GUIDELINES DEVELOPMENT AND OBJECTIVES

Guidelines Development

The work group comprised of Paediatricians. These guidelines are based on the best available current evidence as well as a health technology assessment on this issue.

Objectives

The aim of this guideline is to aid general practitioners and paediatricians in clinical decision making by providing well-balanced information on the rational utilisation of antibiotics in common paediatric conditions.

Clinical Questions

The clinical questions for these guidelines are:

(i) What are the antibiotics recommended to be used in common peadiatric conditions?

Target Population

These guidelines is applicable to paediatric patients with specific conditions

Target Group

These guidelines are meant for all health care providers.

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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

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT, (CAHTA) 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

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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/cubic mm (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, they may have to treated empirically. The risk of infection has been said to increase 10-fold with declining neutrophil counts. It has been shown that with absolute neutrophil counts between 100 and 500/cubic mm infection rates rise from 0.5 to 5 infections per 100 days, while 16 - 20% of patients with neutrophil counts less than 100/cubic mm 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

1) 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 (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*).

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

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

4. In centers where MRSA is prevalent, Vancomycin (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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5. The choice of antibiotics should be based on the local prevalence of infecting bacterial pathogens and antimicrobial resistance patterns, antibiotic toxicity, results of clinical trials, and host factors such as degree of severity and ease of administration **[Grade C**].

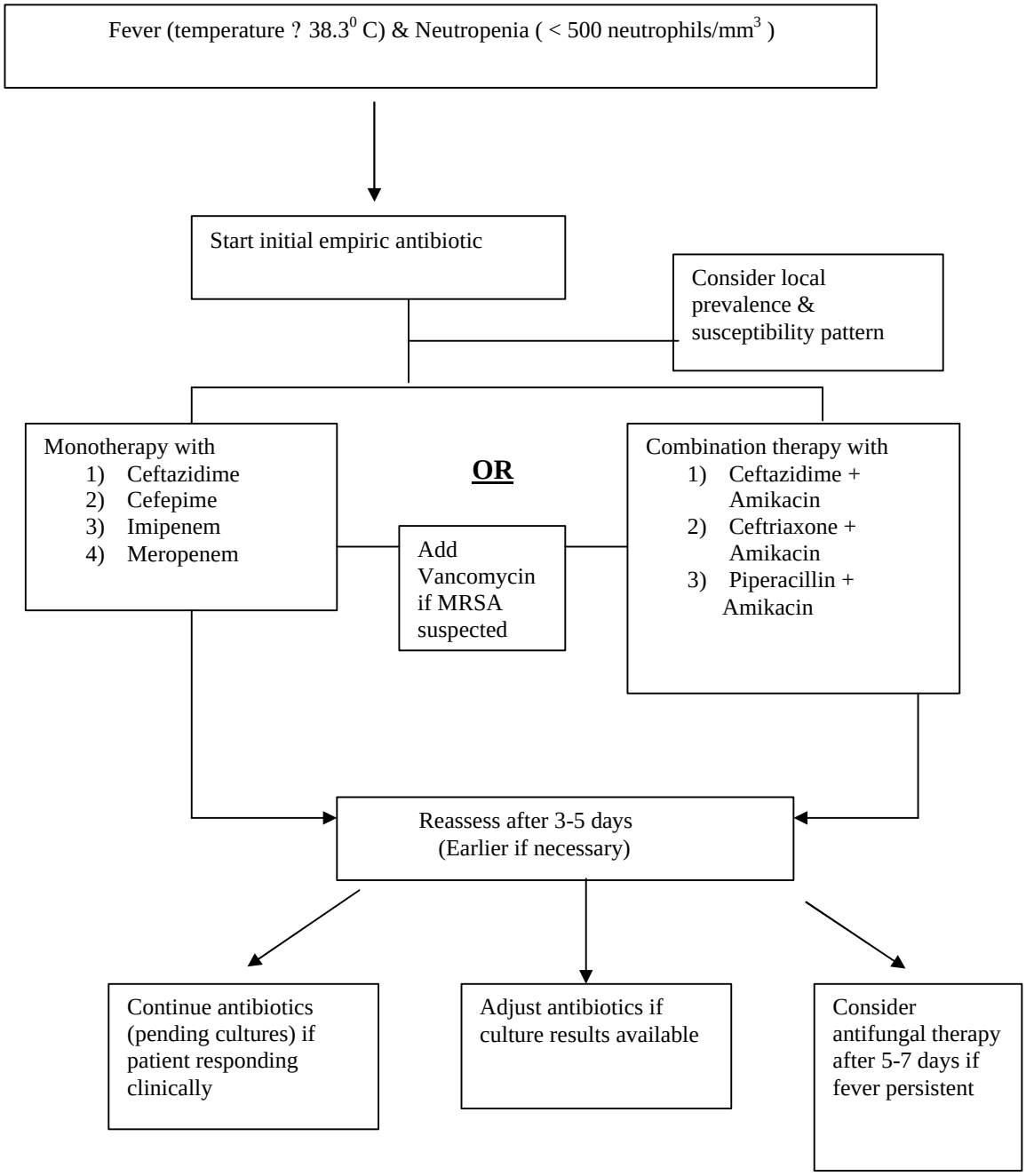
6. Initial antibiotics should be continued for at least 3-5 days to determine efficacy **[Grade C] .**

