CLINICAL PRACTICE GUIDELINES

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RATIONAL ANTIBIOTIC UTILISATION IN SELECTED PAERDIATRIC CONDITIONS

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in very case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally

Review of Guidelines

This guideline was issued in 2004 and will be reviewed in 2006 or sooner if new evidence becomes available

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GUIDELINES DEVELOPMENT AND OBJECTIVES

Guidelines Development

The work group for the development of these guidelines comprised paediatricians and a pharmacist from various Ministry of Health facilities. These guidelines are based on the findings of health technology assessment on the same topic, as well as a systematic review of current medical literature, taking into consideration local medical practice and local microbiology patterns and trends of antimicrobial resistance. The ranking of evidence is based on a modified version of that suggested by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendations in these guidelines emulates those used by the Scottish Intercollegiate Guidelines Network (SIGN). The draft guidelines were posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. These guidelines have also been presented to the Technical Advisory Committee for Clinical Practice Guidelines and Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

Objectives

The aim of this guideline is to aid doctors in general practice and pediatricians in clinical decision making by providing well-balanced evidence based information on the rational utilisation of antibiotics in selected paediatric conditions.

Clinical Questions

The clinical questions for these guidelines are:

(i) Which are the situations in selected paediatric conditions where antibiotic use should be considered?

(ii) Which are the antibiotics recommended to be used in selected paediatric conditions?

Target Population

These guidelines are applicable to paediatric patients with specific conditions.

Target Group

These guidelines are meant for all health care providers who provide clinical management of children.

General Principles of Antibiotics Administration

1. The choice of antibiotics should be based on the local prevalence of infecting bacterial pathogens and antimicrobial resistance patterns, toxicity of antibiotics, results of clinical trials, and host factors such as degree of severity and ease of administration **[Grade C].**

2. Initial antibiotic therapy should be continued for at least 3-5 days for Febrile Neutropenia and for 2 -3 days in Meningitis, Community Acquired Pneumonia, Sepsis in children and neonates to determine its effectiveness **[Grade C].**

3. The choice of subsequent antibiotics should be guided by clinical response and result of cultures and susceptibility **[Grade C].**

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2. All those who had provided valuable input and feedback on the draft guidelines.

LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

(*Adapted from Catalonian Agency for Health Technology Assessment & Research, [CAHTAR] Spain)*

GRADE OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

(Adapted from Scottish Intercollegiate Guidelines Network [SIGN])

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FEBRILE NEUTROPENIA

1. INTRODUCTION

Febrile neutropenia is a common consequence of anticancer chemotherapy, fever being defined as a single oral temperature of more than or equal to 38.3°C with a neutrophil count of less than 500 cells/mm^3 (Hughes et al, 1997, *level 2*). Cancer patients receiving myelosuppressive chemotherapy develop severe neutropenia and are at a high risk of developing life-threatening infections (Charnas, Luthi & Ruch, 1997, *level 1*; Cometta et al, 1996). Bacterial infections are a common cause of morbidity and mortality in neutropenic cancer patients (Freifeld & Pizzo, 1997, *level 9*), with a microbiologic cause for the febrile episode being demonstrated in approximately 40% cases (Charnas, Luthi & Ruch, 1997, *level 1*). These patients are at risk of endogenous flora, especially aerobic Gram-negative bacteria residing in the gastrointestinal tract and also those pathogens colonizing on normal or damaged mucosa or skin surfaces, like Gram-negative bacilli *(Enterobacteriaceae, Klebsiella pneumoniae*) or Gram-positive cocci (*Staphylococcus aureus, Staphylococcus epidermidis* and *viridans streptococci*) (Charnas, Luthi & Ruch, 1997, *level 1*; Patrick, 1997).

Since febrile neutropenic patients fail to mount a full inflammatory response, and the current diagnostic tests are not sufficiently rapid, sensitive or specific for identifying or excluding the microbial cause of a febrile episode, these patients may have to be treated empirically. The risk of infection increases ten-fold with declining neutrophil counts. It has been shown that with absolute neutrophil counts between 100 and 500/mm^3, infection rates rise from 0.5 to 5 infections per 100 days, while 16 - 20% of patients with neutrophil counts less than 100/mm^3 have bacteremia (Hughes et al, 1997, *level 1*). The prompt institution of empiric antibiotic therapy for febrile neutropenic patients, without waiting 24 to 48 hours for the results of blood cultures, has been shown to dramatically reduce infection-related morbidity and mortality in the cancer population undergoing chemotherapy (Freifeld & Pizzo, 1997, *level 9*). Empiric antibiotic therapy has become a standard of care for the febrile neutropenic patient. Numerous clinical trials have demonstrated that any one of a number of empiric antibiotic regimens may preserve the patient through the critical time of fever and neutropenia, including a variety of antibiotic combinations and more recently potent antibiotic monotherapies (Freifeld & Pizzo, 1997, *level 9*). Consequently, there is universal agreement in the literature that broad spectrum antibiotics should be instituted for all cases of febrile neutropenia because of the significant morbidity and mortality associated with bacterial sepsis in patients with fever and cancer (Freifeld & Pizzo, 1997, *level 9*).

2. RECOMMENDATIONS

i. Empirical broad spectrum antibiotics, covering both gram-positive and gram-negative pathogens, should be commenced for all febrile neutropenic patients **[Grade A]**.The choice of initial empirical antibiotics, however, remains controversial (Ministry of Health Malaysia, 2003, *level 1;*Mustafa et al, 2001, *level 3*; Duzova et al, 2001, *level 3;* Fleischack et al, 2001, *level 2;* Kebudi et al, 2001, *level 3*; Furno et al, 2000, *level 2*; Petrilli et al, 2000, *level 3*).

ii. Monotherapy with third-generation cephalosporins such as Ceftazidime (Ministry of Health Malaysia, 2003, *level 1;*Kebudi et al, 2001, *level 3*) and Ceftriaxone (Ministry of Health Malaysia, 2003, *level 1;*Karthaus et al, 1998, *level 3*) or fourth-generation cephalosporins such as Cefepime (Ministry of Health Malaysia, 2003, *level 1;*Mustafa et al, 2001, *level 3*), or Imipenem (Raad et al, 1998, *level 9*) and Meropenem (Ministry of Health Malaysia, 2003, *level 1;*Duzova et al, 2001, *level 3*) are equally efficacious and safe compared to combination chemotherapy with antipseudomonal beta-lactams and aminoglycosides **[Grade A]**

iii. Instead of monotherapy, combination therapy with a beta-lactam antibiotic and an aminoglycoside can also be initiated, like combinations of Ceftazidime and Amikacin (Ministry of Health Malaysia, 2003, *level 1;* Hughes et al, 1997, *level 2*), Ceftriaxone and Amikacin (Ministry of Health Malaysia, 2003, *level 1;*Charnas, Luthi & Ruch, 1997, *level 1*) and Piperacillin and Amikacin (Ministry of Health Malaysia, 2003, *level 1;*Hughes et al, 1997, *level 2*) **[Grade A] .**

