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# REPORT

## RATIONAL ANTIBIOTIC UTILISATION IN SELECTED PEDIATRIC CONDITIONS

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## EXECUTIVE SUMMARY

The wide use of antibiotics has been associated with increasing antimicrobial resistance, both in the community and hospital settings. Multi-resistant organisms such as extended spectrum beta lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli*, Glycopeptide-resistant *Staphylococcus aureus*, Vancomycin-resistant *Enterococcus* (VRE) and also multi-resistant *Acinetobacter* (including Carbapenem-resistant isolates) have appeared worldwide, although the prevalence varies in different countries.

Patient care is threatened by treatment failures arising from infection of organisms leading to morbidity and potential mortality. The treatment of these infections is hampered by the lack of efficacious antibiotics, especially for multi-resistant gram-negative organisms like *Acinetobacter* and *Pseudomonas aeruginosa*. Furthermore, widespread abuse and overuse of antibiotics result in potential drug toxicities leading to increased complications as well as increased healthcare costs.

The objective is to determine the safety, effectiveness, and cost implications of rational antibiotic utilisation in selected pediatric conditions like Febrile Neutropenia, Encephalitis/ Encephalopathy / Meningitis, Pneumonia, Sepsis in Children, and Neonatal Sepsis

For Febrile neutropenia, there is sufficient evidence to recommend the use of either monotherapy or combination therapy antibiotics, using a third or fourth generation Cephalosporin, and Beta-lactam agent and an Aminoglycoside respectively. However, there is scanty data regarding utility of empiric antifungal therapy and no good evidence to support the practice of routine antiviral therapy in neutropenic children with cancer and so routine antifungal or antiviral therapy at the onset of febrile neutropenia is not recommended. There is limited data regarding cost-effectiveness of different antibiotic regimens in the treatment of febrile neutropenia.

As for Meningitis and Encephalitis, there is sufficient evidence of the effectiveness of third generation Cephalosporins to treat *Haemophilus influenzae meningitis type b* and *Streptococcus meningitis*. There is evidence of Dexamethasone used with antibiotics reduces hearing loss in *Haemophilus influenzae meningitis*. However, there is no evidence of effectiveness of antibiotics in viral encephalitis, except the use of Acyclovir in *Herpes encephalitis*.

In community acquired pneumonia, there is inadequate data on the effectiveness of various different antibiotics but there is some evidence to recommend the use of Azithromycin, Amoxicillin Clavulanate, Erythromycin and Cefuroxime, in the outpatient treatment of pneumonia. There was insufficient evidence on adverse effects and costing, there is inadequate data to support. The macrolides may have a role in the older child and for the inpatient treatment of *Pseudomonas* Community Acquired Pneumonia the Penicillin group of drugs may be used.

In treatment of sepsis in children, there is no evidence to support the use of specific antibiotics, although the commonly used antibiotics were found to be Cefuroxime, Metronidazole, Gentamycin and Ampicillin. It was found that there is good evidence to support the use of Polyclonal Intravenous Immunoglobulin as adjuvant treatment for sepsis and septic shock.

There is evidence to recommend the use of Ampicillin, Aminoglycosides, Cephalosporins and Vancomycin in the treatment of neonatal sepsis, there is inconclusive evidence on the appropriate duration of antibiotics. Penicillin is recommended for Group B Streptococcus, while Liposomal Amphotericin B is recommended in Candidiasis, Gentamycin can be given on a once daily dose where indicated. Vancomycin, Penicillin and Teicoplanin can be used for prophylaxis. However, there is insufficient evidence on the use of prophylaxis in specific conditions and antibiotics of choice in specific conditions. There is also insufficient evidence, to support the use of antiviral agents in various conditions, except for evidence of effectiveness of Acyclovir in Herpes simplex infection and neonatal *Varicella* infection. Insufficient evidence was also obtained on and regards to safety and cost effectiveness of antibiotics in neonates.

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## **1. BACKGROUND**

The wide use of antibiotics has been associated with increasing antimicrobial resistance, both in the community and hospital settings (Swartz, 1997; Shales *et al*, 1997; Cohen *et al*, 1997). Multi-resistance organisms such as extended spectrum beta lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli*, Glycopeptide-resistant *Staphylococcal aureus*, Vancomycin-resistant *Enterococcus* (VRE) and also multiresistant *Acinetobacter* (including Carbapenem-resistant isolates) have appeared worldwide, although the prevalence varies in different countries.

