperacillin.

Zosyn is indicated in intra-abdominal and pelvic infections due to aerobic Coliform gram-negative bacilli and B. fragilis. Enterococci are permissive and opportunistic pathogens and do not require special coverage.

Pediatric dose < 10 years: Not established, suggest 65 mg/kg/IV q. 8 hours.

Pediatric > 10 years and adult dose: 4.5 g IV q. 8 h (piperacillin 4 g/tazobactam 0.5 g).

May cause renal impairment; may interfere with platelet function.

7. Sulbactam/ampicillin (Unasyn):

A combination beta-lactam and beta-lactamase inhibitor. It suppresses bacterial cell wall synthesis by binding to specific PBPs. Sulbactam increases effectiveness against beta-lactamase producing microorganisms and increases the activity of ampicillin against S. aureus, Klebsiella, Enterobacter, and Serratia species; I has greatest increase in activity against B. fragilis.

Pediatric < 10 years: Not established, suggest 45 mg/kg IV q. 6 hours.

Pediatric > 10 years and adult: 3 g IV q. 6 h (ampicillin 2 g / sulbactam 1 g).

8. Metronidazole (Flagyl):

Binds to ribosomes in bacterial cells. It is highly active against most anaerobes including B fragilis, but is not active against aerobic gram-positive or gram-negative organisms. In intra-abdominal or pelvic infections, always use this drug in combination with an antibiotic active against aerobic gram-negative bacilli. Pediatric < 10 years: Not established, suggest 15-30 mg/kg IV in divided doses.

Pediatric > 10 years and adult: 1 g IV q. 24 h.

9. Clindamycin (Cleocin):

Exerts a bacteriostatic effect and interferes with bacterial metabolism at the ribosomal level. It is highly active against all staphylococci except MRSA.

It has no anti-enterococcal activity, excellent against B. fragilis, but is not active against aerobic gram-negative bacilli. In mixed intra-abdominal or pelvic infections, always use in combination therapy with an antibiotic active against aerobic gram-negative bacilli.

Pediatric: < 10 years: Not established, suggest 8-10 mg/kg IV q. 8 hours.

Pediatric: > 10 years and adult: 600 mg IV q. 8 h.

10. Aztreonam (Azactam):

A monobactam that inhibits cell wall synthesis during bacterial growth.

It is active against most gram-negative bacilli, but is not active against B. fragilis or enterococci. Adjust dose in renal insufficiency.

Children: 90-120 mg/kg/day divided IV/IM q. 6-8 h.

Adult: 2 gm IV q. 8 h.

11. Ertapenem (Invanz):

Ertapenem binds to penicillin binding proteins and inhibits bacterial cell wall synthesis. Stable against degradation by various beta-lactamases, penicillinases, cephalosporinases, and it has extended spectrum against beta-lactamases, but it is hydrolyzed by metallo-beta-lactamases. Exercise caution if hypersensitivity reactions to penicillin, cephalosporins, other beta lactams, or other allergens occur.

Children: (> 3 months to 12 years): 15 mg/kg IV q. 12 h; not to exceed 1 gm /day..

Children (> 12 years) and adults: 1 gm q. daily for 14 days (IV) and 7 days (IM).

Decreased dose in renal failure: Creatinine clearance (CrCl) < 30 mL / min /1.73 m^2: 500 mg IV q. d.

10.6 Antimicrobial Prophylaxis

Used in pre / perioperative care 1) to reduce the incidence of postoperative wound infection and 2) to prevent infective endocarditis.

10.6.1 Prophylaxis of Wound Infections

i) General selection of an antibiotic:

An appropriate prophylactic antibiotic should be:

a) Effective against microorganisms anticipated to cause postoperative infection.

b) Achieve adequate local tissue levels and cause minimal side effects.

c) Not expensive and not likely to select virulent organisms.

d) Microbial context of the wound and the hospital environment may influence the choice.

First-generation cephalosporin (cefazolin) is an adequate prophylaxis for the majority of procedures as staphylococcus species may cause infection in the majority of procedures that do not violate mucosa or a hollow viscus.

For alimentary, hepatobiliary, and genitourinary tract procedures, the coverage should be influenced by site-specific flora (i.e., gram-negative and anaerobic microorganisms). In these cases cefotetan or cefoxitin is a suitable agent.

ii) For patients allergic to cephalosporins:

Staphylococcus coverage: Vancomycin is an alternative drug.

Gram-negative organism's coverage: Aminoglycoside may be used.

Anaerobic organism's coverage: Metronidazole or clindamycin may be used.

Aztreonam can also be combined with clindamycin but not with metronidazole in the above setting.

iii) Administration of an antibiotic:

The timing of an administration is critical, ideally within 30 minutes, and certainly within two hours of the time of incision. One should always give first dose before the skin incision is performed.

For longer procedures, readminister the drug at intervals of 1 or 2 times the half-life of the drug (using the same dose). For gross contaminated wounds, due to severe trauma require a repeated dosage.

10.6.2 Antimicrobial Prophylaxis of Cardiac Procedures

For patients undergoing cardiac procedures, the following guidelines may be followed for using antimicrobials as prophylaxis.

Prophylaxis against S. aureus and S. epidermidis is indicated.

There is no superiority of any particular antibiotic regimen, and all are equally effective (i.e., penicillin, 1st and 2nd generation cephalosporins, or vancomycin).

Usually cefazolin is an ideal agent, but consider institutional choice due to high rates of methicillin-resistant S. aureus or S. epidermidis.