iv. In centers where Methicillin Resistant *Staphylococcal areus*(MRSA) is prevalent, Vancomycin (Ministry of Health Malaysia, 2003, *level 1;* Hughes et al, 1997, *level 2*) may be considered in addition to broad gram-negative coverage with third generation cephalosporins such as Ceftazidime, or fourth-generation cephalosporins such as Cefepime **[Grade C].**
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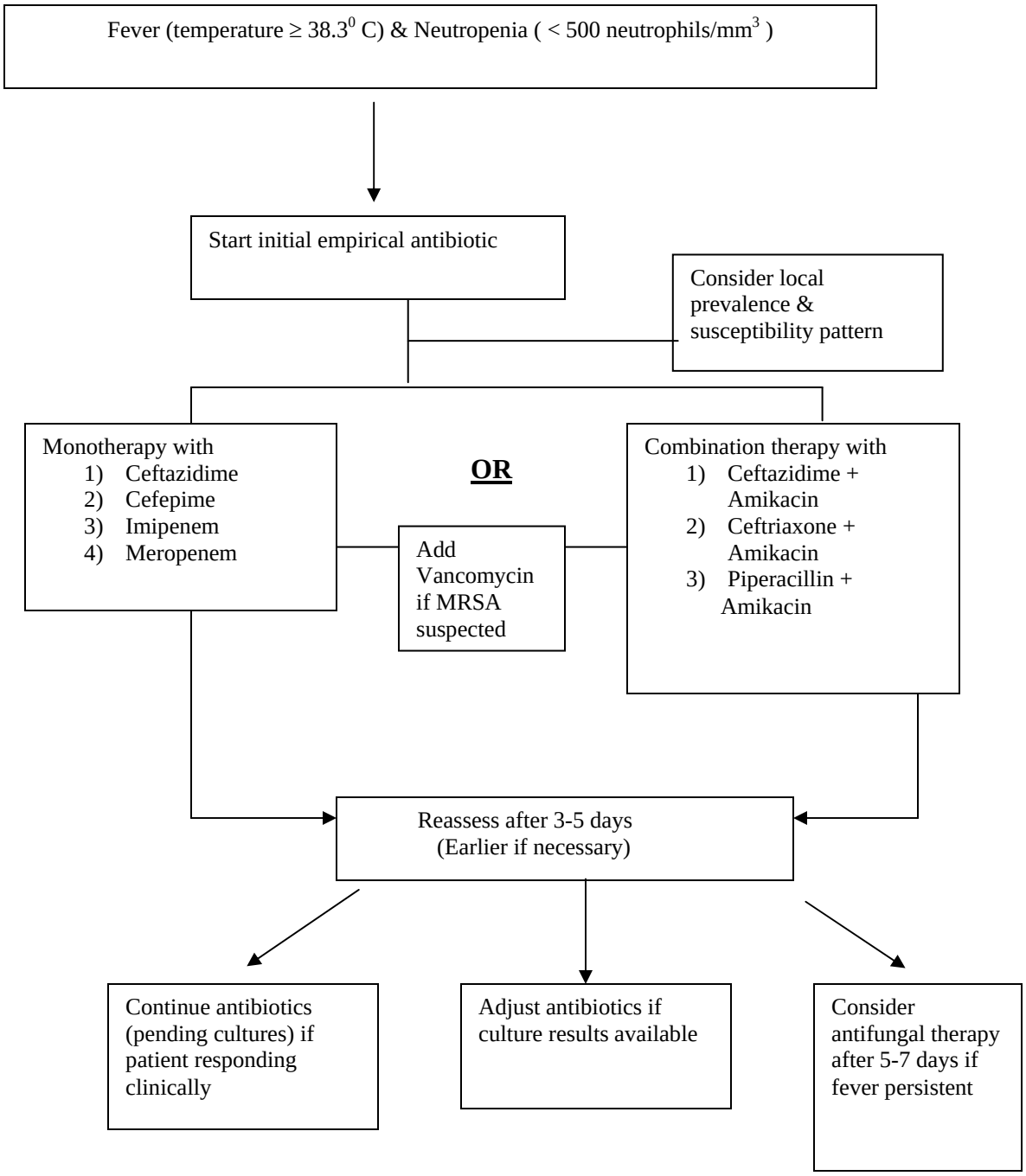
v. Antifungal therapy may be considered after 5-7 days of persistent fever in cancer patients with febrile neutropenia who have received adequate and appropriate antibacterial therapy **[Grade B].**

vi. Routine antiviral therapy at the onset of febrile neutropenia is not recommended **[Grade C].**

ALGORITHM FOR MANAGEMENT OF FEBRILE NEUTROPENIA



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COMMUNITY ACQUIRED PNEUMONIA

1. INTRODUCTION

Community acquired *pneumonia* may be defined as the presence of clinical signs and symptoms of *pneumonia* in a previously healthy child due to an infection acquired outside the hospital (British Thoracic Society, 2002). However, definitive information about causative organisms is seldom available at clinical presentation (McCracken, 2000), and current diagnostic techniques are not sufficiently sensitive to detect all relevant pathogens.

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2. AETIOLOGY

A causative pathogen is identified in 43% - 85% of community acquired pneumonias in childhood (Wubbel et al, 1999, *level 3*; Juven et al, 2000; *level 8*), with a significant proportion (8% - 40%) being mixed infections. Studies have shown prevalence of particular pathogens at specific age groups as indicated below:

2.1 Bacterial Aetiological Agents

Streptococcus pneumoniae while being the most common bacterial cause of pneumonia in children under 2 years (Drummond et al, 2000, *level 8*), remains an important organism in the aetiology of community acquired pneumonias in children of all ages. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* become more prevalent with increasing age from above 5 years (Heiskanen-Kosma et al, 1998, *level 5;*Wubbel et al, 1999, *level 3*).

2.2 Viral Aetiological Agents

Respiratory *syncytial virus* (RSV) is the commonest cause of lower respiratory infections in infants and younger children (Sonoda et al, 1999, *level 5*; Videla et al, 1998, *level 8*; Hijazi et al, 1997, *level 8*), while other viruses are *Parainfluenza, Influenza, Adenovirus* (Juven et al, 2000, *level 8;*; Chan et al, 1999).

3. CLINICAL ASSESSMENT AND INVESTIGATION

3.1 Clinical Diagnosis

Viral and bacterial pneumonia cannot be distinguished on clinical features alone. However, clinical signs such as tachypnoea (defined by WHO's ARI case management guideline as respiratory rate > 60/min.in infants under 2 months, > 50/min in infants 2 – 12 months and > 40/min for children more than 12 months) is a useful sign, where the severity of the tachypnoea relates to the severity of the illness. In children older than 3 years, pneumonia can occur even in the absence of tachypnoea.

Fever is an important clinical sign. A young child with mild symptoms and low grade temperature is most likely to have a viral infection, whereas, high fever of more than 39°C with a history of rapid onset, with signs and symptoms of respiratory distress is suggestive of pneumonia of bacterial origin.

Wheezing is likely to be associated with viral lower respiratory infection in younger children. However, when wheezing is present in older school-going children associated with fever, headache, arthralgia and cough, *mycoplasma* infection has to be considered. While auscultatory findings are not useful in differentiating viral from bacterial causes, the presence of staphylococcal skin infections or history of contact may point to the probable cause causative agent.

3.2 Laboratory Diagnosis

Laboratory investigations to establish the aetiological agent are not indicated in children with community acquired pneumonias well enough to receive ambulatory treatment. However, in children with pneumonias requiring inpatient treatment, investigations to identify the probable aetiological agents should be carried out:

i. Culture of lung aspirate/pleural fluids, nasopharyngeal secretions and blood sample. Invasive procedures like biopsy or needle aspirate of lung tissues are rarely carried out in children with acute pneumonias. Where significant pleural effusion is present, the pleural fluid is aspirated for culture, direct microscopic examination and antigen detection. Nasopharyngeal bacterial secretions correlate poorly while viral culture is time consuming. Blood culture should be done for any ill child with pneumonia, for which most studies report not more than 10% positive results.

ii. Rapid antigen identification for viral pathogens especially RSV should be carried out for young infants with lower respiratory tract infections.

iii. Serological testing for *Mycoplasma pneumonie*, if available, may be considered to assist in the management of suspected cases.