Patient care is threatened by treatment failures arising from infection of organisms leading to morbidity and potential mortality (Tomasz, 1998; Gold *et al*, 1996; Gomez *et al*, 1999). The treatment of these infections is hampered by the lack of efficacious antibiotics, especially for multi-resistant gram-negative organisms like *Acinetobacter* and *Pseudomonas aeruginosae*. Furthermore, widespread abuse and overuse of antibiotics result in potential drug toxicities leading to increased complications as well as increased healthcare costs.

## **2. OBJECTIVES**

To determine the safety, effectiveness, and cost implications of rational antibiotic utilisation in selected pediatric conditions - Febrile Neutropenia, Encephalitis/ Encephalopathy / Meningitis, Pneumonia, Sepsis in Children, and Neonatal Sepsis

## **3. TECHNICAL FEATURES**

### **3.1 Febrile Neutropenia**

Febrile neutropenia is a common consequence of anticancer chemotherapy. Cancer patients receiving myelosuppressive chemotherapy develop severe neutropenia and, consequently, are at high risk of developing life-threatening infections (Cometta *et al*, 1996; Charnas *et al*, 1997), and bacterial infections are a common cause of morbidity and mortality in such patients (Freifeld *et al*, 1997). These patients are at risk of endogenous flora infection, especially aerobic Gram-negative bacteria residing in the gastrointestinal tract and also those pathogens colonizing on normal or damaged mucosa or skin surfaces, namely Gram-negative bacilli such as *Enterobacteriaceae*, *Klebsiella pneumoniae* or Gram-positive cocci like *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus viridans* (Charnas *et al*, 1997, Patrick, 1997).

Since, febrile neutropenic patients fail to mount a full inflammatory response, and the currently available diagnostic tests are not sufficiently rapid, sensitive or specific for identifying or excluding the microbial cause of a febrile episode, they may have to be treated empirically. The risk of infection increases 10-fold with declining neutrophil counts, so that infection rates rise from 0.5 infection per 100 days, with absolute neutrophil counts between 100 and 500/cubic mm, to 5 infections per 100 days, with absolute neutrophil counts of 100/cubic mm (Mustafa *et al*, 2001). Between 48 and 60%

of febrile neutropenic patients have an established or occult infection, and between 16 and 20% of those with neutrophil counts of <100/cubic mm have bacteremia (Hughes *et al*, 1997) The prompt institution of empiric antibiotic therapy for febrile neutropenic patients, has been shown to dramatically reduce their infection-related morbidity and mortality (Freifeld *et al*, 1997). Numerous clinical trials have demonstrated that empiric antibiotic regimens including potent antibiotic mono-therapies and antibiotic combinations may preserve the patient through the critical time of fever and neutropenia, (Freifeld *et al*, 1997).

In a study in University Hospital, Kuala Lumpur in children with febrile neutropenia Ceftazidime-resistant *Klebsiella pneumoniae* was seen in 51.6% of all bacteremic isolates, suggesting a high prevalence of ESBL-infections in that setting. (Ariffin *et al*, 2000)

### **3.2. Meningitis and Encephalitis**

In children, acute infection of the central nervous system is the most common cause of fever associated with signs and symptoms related to the central nervous system. The specific causative pathogen depends on age and immune status of patients. While meningitis implies primary involvement of the meninges, and encephalitis indicates brain parenchymal involvement, in clinical practice, it may be extremely difficult to distinguish the two.

#### *3.2.1 Bacterial meningitis*

Bacterial meningitis in children aged between 2 months to 12 years is usually caused by *Haemophilus influenzae type B*, *Streptococcus pneumoniae* or *Neisseria meningitidis* in Malaysia, Saudi Arabia, Philippines and many other countries in the South Asia and South East Asia. (Limcangco *et al*, 2000; Uduman *et al*, 2000; Lee, 1998; Hussein *et al*, 1998; Almuneef *et al*, 1998). Less common pathogens like *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella* and *Listeria monocytogenes* can be involved if host defense mechanisms are altered. Developed countries like USA, United Kingdom, Canada, Greece, Italy Holland, and Taiwan, have reported a marked decline on the incidence of *Haemophilus influenzae meningitis* (Gold, 1999, Dawson *et al*, 1999), with *Streptococcus pneumoniae* being the leading cause of bacterial meningitis. In Hong Kong, *Mycobacterium tuberculosis* was the common aetiological agent of meningitis, with very low incidence of *Haemophilus influenzae* and *Meningococcal Meningitis* ( Sung *et al*, 1997). In India, no cases of late onset group B *Streptococcus* disease were noted. This low incidence could be attributed to the low rate of colonisation and high prevalence of protective antibodies in mothers (Kuruvilla & Thomas, 1999).