7. The subsequent choice of antibiotics should be guided by clinical response and results of cultures and susceptibility [**Grade C }.**

8. 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].**

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

ALGORITHM FOR INITIAL 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. 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; Juven et al, 2000), 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), 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; Wubbel et al, 1999).

2.2 Viral Aetiological Agents

Respiratory *syncytial virus* is the commonest cause of lower respiratory infections in infants and younger children (Sonoda et al, 1999; Videla et al, 1998;Hijazi et al,1997), while other viruses are *Parainfluenza, Influenza, Adenovirus* (Juven et al, 2000 ; 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; respiratory rate > 50/min in infants 2 – 12 months and respiratory rate > 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 older 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, *mycoplasmal* 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:

1. 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, except one (Tran et al 1998), report more than 10% positive results.
2. Rapid antigen identification for viral pathogens especially RSV should be done for young infants with lower respiratory tract infections.
3. Complement fixation test is the gold standard for diagnosis of *Mycoplasma pneumoniae* infection although the rapid cold agglutination test, if positive, provides an early guide for specific treatment.

4. MANAGEMENT

The decision to initiate antibiotic therapy and the choice of antibiotic depends on the severity of illness at presentation, age (different pathogens are prevalent at different age groups) and clinical findings associated with particular pathogens.

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 (temp>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 (Grant & Ingram, 2000, *level 9*) **[Grade B]**

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

4.2 Specific Treatment

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

a) Pneumonia due to *Pneumococcus, Streptococcus, Haemophilus*

- Clavalunic acid, Amoxycillin, Penicillin G or Cefuroxime (Wubbel et al, 1999, *level 1*;
Grimwood et al, 1997, *level 9*; Olivier, 2000, *level 9*) **[Grade B]**