4. MANAGEMENT

Pneumonia in young children with mild symptoms of lower respiratory infections are likely to be viral in aetiology and hence antibiotics need not be used **[Grade B]**

4.1 Empirical Treatment

Children of all age groups who are toxic, febrile (temperature >39°C) and with respiratory distress (tachypnoea or difficulty in breathing) are most likely to have bacterial pneumonias that warrant empirical antibiotic therapy.

For ambulatory treatment, oral Amoxicillin is recommended for children aged 5 years or below, and Macrolides for older children and adolescents (Ministry of Health Malaysia, 2003, *level 1;*Grant & Ingram, 2000, *level 9*) **[Grade B]**

For hospitalized patients, Penicillin, Macrolides or Cefuroxime plus Macrolides are recommended (Ministry of Health Malaysia, 2003, *level 1;*Ruskanen & Mertsole, 1999, *level 9*). In ill young patients where *Staphylococcus pneumonia* is suspected, intravenous Cloxacillin or Flucloxacillin should be added (Ministry of Health Malaysia, 2003, *level 1;* Straus et al, 1998, *level 1*) **[Grade A]**

4.2 Specific Treatment

Specific therapy can be instituted if the causative organism is identified by culture or antigen detection.

a) Pneumonia due to *Pneumococcus, Group A Streptococcus, Haemophilus influenzae b*

- Amoxycillin-Clavulanate , Amoxycillin, Penicillin G or Cefuroxime (Ministry of Health Malaysia, 2003, *level 1;* Olivier, 2000, *level 9;* Wubbel et al, 1999, *level 1*; Grimwood et al, 1997, *level 9*) **[Grade B]**

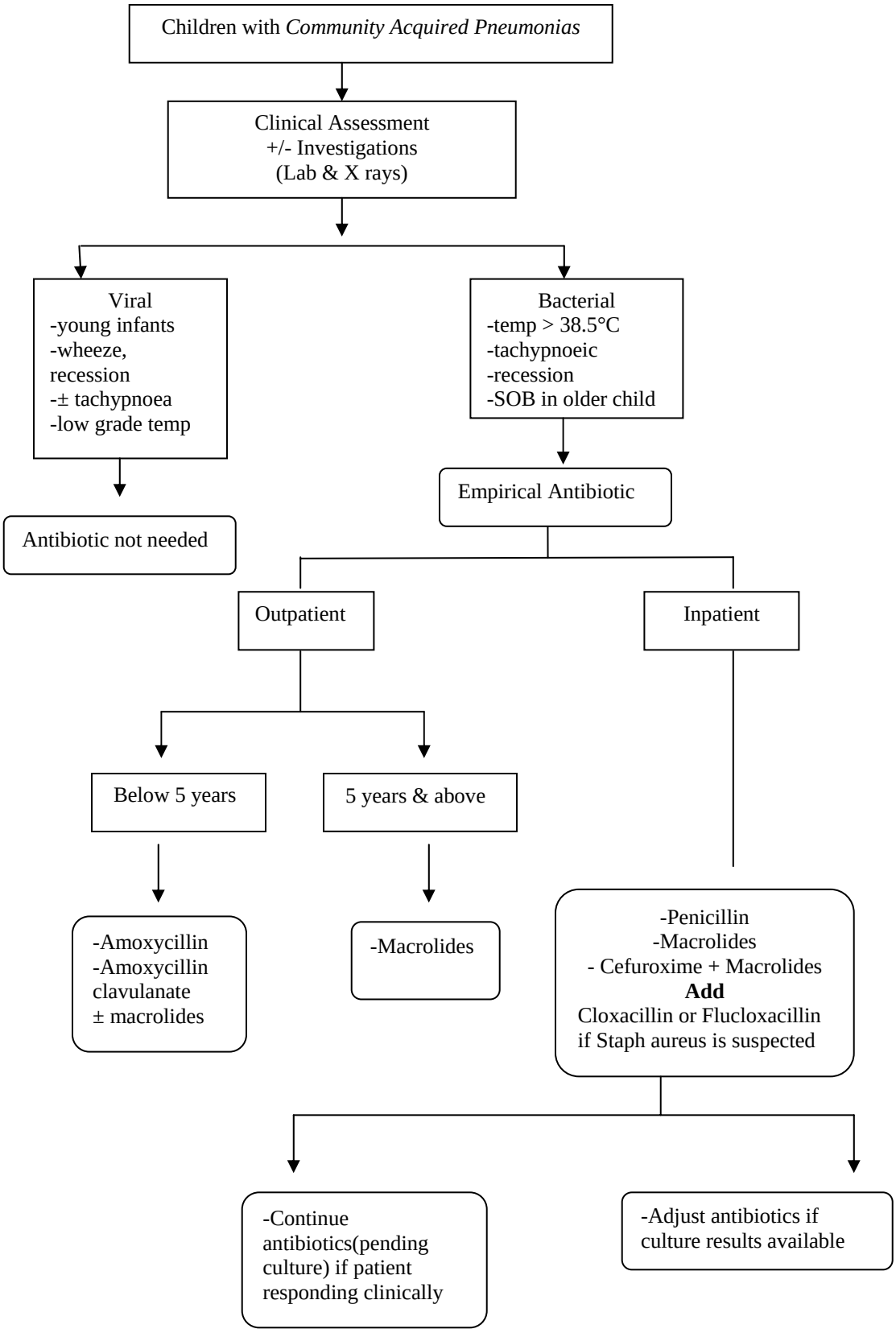
b) Pneumonia due to *penicillin resistant Streptococcus pneumoniae*

- No significant difference in response to conventional antibiotic regimes (Ministry of Health Malaysia, 2003, *level 1;* Tan et al, 1998, *level 8*)

c) *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*

- Macrolides is recommended as empirical antimicrobial treatment in children 5 years and above. Of the Macrolides, Azithromycin has better eradication of *C. pneumoniae and M .pneumoniae* (Ministry of Health Malaysia, 2003, *level 1;* Harris et al, 1998, *level 1*). Macrolides is considered since *C pneumoniae* is an important cause of community acquired pneumonia in school children (Ministry of Health Malaysia, 2003, *level 1;* Heiskanan–Kosma et al, 1999, *level 8*) **[Grade B]**

ALGORITHM MANAGEMENT OF *COMMUNITY ACQUIRED PNEUMONIAS*



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BACTERIAL MENINGITIS

1. INTRODUCTION

Bacterial meningitis is defined as an inflammation of the pia – arachnoid meninges and the fluid residing in the space that it encloses. The infective agent upon entry will extend to all the sub-arachnoid space, which is continuous around the brain, spinal cord and optic nerves. The ventricular fluid becomes infected as well.

Aseptic meningitis refers to meningitis with CSF pleocytosis but an aetiological agent is not apparent on CSF gram stain and bacterial culture. Clinicians who assess children with aseptic meningitis recognize that the majority of cases are caused by viruses but are often faced with having to exclude partially treated bacterial meningitis in children who had been on oral antibiotics.