#### *3.2.2 Encephalitis*

Viral encephalitis is characterized by pleocytosis with negative gram stain and negative culture of cerebral spinal fluid. The recent Viral Encephalitis (EV 71) outbreak in several parts of the world, including Taiwan and Malaysia highlights the demand for rapid and accurate diagnostic tests. (Liu *et al*, 2000; Monto Ho *et al*, 1999; Lum *et al*, 1998).

While the isolation of virus in cell culture is the mainstay of viral identification, such cultures have a low sensitivity (<75%), and are usually not available in time (Traller & Casas, 2000). Serology testing may be slow, usually requiring acute and convalescent samples (McMinn *et al*, 2001). PCR is superior to viral culture since it is accurate and more sensitive than viral culture. However, contamination in the laboratory may give rise to a false positive PCR result (Hsiung & Wary, 2001; Dannet *et al*, 1997).

*Herpes simplex* encephalitis is usually considered in the presence of a focal neurological finding on clinical examination. Diagnosis is established by the detection of *Herpes Simplex* Viral (HSV) DNA by PCR, considered the gold standard for the diagnosis of herpes simplex encephalitis (Sauerbrei *et al*, 2000; Atkins, 1999; Lahat *et al*, 1999; Dominique *et al*, 1998; McGrath N *et al*, 1997; Dennet *et al*, 1997). HSV DNA is readily detected during the first week, but declines during the second week. EEG and CT Scan of the brain are only supporting tests (Ito *et al*, 1998).

### **3.3 Pneumonia**

Lower respiratory tract infection is a common cause of mortality and morbidity in children. In acute pneumonia, biopsy or needle aspiration of lung tissue are rarely carried out, because only a small fraction of children with pneumonia have bacteremia or pleural effusion. Apart from this, bacterial cultures of the nasopharynx or throat correlate poorly with cultures of lung tissue, while clinical and radiographic signs of viral, bacterial or mycoplasma etiology have little diagnostic value (Nelson, 2000). Antigen detection and specialized serologic techniques are thus used to confirm etiological agents. Hence, empiric treatment is necessary because definitive information about causative pathogens is seldom available (McCracken, 2000).

#### **(a) Etiological Agents Paediatric Community Acquired Pneumonia (PCAP)**

In most studies pneumonia can be attributed to a specific etiology (Table 1) from culture, antigen detection and specialized serologic techniques. These had detected 87% and 85% respectively of the etiological agents (Gendrel *et al*, 1997; Juven *et. al*, 2000).

Table 1 Etiology of childhood PCAP

Study	No.	Country	Age (yrs)	Blood Culture	Strep Pneumoniae	Mycopl Pneumo.	Total Bacterial	RSV	Total viruses	Etiology detected total
Gendrel 1997	104	France	Mean 5.6	8	13	41	55	10	29	84
Heiskanen-Koma 1998	201	Finland	105<5 96>5	Serology used	28	22	51	21	25	66
Wubbel 1999	168	USA	106<5	0	27	7	28	8	20	43
Vouri 1998	79	Finland	3/12-15	10	45	1	78	5	15	61
Tran 1998	300	Vietnam	1/12-5	213	65		71			
Drummond	122	England	0-16	1	4		14	24	37	51
Clements 2000	89	England	1/12-16		8	16		13	26	54
Juven 2000	254	Finland	Children	1	37	7	53	29	62	85
Miranda Novales 1999	101							23.7		
Harris JA 1998	420	USA	6/12-6			29.5				46
Rowe 2000	371	Central Africa	2-59 months	NPA culture	73(NP A culture)					

Several large prospective studies have investigated the cause of PCAP in Europe and North America using serology alone or serology combined with culture and PCR to define etiology. The percentage of bacterial etiology was consistently higher than virus. (Table 1, ) except in the study done by Juven *et al*, (2000.)