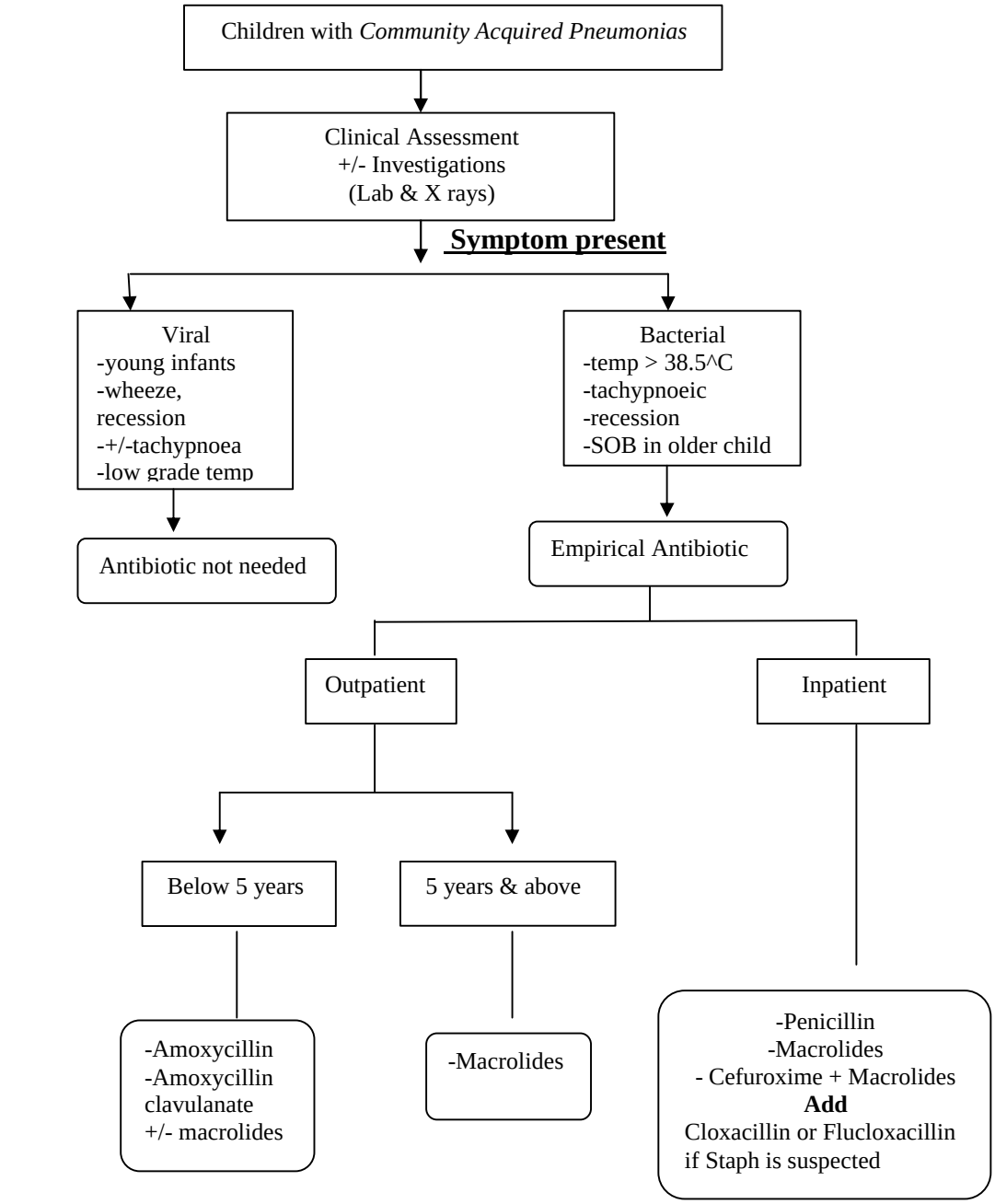
b) Pneumonia due to *penicillin resistant Streptococcus pneumoniae*

- No significant difference in response to conventional antibiotic regimes (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* (Harris et al, 1998, *level 1*). Macrolides is considered as empirical antimicrobial treatment since *C pneumoniae* is an important cause of community acquired *pneumonia* in school children (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 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 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 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; Uduman et al, 2000; Lee, 1998; Hussein et al, 1998; Almuneef et al, 1998) 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. (Lee et al, 1977; *level 8*, Choo et al,1990; *level 8*, Hussein et al,1998; *level 8*). In the treatment of *Haemophilus influenza* meningitis, Cefotaxime, Ceftriaxone, Ampicillin and Chloramphenicol 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 has been proven to be safe and immunogenic.

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 (Jadarji , 1986, *level 6)*

2.3 Penicillin Resistant *Streptococcus Pneumonia*e 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% and 12.7% in Sweden and USA respectively, 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 (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;* Jamal et al, 1987; Jamal, 1997).

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 (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 (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 (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 from 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. (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 (McIntyre et al 1997 *level* 1). While those receiving Dexamethasone had less hearing deficit episodes, there was 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 (McIntyre et al, 1997, *level 1*).