1.1 Bacterial meningitis

Bacterial meningitis in children between 2 months to 12 years of age in Malaysia is usually due to *Haemophilus influenza type B Streptococcus pneumoniae* or *Neisseria meningitides* (Limcangco et al, 2000, *level 8;* Uduman et al, 2000, *level 8*; Lee, 1998, *level 8*; Hussein et al, 1998, *level 8*; Almuneef et al, 1998, *level 8*) If there are alterations of host defense mechanisms there is an increased risk of meningitis from less common pathogens such as *Pseudomonas aeroginosa, Staphylococcus aureus, Staphylococcus epidermidis, Salmonella* and *Listeria monocytogenes*.

2. EFFECTIVENESS OF ANTIBIOTIC USE

2.1 *Haemophilus Influenza type b* Meningitis

Local data from the 1970's through mid 1990's have revealed *Haemophilus influenza type b* as the leading pathogen in childhood bacterial meningitis (Ministry of Health Malaysia, 2003, *level 1;* Hussein et al, 1998; *level 8;* Choo et al, 1990; *level 8*). Antibiotics like Cefotaxime, Ceftriaxone, Ampicillin and Chloramphenicol all cross the blood brain barrier during acute inflammation in concentrations adequate to render them effective.

Recent reviews from Taiwan (Ma et al, 2000; *level 7*), USA (Dawson et al 1999, l*evel 7*), Canada (Gold, 1999, *level 7*), Greece (Syriopoulou et al, 2000, *level 7*) and Italy (Principi, 2000, *level 7*) have reported a marked decline in the incidence of *Haemophilus influenza* meningitis following the success of the conjugate HIB vaccines.

2.2 *Streptococcus pneumoniae* Meningitis

Streptococcus pneumoniae is the leading cause of bacterial meningitis in USA, Canada and several European countries. Historically, penicillin, a cheap and safe antibiotic , has been the treatment of choice. Chloramphenicol monotherapy has been used in the past but treatment failures have been reported (Ministry of Health Malaysia, 2003, *level 1;* Jadavji, 1986, *level 6)*

2.3 Penicillin Resistant *Streptococcus Pneumoniae* Meningitis

The incidence of reported Penicillin resistant *Streptococcus pneumoniae* infections (not exclusive to meningitis alone) from various countries are 1% in Taiwan, 10.2% in Italy, 11% in Sweden, 12.7% in USA, and 13% in Canada in 1998. In Malaysia there has been an increase from 2.4% to 7% in 1978-1988 to 8% in 1995 - 1996 (Ministry of Health Malaysia, 2003, *level 1;* Ma et al, 2000, *level 7*, Principi, 2000, *level 7*; Eriksson et al, 2000, *level 7*; Moshe Arditi et al, 1998, *level 5*; Scheifele et al, 2000, *level 7*).

In response to the increasing trend of penicillin resistant *Streptococcus pneumoniae*, both the American Academy of Paediatrics and the Canadian Paediatric Society have recommended empirical antibiotics for suspected bacterial meningitis, comprising a combination of IV Vancomycin plus either IV Cefotaxime or Ceftriaxone for all children 1 month or more in age with probable or definite meningitis (Ministry of Health Malaysia, 2003, *level 1;* Infectious Diseases and Immunization Committee, Canadian Paediatric Society 2001, *level 4).*

The third generation cephalosporins such as Ceftriaxone and Cefotaxime are the next antibiotic of choice, with approximately 50% penicillin resistant *Streptococcus pneumoniae* being also resistant to both Ceftriaxone and Cefotaxime (Ministry of Health Malaysia, 2003, *level 1;* Infectious Diseases and Immunization Committee, Canadian Paediatric Society, 2001, *level 4*).

New vaccination strategies against pneumococcus are being developed, but are facing difficulties due to the significant variation in the population of isolates. A 23 valent vaccine has been available since the 1980s but provokes less antibody response in children less than 2 years (Ministry of Health Malaysia, 2003, *level 1;* Scheifele, 2000, *level 7).*

2.4 *Neisseria Meningitides* Meningitis

Neisseria meningitides serogroup A, B and C are the causative organisms for meningitis. While *N. meningitides* meningitis is not common in Malaysia, occasionally children may be at risk of exposure from their relatives who have returned after performing the *Haj*. Intravenous Penicillin remains the drug of choice. Chloramphenicol still provides effective treatment for patients who are allergic to Penicillin. In 2000, it was reported that there were 38 cases of serogroup W135 *Neisseria meningitides* in England and Wales, of whom 80% that had died had received serogroup C vaccine previously (Ministry of Health Malaysia, 2003, *level 1;* Bolt et al 2001 *level 8*). This has highlighted the need for continuing epidemiological vigilance. The quadrivalent A, C, Y, W 135 is replacing the previously bivalent vaccine.

3. ADJUVANT DEXAMETHASONE ADMINISTRATION IN BACTERIAL MENINGITIS.

Dexamethasone reduces the inflammatory response in CSF in bacterial meningitis, but also reduces the penetration of antibiotics, especially Vancomycin and Ceftriaxone, into the CSF. A meta-analysis supports the use of Dexamethasone only for *Haemophilus influenza* meningitis whether administered before or after antibiotic treatment (Ministry of Health Malaysia, 2003, *level 1;* McIntyre et al, 1997, *level* 1). While those receiving

Dexamethasone had less hearing deficit episodes, this was of no benefit in reducing the incidences of neurological deficits. A similar finding has been reported for *Streptococcus pneumoniae* meningitis (Moshe et al, 1998, *level 7).* There is no evidence to support Dexamethasone use for *Neisseria* meningitis (Ministry of Health Malaysia, 2003, *level 1;* McIntyre et al, 1997, *level 1*).

4. RECOMMENDATIONS

i Empirical treatment of bacterial meningitis should be a combination of crystalline Penicillin and a third generation cephalosporin **[Grade B]**

ii Definitive therapy and duration of therapy should be guided by susceptibility results of the organism identified **[Grade C]**

iii. Penicillin is recommended for meningitis caused by penicillin-susceptible *Pneumococcus* and *Neisseria meningitides*.[**Grade B]**