Cardiopulmonary bypass (CPB) reduces the elimination of drugs, and additional operating room (OR) doses are not necessary.

Most centers continue therapy for 24 hours, or until invasive lines and chest tubes are removed.

♥ Note:

1). On meta-analysis, second-generation cephalosporins, cefamandole, and cefuroxime performed better than cefazolin, with an approximate one and one-half-fold reduction in wound infection rate, in cardiothoracic prophylaxis.

2). Prophylaxis > 48 hours was not associated with improved infectious outcomes.

10.6.3 Antibiotic Prophylaxis of Infective (Bacterial) Endocarditis (IE or BE)

It is not necessary for most patients, as it might create more harm than good.

Prophylaxis is recommended for high and moderate risk cardiac conditions in the perioperative period in patients undergoing dental and other procedures.

i) High risk cardiac pathology:

a) Prosthetic cardiac valves, including bioprosthetic and homograft valves, and history of prior infective endocarditis.

b) Complex cyanotic congenital heart disease:

Single ventricle states, transposition of the great arteries, and tetralogy of Fallot.

c) Unrepaired or incompletely repaired cyanotic congenital heart disease.

d) Completely repaired congenital heart defect with prosthetic material or device, i.e., during the first 6 months after the procedure.

e) Repaired congenital heart defect with a residual defect at the site of a prosthetic material.

f) Surgically constructed systemic-pulmonary artery shunts or conduits.

g) Cardiac transplant which develops a problem in a heart valve.

ii) Moderate risk cardiac pathology:

a) Acquired valvular dysfunction (e.g., rheumatic heart disease).

b) Hypertrophic cardiomyopathy.

c) Mitral valve prolapse with valvular regurgitation and/or thickened leaflets.

d) Cardiac malformations other than those listed in the high-risk or negligible-risk categories.

iii) Negligible risk cardiac disease/procedure, (BE prophylaxis is not recommended):

a) Isolated secundum atrial septal defect (ASD).

b) Surgical repair of ASD, VSD or PDA (without a residual defect beyond six months).

c) Previous coronary artery bypass graft surgery.

d) Mitral valve prolapse without valvular regurgitation or thickened leaflets.

e) Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators.

f) Previous Kawasaki disease without a valvular dysfunction.

g) Previous rheumatic fever without a valvular dysfunction.

h) Physiologic, functional, or innocent heart murmur.

The presence of non-ejection click even without a murmur may warrant prophylaxis.

10.6.4 Procedures Requiring Endocarditis Prophylaxis

i) Dental Procedures:

a) Dental extractions.

b) Periodontal procedures including surgery, scaling, root planing, probing, and intraligamentary local anesthetic injections.

c) Prophylactic cleaning of teeth or implants, where bleeding is anticipated.

d) Root canal instrumentation or surgery only beyond the apex.

e) Subgingival placement of antibiotic fibers or strips.

f) Dental implant placement and re-implantation of avulsed teeth.

ii) Other Procedures:

a) Tonsillectomy and/or adenoidectomy, and procedures that involve respiratory mucosa.

b) Bronchoscopy with a rigid bronchoscope.

c) Sclerotherapy for esophageal varices and esophageal stricture dilation.

d) Endoscopic retrograde cholangiography with biliary obstruction and biliary tract surgery.

e) Procedures that involve intestinal mucosa, prostate, cystoscopy and urethral dilation.

10.6.5 Procedures Not Requiring Endocarditis Prophylaxis

i) Cardiac catheterization, including balloon angioplasty.

ii) Implanted cardiac pacemakers, implanted defibrillators, and coronary stents.

iii) Incision or biopsy of surgically scrubbed skin, circumcision and endotracheal intubation.

iv) Tympanostomy and tube insertion uninfected urethral catheterization.

v) Bronchoscopy using a flexible bronchoscope with or without biopsy.*

vi) Transesophageal echocardiography* or endoscopy with or without gastrointestinal biopsy.*

(* prophylaxis may be optional for high risk patients).

10.6.6 Prophylactic Antibiotics

Standard general prophylaxis:

Amoxicillin: Children 50 mg/kg, adults 2.0 g PO 1 hour before the procedure.

Ampicillin: It is given if the patient is unable to take oral medications. Children 50 mg/kg IM or IV; adults 2.0 g IM or IV within 30 minutes before the procedure.

If the patient is allergic to penicillin, consider following antibiotics.

i) Clindamycin: Children 20 mg/kg; adults 600 mg PO 1 hour before the procedure or/

ii) Cefadroxil or Cephalexin: Children 50 mg/kg; adults 2 g PO 1 hour before the procedure or/

iii) Azithromycin or Clarithromycin: Children 15 mg/kg; adults 500 mg PO 1 hour before the procedure.

If the patient is allergic to penicillin, and is unable to take oral medicines use one of the following drugs:

i) Clindamycin: Children 20 mg/kg, IV, adults: 600 mg IV within 30 minutes before the procedure or/

ii) Cefazolin: Children 25 mg/kg IM or IV; adults: 1.0 g IV within 30 minutes before the procedure.

The total pediatric dose should not exceed the adult dose. Cephalosporins should not be used in patients with an immediate-type hypersensitivity reaction (i.e., urticaria, angioedema, or anaphylaxis) to penicillins, though some prefer IV prophylaxis for high risk patients, i.e., recurrent endocarditis or prior prosthetic valve endocarditis.