4. RECOMMENDATIONS

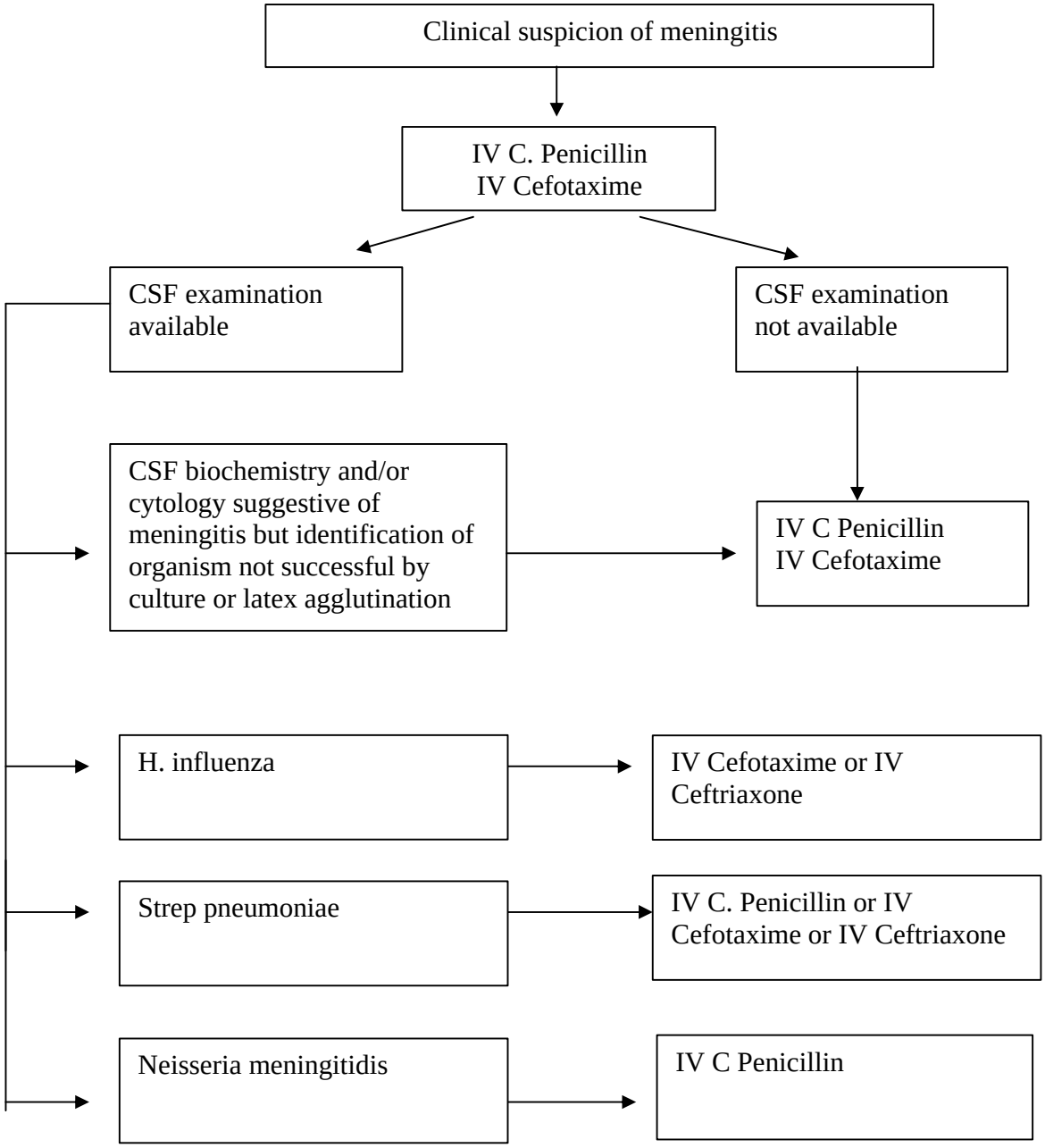
1. Empirical treatment of bacterial meningitis should be a combination of C. Penicillin and a third generation cephalosporin **[Grade B]**

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

3 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. INVESTIGATION

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 (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 Cloxacillin/Vancomycin, a third generation Cephalosporin/Gentamycin and Metronidazole, but no evidence could be obtained related to their use **(Grade C).**

3.2 Nosocomial Sepsis

The pattern of blood stream infections in Paediatric ICU is partly determined by the type of patient treated, and broad- spectrum empiric antibiotics not only risks promoting further antibiotic resistance, but may also not improve patient outcome (Gray, 2001, *level 9*), although appropriate empirical antibiotic treatment was associated with a significant reduction in fatality in patients with bloodstream infection (Leibovici, 1998; *level 5*). Ruling out suspected ventilator-associated pneumonia, and curtailing extended prophylaxis, would assist in reduction in antibiotic use (Fisher, 2000, *level 5*).