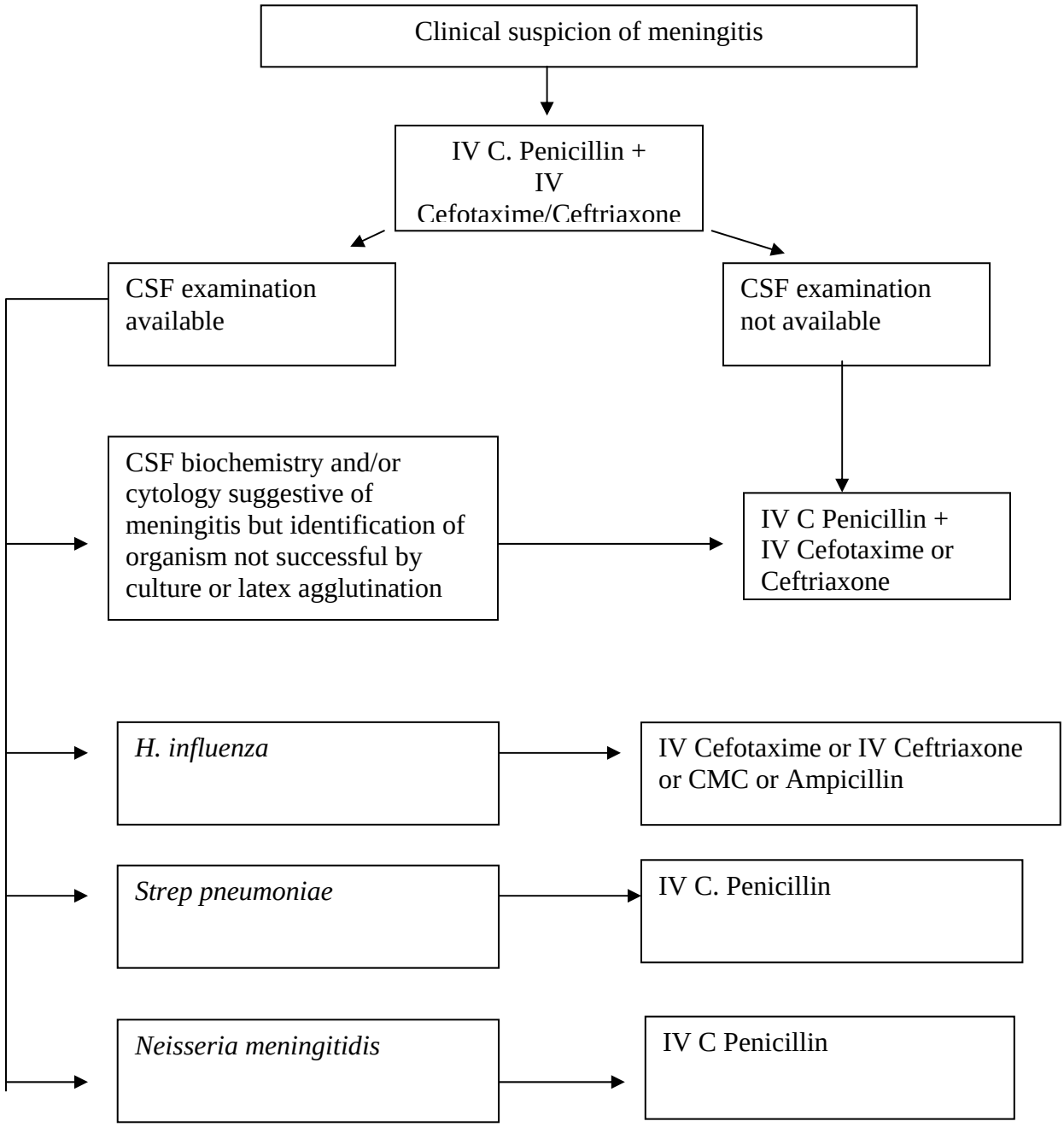
iv.. For penicillin-resistant pneumococcal meningitis, a combination of vancomycin and third-generation cephalosporin such as cefotaxime or ceftriaxone is recommended. **[Grade B]**

v. For Hib meningitis , cefotaxime or ceftriaxone or ampicillin(non-beta lactamase producer) or chloramphenicol is recommended. [**Grade B]**

vi. It is difficult to recommend the routine use of dexamethasone as the causative organism is not known in most cases, and the initial dose of dexamethasone is effective mainly for *Haemophilus influenza* meningitis. **[Grade A]**

Recommended doses of antibiotics are indicated in Appendix 1

ALGORITHM FOR TREATMENT OF BACTERIAL MENINGITIS



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SEPSIS IN CHILDREN

1. INTRODUCTION

Sepsis and septic shock constitute an important cause of morbidity and mortality in critically ill children, with approximately 2% of all hospitalized patients having sepsis. The outcome is affected by the causative agents, with infections due to gram negative rods having a significantly higher mortality (25%) than gram-positive bacteria (10%) (Oda & Matsuo, 2000, *level 7*). In Kuwait it was found that 52% of the 70 deaths in patients were due to nosocomial bacteremia (Jamal & El-Din, 1999, *level 7).*

2. INVESTIGATIONS

Rapid identification of the causative agents in septicaemia is crucial for selecting appropriate antimicrobial agents. It has been suggested that Fluorescent in-situ hybridization (FISH) with ribosomal RNA targeted fluorescently labeled oligonucleotide probes be used for the rapid detection and identification of pathogens, without cultivation and biotyping (Ministry of Health Malaysia, 2003, *level 1;* Kempf & Volkhard, 2000, *level 9*).

3. MANAGEMENT

With respect to management, apart from antibiotic administration, supportive strategies are essential to optimize outcome.

3.1 Community Acquired Bacterial Sepsis in Previously Healthy Children

(i) Sepsis with no obvious source or with respiratory or urinary tract infection, or central nervous system involvement

Though the commonly used antibiotics are cloxacillin/penicillin and a third generation cephalosporin/gentamycin, no evidence could be obtained related to their use **(Grade C).**

(ii) Sepsis with genito-urinary or gastrointestinal tract involvement

The commonly used antibiotics are a third generation cephalosporin or gentamycin with metronidazole for intra-abdominal infections, but again no evidence could be obtained related to their use **(Grade C).**

3.2 Nosocomial Sepsis

There are multiple causative agents that cause nosocomial sepsis in children. It is therefore recommended that the use of antibiotics be dependent on the causative agents.

3.3 Adjuvant therapy

It has been found that Polyclonal Intravenous Immunoglobulin significantly reduces mortality and can be used as adjuvant treatment for sepsis and septic shock, but the number of patients involved in this study was small (Ministry of Health Malaysia, 2003, *level 1,* Alejandria et al, 2001, *level 1*).

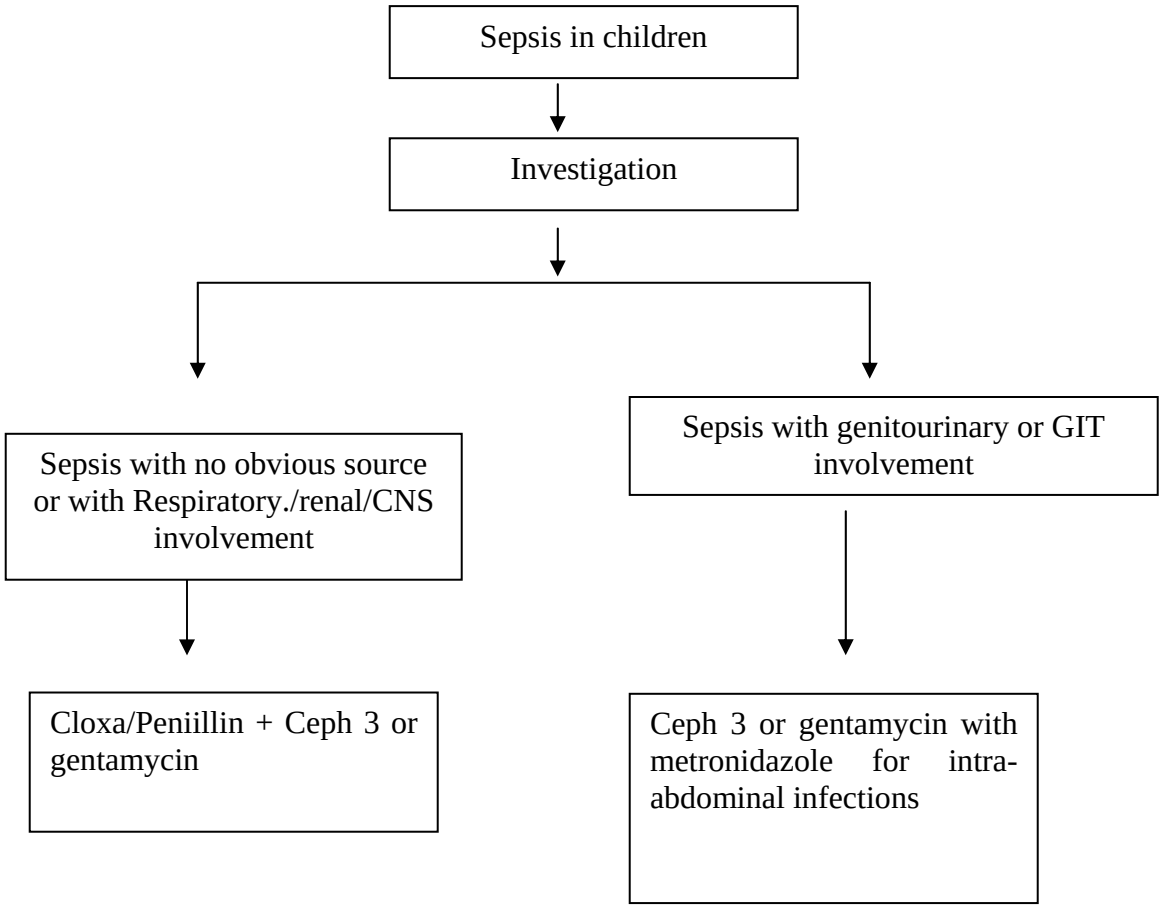
4. RECOMMENDATIONS

i. For sepsis with no obvious source or with respiratory or urinary tract infection, or central nervous system involvement, cloxacillin or penicillin and a third generation cephalosporin or gentamycin are recommended (**Grade C**)

ii. For sepsis with genito-urinary or gastrointestinal tract involvement, a third generation cephalosporin or gentamycin with metronidazole for intra abdominal infections is recommended (**Grade C**)

iii. Polyclonal Intravenous Immunoglobulin can be used as an adjuvant treatment for sepsis and septic shock **(Grade A)**

ALGORITHM FOR TREATMENT OF SEPSIS IN CHILDREN



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NEONATAL SEPSIS

1. INTRODUCTION

Neonates, especially premature babies, are predisposed to infection as they are deficient in host defences and are at risk of acquiring infections from mothers during the perinatal period (Anwer et al, 2000, *level 8*). In order to rationalise the use of antibiotics, continuous surveillance is recommended with emphasis on primary prevention and prevention of cross infection (Musoke, 1997, *level 9*).

2. CLINICAL PRESENTATION

Early clinical presentation of sepsis in newborn includes hypothermia, hyperthermia, poor feeding, poor weight gain, lethargy, hypotonia, pallor, mottled skin, irritability, jaundice, vomiting, ileus, pseudoparalysis, apnea, tachypnoea, cardiovascular signs, hemorrhagic diasthesis and sclerema. Late signs are usually specific to a single organ system. Septicemic shock and death often occur within 12 hours of the first sign of illness (Anwer et al, 2000, *level 8).*

3. DIAGNOSIS AND INVESTIGATIONS

Early diagnosis and therapy initiated on the basis of clinical suspicion is important. Criteria for treatment could be defined by limited predictors or parameters as follows:

1. Maternal fever, chorioamniotis, initial neonatal examination and absolute count. (Escobar, Li & Armstrong , 2000, *level 5*)
2. Abnormal immature to total neutrophil ratio (I: T), followed by an abnormal immature to mature neutrophil (I: M) ratio, thrombocytopenia (Ghosh, Mittal & Jaganathan, 2001, *level 9*).

While blood culture is the gold standard for the diagnosis of sepsis (Aggarwal et al, 2001, *level 9*), rapid identification systems help in the early identification of neonatal bacteraemia (within 24- 30 hours) (Ministry of Health Malaysia, 2003, *level 1;* Pauli et al, 1999, *level 9*).

Other investigations found to be useful are:

- C-reactive protein (CRP) (Ministry of Health Malaysia, 2003, *level 1;* Dollner, Vatten & Austgulen , 2001, *level 9*; Icagasloglu et al, 2002).
- Neutrophil CD64 expression - the addition of interleukin-6 (IL-6) or CRP further enhances the sensitivity and negative predictivity (Ministry of Health Malaysia, 2003, *level 1;* Ng, 2002, *level 9*)
- Interleukins (IL) (Ministry of Health Malaysia, 2003, *level 1;* Santana et al, 2001, *level 7*; Martin, Olander & Norman 2001, *level 9;* Krueger et al, 2001, *level 7;* Gonzalez et al, 2003 *level 8;* Icagasloglu et al, 2002, *level 9*) - diagnostic accuracy is improved by combining CRP and IL-6 (Dollner, Vatten & Austgulen, 2001, *level 9*).

4. MANAGEMENT

The appropriate antibiotics for the treatment of infections in neonates would vary from centre to centre as would the organisms causing the various infections (Chang Chien et al,

2000, *level 9*). Hence, local data on aetiology of sepsis and the sensitivity of the organisms need to be reviewed.

Group B *streptococcus* was the major pathogen of early onset septicemia (Ministry of Health Malaysia, 2003, *level 1;* Berger et al, 1998, *level 9;* Luck et al, 2003, *level 9;* Mehr et al, 2002, *level 9;* Yurdakok, 1998, Ronnestad et al, 1998, *level 9*). Penicillin is the drug of choice for group B *Streptococcus* infections (Ministry of Health Malaysia, 2003, *level 1;* Lin et al, 2000, *level 9;*Aitmhand & Moustaoui, 2000, *level 9*). Other organisms implicated in early onset sepsis are Enterobactericaea and *Listeria*, (Yurdakok,, 1998), *E. coli* (Ministry of Health Malaysia, 2003, *level ;* Kuruvilla et al 1998, *level 9;* Ronnestad et al 1998, *level 9*), Coagulase-negative *Staphylococci* (CoNS), anaerobic bacteria(Ministry of Health Malaysia, 2003, *level 1;* Ronnestad et al, 1998, *level 9*), *Klebsiella* species, *Enterococcus* (Ministry of Health Malaysia, 2003, *level 1;*Anwer et al, 2000, *level 8*).

Empiric therapy for neonates who develop sepsis beyond the first day of life must cover Gram positive organisms like *Staph. aureus* (Ministry of Health Malaysia, 2003, *level 1*; Karunasekara & Pathirana, 1999, *level 8*; Ronnestad et al 1998, *level 9*; Yurdakok, 1998; Anwer et al, 2000, *level 8*), Coagulase negative *staphylococcus* (Ministry of Health Malaysia, 2003, *level 1;* Ho, 2001, *level 9;* Berger et al, 1998, *level 9*; Mehr et al, 2002, *level 9*); *S. epidermidis* (Anwer et al, 2000, *level 8)* For *Staphylococcus*, penicillinase resistant penicillin e.g. Oxacillin, Nafcillin and Methicillin and for resistant strains of *Staphylococcus*, Vancomycin is recommended (Ministry of Health Malaysia, 2003, *level 1;*Yurdakok, 1998, Ronnestad et al, 1998, *level 9*). Enterococci must also be covered (Yurdakok, 1998, Kuruvillla et al, 1998), with Ampicillin and Gentamicin for sensitive strains and Vancomycin for Gentamicin resistant strains (Ministry of Health Malaysia, 2003, *level 1*; Bhat, Paul & Bhat, 1997, *level 9;* Yurdakok, 1998).

Therapy must also cover Gram negative organisms like *Klebsiella* (Karunasekara & Buescher, 1999, Kuruvillla et al, 1998, Ho, 2001), using Imipenem which is a good drug for neonatal Klebsiella pneumonia (Ministry of Health Malaysia, 2003, *level 1;* Oral, Akisu & Kultursay 1998, *level 9;* Roilides & Kyriakides, 2000, *level 9*), and Ciprofloxcin as an alternative in multidrug resistant *Klebsiella pneumonia* (Ministry of Health Malaysia, 2003, *level 1;* Khaneja & Naprawa, 1999, *level 9;* Roilides & Kyriakides, 2000, *level 9*). Other combinations include Cefotaxime or Ceftazidime and Ampicillin (Akindele & Rotilu 1997, *level 9*), Ciprofloxacillin and Gentamicin (Ministry of Health Malaysia, 2003, *level 1;* Khaneja & Naprawa, 1999**,** *level 9*), aminoglycoside and a third generation cephalosporin such as Cefotaxime (Ministry of Health Malaysia, 2003, *level 1*,), and Imipenem or Ciprofloxacin (Ministry of Health Malaysia, 2003, *level 1;* Roilides & Kyriakides, 2000, *level 9*).