There was no significant difference among patients with hospital acquired *Candidaemia* treated with Amphotericin B and Fluconazole (Al Soub & Estinoso, 1997). 60% of gram negative rods were Ampicillin resistant, although sensitive to third generation empirical

antibiotics like Cefotoxime and Gentamicin. (Sadow, 1999; *Level 8*) *Staphylococci* in an intensive care unit was found to be susceptible to Vancomycin, but 97% were resistant to Methicillin and 30% resistant to Mupirocin. However, *S epidermidis* was susceptible to Amoxycillin, Clavalunic acid and Cephalosporin. (Sewezyk, 2000, *Level 8*) A rational policy in antibiotic therapy in intensive care found that its use was decreased by 19% and 22% in 1995 and 1996 respectively. (Blanc, 1999, *level 8*)

3.3 Adjuvant therapy

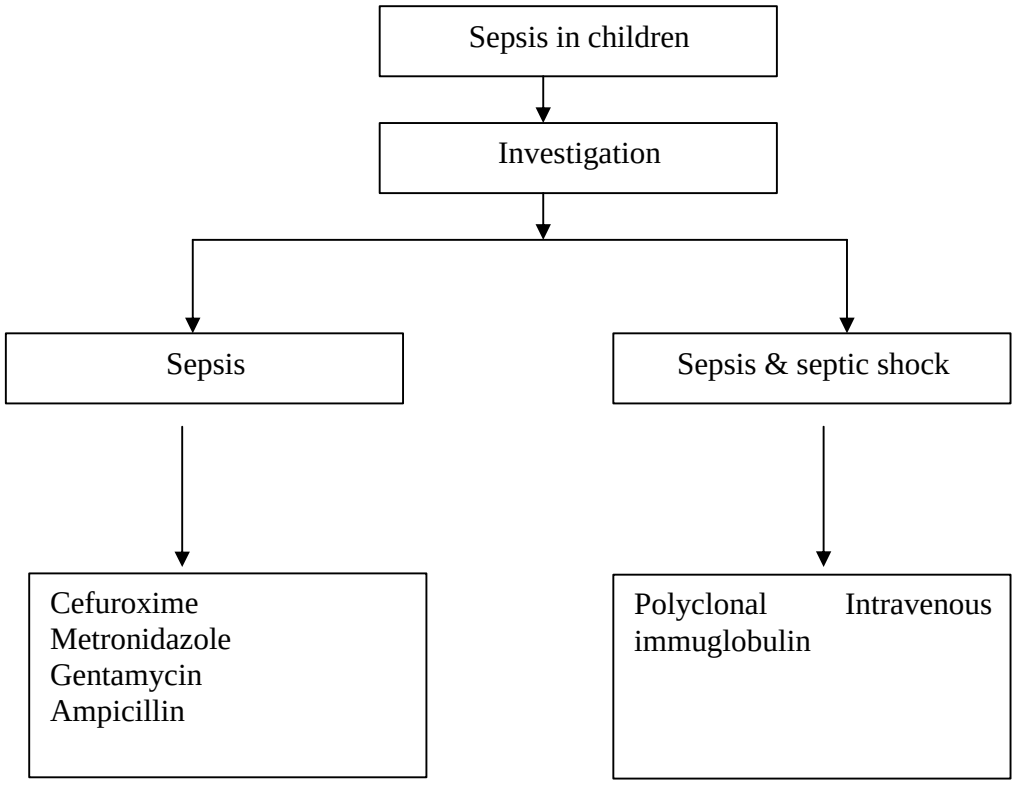
A Cochrane Review found that Polyclonal Intravenous Immunoglobulin significantly reduces mortality and can be used as an adjuvant treatment for sepsis and septic shock. (Alejandria et al, 2001, *level 1*)

4. RECOMMENDATION

(i) Antibiotics like Cefuroxime, Metronidazole, Gentamycin and Ampicillin can be used to treat sepsis in children **[Grade C]**

(ii) 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 defenses 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 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 (Roberton, 2000). 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 on a limited set of predictors or parameters like

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*).

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) (Pauli et al, 1999, *level 9*).
Other investigations found to be useful are:

- C-reactive protein (CRP) (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 (Ng, 2002, *level 9*)
- Interleukins (IL) (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 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 (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 (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*. (Stoll, 2002; Kuruvilla et al 1998, *level 9;* Ronnestad et al 1998, *level 9*), Coagulase-negative *Staphylococci* (CoNS), Anaerobic bacteria(Ronnestad et al, 1998, *level 9*), *Klebsiella* species, *Enterococcus* (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*. (Karunasekara & Pathirana, 1999; Ronnestad et al 1998, *level 9*; Yurdakok, 1998; Anwer et al, 2000, *level 8*); Coagulase negative *staphylococcus* (Jacqueline 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 (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 (Bhat, Paul & Bhat, 1997, *level 9;* Yurdakok, 1998).

Therapy must also cover Gram negative organisms like *Klebsiella* (Karunasekara & Buescher, 1999, Kuruvillla et al, 1998, Jacqueline Ho, 2001), using Imipenem which is a good drug for neonatal Klebsiella pneumonia (Oral, Akisu & Kultursay 1998, *level 9;* Roilides & Kyriakides, 2000, *level 9*), and Ciprofloxcin as an alternative in multidrug resistant *Klebsiella pneumonia* (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 (Khaneja & Naprawa, 1999**,** *level 9*). Aminoglycoside and a 3rd generation cephalosporin such as Cefotaxime (Schwarze & Baver, 2000, *level 9*), and Imipenem or Ciprofloxacin. (Roilides & Kyriakides, 2000, *level 9*).

For *Pseudomonas. sp.* (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. (Yurdakok, 1998). Treatment for *Ecoli is also important.* (Ronnestad et al, 1998, *level 9*).

There has generally been an increase in the resistance of gram-negative bacteria to Cephalosporins and Gentamicin (Joshi et al 2000, *Level 9* & Revathi 2000). Ciprofloxacillin was found to be useful for these resistant bacteria. (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. (Boswald, Dobig & Kandler , 1999, *Level 9*)

In a local study, the incidence of nososcomial sepsis was 32.6% of whom 43.3% died. 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 (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 (Scarcella & Pasquariello, 1998, *level 9;* Weitkamp & Poets, 1998, *level 9*).