For *Pseudomonas. sp.* (Ministry of Health Malaysia, 2003, *level 1;* Karlowicz, Buescher & Surlear, 2000, *level 5*; Yurdakok, 1998) especially in *fulminant* sepsis, treatment with Piperacillin and Azlocillin, Cefoperazone and Ceftazidime were the most active against Pseudomonas (Ministry of Health Malaysia, 2003, *level 1;*Yurdakok, 1998). Treatment for *E. coli* is also important (Ministry of Health Malaysia, 2003, *level 1;* Ronnestad et al, 1998, *level 9*).

There has generally been an increase in the resistance of gram-negative bacteria to Cephalosporins and Gentamicin (Ministry of Health Malaysia, 2003, *level 1;* Joshi et al 2000, *level 9*). Ciprofloxacillin was found to be useful for these resistant bacteria (Ministry of Health Malaysia, 2003, *level 1;* Joshi et al 2000, *level 8;* Van den Vever & Vers teegh, 1998, *level 8;* Yurdakok, 1998)

Imipenam cilastin is effective in premature babies and newborns with serious nosocomial infections even after failure of other broad-spectrum antibiotics (Ministry of Health Malaysia, 2003, *level 1;* Boswald, Dobig & Kandler , 1999, *level 9*)

In a local study, the incidence of nososcomial sepsis was 32.6% of whom 43.3% died, and 80% of the babies had gram negative organisms (Halder et al, 1999, *level 9*)

Fungal:
For treatment of *Candida species* (Ronnestad et al, 1998, *level 9*), amphotericin has been found to be effective in babies at risk for fungal infections and blood culture confirmed sepsis (Ministry of Health Malaysia, 2003, *level 1;* Benjamin, Ross & McKinney, 2000, *level 5*, Rowen & Tate, 1998). Liposomal Amphotericin B has also been found to be effective and safe for the treatment of fungal infections (Ministry of Health Malaysia, 2003, *level 1;* Scarcella & Pasquariello, 1998, *level 9;* Weitkamp & Poets, 1998, *level 9*).

5. RECOMMENDATIONS

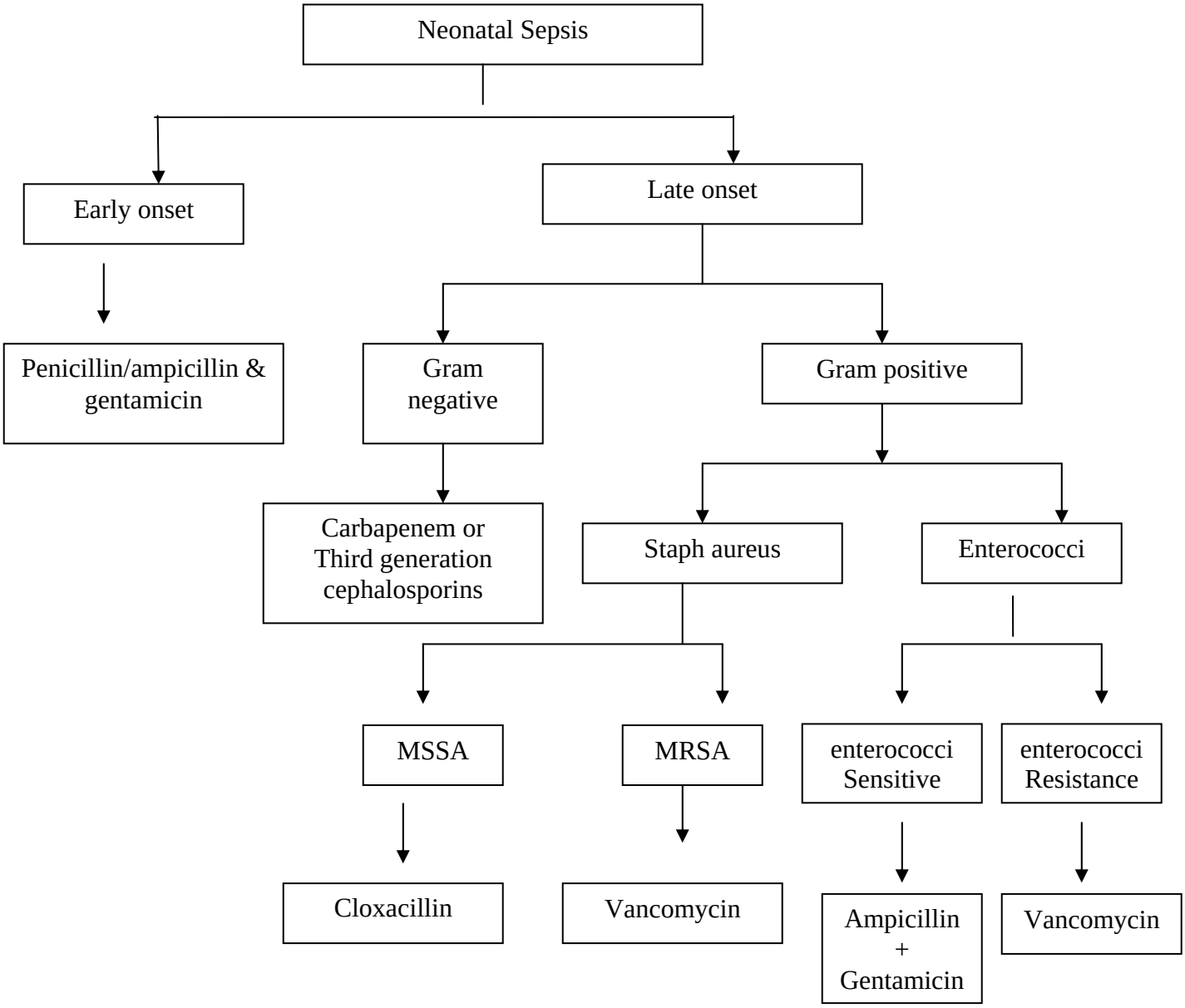
i. For early onset sepsis, penicillin or ampicillin and gentamicin are recommended **[Grade C]**

ii. For late onset gram positive sepsis, cloxacillin is recommended in sensitive strains of *Staph aureus*. Combination of ampicillin and gentamicin is recommended for sensitive enterococcal infections. Vancomycin is recommended for MRSA, Coagulase negative *staphylococcus* (CONS) and resistant enterococal infections. [**Grade C]**

. iii For late-onset gram negative sepsis, carbapenems or third generation cephalosporins are recommended [**Grade C]**

v Amphotericin B is recommended for babies at risk for fungal infections and blood culture confirmed sepsis**(Grade C).**

ALGORITHM FOR TREATMENT OF NEONATAL SEPSIS



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Appendix 1

RECOMMENDED DOSAGE OF ANTIBIOTICS

Antibiotic	Dosage
Amikacin (I/V)	Neonates : 0-4 weeks,<1200g: 7.5 mg/kg/dose q18-24 hours Postnatal age < 7 days : 1200-2000g : 7.5 mg/kg/dose q12 hours >2000g : 7.5-10 mg/kg/dose q12 hours Postnatal age > 7 days : 1200-2000g : 7.5-10 mg/kg/dose q 8-12 hours > 2000g : 10 mg/kg/dose q 8 hours Infants & Children : 15-22.5 mg/kg/day q 8 hours
Amoxicillin (PO)	Infants < 3 months : 20-30 mg/kg/day q 12 hours Infants > 3 months & children : 25-50 mg/kg/day q 8 hours
Amoxycillin clavulanate (PO/IV)	PO : Based on amoxycillin component 30 mg/kg/day q 8 hours (4:1 formulation) 45 mg/kg/day q 12 hours (7:1 formulation) IV : 10-25 mg/kg/dose q 8 hours
Ampicillin (PO/IV)	PO : Children : 50-100 mg/kg/day q 6 hours (max. 2-3 g/day) IV : Neonates : Postnatal age < 7 days : < 2000g : 50 mg/kg/day q 12 hours 100 mg/kg/day q 12 hours (meningitis) > 2000g : 75 mg/kg/day q 8 hours 150 mg/kg/day q 8 hours (meningitis) Postnatal age > 7 days : <1200g : 50 mg/kg/day q 12 hours 100 mg/kg/day q 12 hours (meningitis) 1200-2000g : 75 mg/kg/day q 8 hours 150 mg/kg/day q8 hours(meningitis) > 2000g : 100 mg/kg/day q 6 hours 200 mg/kg/day q 6 hours(meningitis) Infants & Children : 100-200 mg/kg/day q 6 hours 200-400 mg/kg/day q 6 hours(meningitis)(max. dose:12g/day)
Azithromycin (PO)	10 mg/kg/day x 3 days
Cefepime (IV)	50 mg/kg/dose q 8 hours (febrile neutropenia)
Cefotaxime(IV)	Neonates: 0-4 weeks : <1200g : 100mg/kg/day q 12 hours Postnatal age < 7 days : 1200-2000g : 100mg/kg/day q12 hours >2000g : 100-150 mg/kg/day q8-12 hours Postnatal age > 7 days : 1200-2000g : 150 mg/kg/day q 8 hours >2000g : 150-200 mg/kg/day q6-8 hours Infants & Children 1 mth-12 years :

Antibiotic	Dosage
	<50kg : 100-200 mg/kg/day q 6-8 hours Meningitis : 200 mg/kg/day q6 hours >50kg : Moderate-severe infection : 1-2 g q 6-8 hours
Ceftazidime(I/V)	Neonates : 0-4 weeks : <1200g : 100mg/kg/day q 12 hours Postnatal age < 7 days : 1200-2000g : 100 mg/kg/day q 12 hours >2000g : 100-150 mg/kg/day q 8-12 hours Postnatal age > 7 days : > 1200g : 150 mg/kg/day q 8 hours Infants & Children 1 mth-12 yrs : 100-150 mg/kg/day q 8 hours (Max. 6g/day) Meningitis : 150 mg/kg/day q 8 hours(max. dose 6g/day)
Ceftriaxone(I/V)	Neonates : Postnatal age < 7 days : 50 mg/kg/day q 24 hours Postnatal age > 7 days : <2000g : 50 mg/kg/day q 24 hours > 2000g : 50-75 mg/kg/day q 24 hours Infants & Children : 50-75 mg/kg/day q 12-24 hours q 12-24 hours Meningitis : 100 mg/kg/day q 12 -24 hours
Cefuroxime(I/V& PO)	I/V : Neonates : 50-100 mg/kg/day q 12 hours Children : 75-150 mg/kg/day q 8 hours (max. 6g/day) PO : 20-30 mg/kg/day bid
Chloramphenicol(I/V)	100 mg/kg/day q 6 hours
Cloxacillin (1/V & PO)	I/V : Neonates < 7 days : < 2000g : 50 mg/kg/day q 12 hours :>2000g : 75 mg/kg/day q 8 hours 8-28 days : < 2000g : 75 mg/kg/day q 8 hours >2000g : 150 mg/kg/day q 6 hours Infants & Children : 150-200 mg/kg/day q 6 hours PO : Infants & Children : 50-100 mg/kg/day q 6 hours
Dexamethasone (IV) for Hib meningitis	0.6 mg/kg/day q 6 hours for 2-4 days OR 0.8 mg/kg/day q 12 hours for 2-4 days
Erythromycin (PO / IV)	PO : EES : 40 mg/kg/day q 8 hours IV : Erythromycin lactobionate 20-40 mg/kg/day q 6 hours
Imipenem (IV)	Neonates : 0-4 weeks,<1200g : 20 mg/kg/dose q18-24 hours <7 days,1200-1500g : 40 mg/kg/day q 12 hrs <7 days , >1500 g : 50 mg/kg/day q 12 hours > 7 days , 1200-1500g : 40 mg/kg/day q 12 hours > 7 days , >1500g : 75 mg/kg/day q 8 hours Children & Infants < 40kg : 15 mg/kg/dose q 6 hours
Meropenem(IV)	Neonates : Postnatal age 0-7 days : 20 mg/kg/dose q 12 hours Postnatal age > 7 days : 1200-2000g : 20 mg/kg/dose q 12 hours >2000g : 20 mg/kg/dose q 8 hours Children > 3 months : 60 mg/kg/day q 8 hours
Metronidazole(IV)	Neonates : <2000g , 0-7 days : 7.5mg/kg/day q 24 hours 8-28 Days : 15mg/kg/day q 12 hours >2000g , 0-7 days : 15 mg/kg/day q 12 hours 8-28 days : 30 mg/kg/day q 12 hours Children : 30 mg/kg/day q 6 hours

Antibiotic	Dosage
Penicillin G (IV)	Neonates:<2000g , 0-7 days : 50,000 u/kg/day q 12 hours Meningitis : 100,000 u/kg/day q 12 hours >2000g , 0-7 days : 75,000 u/kg/day q 8 hours Meningitis : 150,000 u/kg/day q 8 hours <1200g , >7 days : 50,000 u/kg/day q 12 hours Meningitis : 100,000 u/kg/day q 12 hours 1200-2000g : 75,000 u/kg/day q 8 hours >2000g : 100,000 u/kg/day q 6 hours Meningitis : 200,000 u/kg/day q 6 hours Infants & Children : 100,000-250,000 u/kg/day q 4-6 hours Severe infections : 250,000-400,000 u/kg/day q 4-6 hours Severe infections : (max. dose : 24 million u/day)
Piperacillin(IV)	Neonates < 7 days : 150 mg/kg/day q 8 hours >7 days : 200 mg/kg/day q 6 hours Infants & Children : 200-300 mg/kg/day q 4-6 hours (Max. dose:24 g/day)
Vancomycin(IV)	Neonates < 7 days , <1200g : 15 mg/kg/day q 24 hours 1200-2000g : 10-15 mg/kg/dose q 12-18 hours >2000g : 10-15 mg/kg/dose q 8-12 hours >7 days , <1200g : 15 mg/kg/day q 24 hours 1200-2000g : 10-15 mg/kg/dose q 8 hours >2000g : 15-20 mg/kg/dose q 8 hours For meningitis : the larger dose is recommended Infants > 1 month & Children : 40 mg/kg/day q 6-8 hours Meningitis : 60 mg/kg/day q 6 hours

Source :

Nelson JD,Bradley JS :Nelson 's Pocket Book of Pediatric Antimicrobial Therapy,14th ed, 2000
Pediatric Lexi-Drugs Online
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