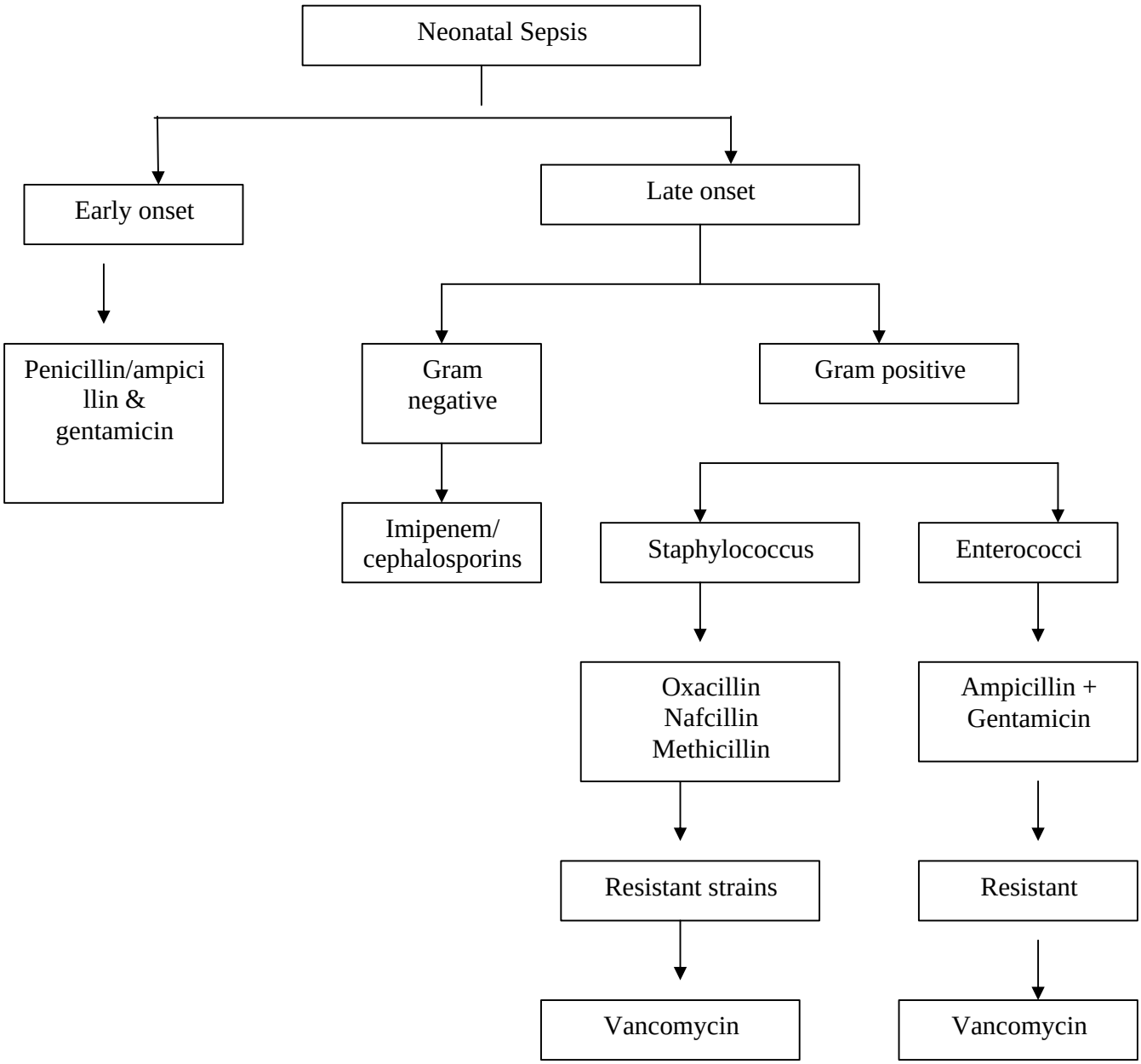
5. RECOMMENDATIONS

1. In early onset sepsis, *group B streptococcus*, was the major pathogen. Other organisms like enterobactericaea , listeria , E.coli are also implicated. Penicillin or Ampicillin and Gentamicin are recommended **[Grade C]**

2. In late onset sepsis, a combination of antibiotics to cover for the commonly isolated organisms in late onset sepsis is indicated. In gram positive sepsis, Oxacillin, Nafcillin and Methicillin are indicated in sensitive strains of *Stap aureus*. In resistant organisms, Vancomycin is recommended. In enterococci, Ampicillin and Gentamicin in sensitive organisms and Vancomycin in resistant strains are recommended. In gram negative organisms, Imipenem/cephalosporins are recommended **[Grade C**

3. Amphotericin has been found to be effective in those babies at risk for fungal infections and blood culture confirmed sepsis.**[Grade C]**

ALGORITHM FOR TREATMENT OF NEONATE SEPSIS



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Appendix 1

RECOMMENDED DOSAGE OF EACH ANTIBIOTIC

Antibiotic	Dosage (Frank Shann)	Dosage (Article/journal)
Carbapenam Meropenem Imipenem	10-20 mg/kg/dose 8 H iv over 5-30 min. Severe inf 20-40 mg/kg/dose 8H or constant infusion	10-20mg/kg every 8H (J Antibiotik Chemother.1995 Jul; 36 Suppl A:99-108)
2nd Gen Cephalosporin Cefuroxime	Oral: 10-15mg/kg/dose 12H, IV : 25mg/kg/dose 8 H . Severe inf 50mg/kg/dose IV 12H(1st wk life), 8H (2nd wh),6H or constant infsn (>2wk)	
3rd Gen Cephalosporin 1)Ceftriaxone 2)Ceftazidime 3) Cefixime 4) Cefotaxime Sodium 5) Cefoperazone	25mg/kg/dose 12-24H IV or IM. Severe inf 50mg/kg/dose daily (1st wk life),12H(2+wk) Epilogttitis 100mg/kg stat, then 50mg/kg after 24hr. 15-25mg/kg/dose 8H IV or IM. Severe inftn :50mg/kg/dose 12H(1st wk life), 8H(2-4wk), 6H or constant infsn (4+wk) 5mg/kg/dose 12-24H IV 25mg/kg/dose 12H(<4 wk), 8H (4+wk) IV. Severe inftn: 50mg/kg/dose IV 12H(preterm), 8H (list wk life), 6H (2-4wk), 4-6H or constant infsn (4+wk) 25-60 mg/kg/dose 6-12H IV	50mg/kg/day (Drugs, 1994:47 Suppl 3:43-5.) 50mg/kg every 6h. or 75mg/kg every 8h or 12 h (Clin Pharmacokinet. 1992 Apr:22(4):284-97.
6)Ciprofloxacin	5-10mg/kg/dose 12H oral, 4-7mg/kg/dose 12H IV. Severe inf 20mg/kg/dose 12H oral, 10mg/kg/dose 8H IV	20mg/kg/day, (J Int Med Res. 1997 Sept-Oct;25(5):302-6)
Ampicillin	10-25mg/kg/dose 6H IV, IM or oraloral. Svere inft: 50mg/kg/dose (max 2gm)IV 12H(1st wk life) , 6H (2-4wk), 3-6H or constant infsn (4+wk).	