### (b) Bacteria etiological agents

The most common bacteria are *Streptococcus pneumoniae* followed by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (Table 1; Greenwood, 1999; McCracken, 2000). Patients with pneumonia were found more likely to have nasopharyngeal colonization with *S. pneumoniae* (Levine, 2000). Blood cultures are a poor investigation tool to detect the etiological agent (Table 1). However, in Vietnam, one study found that 71% positive blood culture in patients with pneumonia detected by using blood culture (Tran *et al*, 1998). Most studies used serological and blood culture markers to detect organisms (Heiskanen-Koma, 1998; Tran, 1998; Vouri, 1998; Drummond, 2000; Juven, 2000; Rowe, 2000; Wubbel, 1999). *Haemophilus influenzae* was found as a causative organism in some studies (Tran, 1998; Rowe, 2000; Juven, 2000; Yang, 1998). *Mycoplasma* and *Chlamydia* are the other common bacterial organisms (Wubbel *et al*, 1999; Chaudhry *et al*, 1998; Chugh, 1999; Heiskanen-Kosma *et al*, 1999). Differences in the incidence of *Mycoplasma* and *Chlamydia* can be affected by geographical location, season, and type of test used (Wubbel *et al*, 1999). It has also been found that a positive PCR for *Chlamydia pneumoniae* in the upper respiratory tract does not necessarily imply it be the etiological agent of a lower respiratory tract infection (Flack *et al*, 1997).

### (c) Viral etiological agents

The commonest virus is *Respiratory syncytial virus* (RSV) (Heiskanen-Kosma *et al*, 1998; Wubbel *et al*, 1999; Juven *et al*, 2000; Sonoda *et al*, 1999; Videla, 1998; Hijazi, 1997). A local study also had a similar finding, 84% of the viruses being RSV (Chan *et*

al, 1999). Other viral agents detected were *Parainfluenza*, *Influeza*, *Adenovirus* (Juven *et al*, 2000; Chan *et al*, 1999).

**(d) Multiple etiological agents**

There have been serological evidence of more than one etiological agent - Wubbel *et al*, (1999) found 40% of those with *S. pneumoniae* had co-infection with *C. pneumonia* or *M. Pneumonia* viruses. Others studies also found similar bacterial-viral co-infection from 8-34% (Juven *et al*, 2000; Ruuskanen & Mertsola, 1999; Heiskanen-Kosma *et al*, 1998; Vouri *et al*, 1998). Bacterial–bacterial co-infection was found to be less common, only two studies found *S pneumonia* and *M pneumonia* (Heiskanen-Kosma *et al*, 1998, Toika *et al*, 2000).

**(e) Distribution of etiological agents across age groups**

*Streptococcus pneumoniae* infection rates were stable across all age groups (Juven *et al*, 2000; Heiskanen-Kosma *et al*, 1998; Wubbel *et al*, 1998), while *Streptococcal pneumoniae* was the most common bacterial cause of pneumonia under 2 years (Drummond *et al*, 2000). Most studies found that *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections became more prevalent with increasing age, while *C. pneumoniae* was found to play a minor role in the aetiology of pneumonia in children less than 9 years of age (Martinez *et al*, 2000).

**3.4 Sepsis in Children**

The systemic response to infection and its management remains a major challenge in clinical medicine. 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, 2000). In a study in Kuwait it was found that 52% of the 70 deaths in patients was due to nosocomial bacteremia (Jamal & El-Din, 1999).

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, 2000).

With respect to management, apart from antibiotic administration, most therapies are limited to being supportive strategies. Close attention to cardiovascular, respiratory, fluid and electrolytes, haematological, renal and metabolic/nutritional support is essential to optimize outcome. Fluid resuscitation is of utmost importance to overcome the hypovolaemia resulting from diffuse capillary leak.

**3.5 Neonates Sepsis**

Neonates, especially premature babies, are deficient in host defenses i.e. physical, cellular, humoral, and are thus predisposed to infection. They are also at risk of acquiring infections from mothers during the perinatal period. Infections disseminate very rapidly

in neonates, with septicaemic shock and death often occurring within 12 hours of the first sign of illness.

Consequently, early diagnosis and therapy initiated on the basis of clinical suspicion is important. Rapid identification of neonatal sepsis by various tests may allow early discharge, as well as reducing the cost of treatment and anxiety for family, apart from reducing the use of antibiotics (Anwer, 2000). The use of rapid identification systems like BACTEC<sup>®</sup> helps in the early identification of neonatal bacteremia (within 24- 30 hours), with gram negative organisms being detected earlier than gram positive ones, thus allowing earlier diagnosis and appropriate treatment (Pauli *et al*, 1999).

The choice of antibiotics in neonates is difficult. The combinations of antibiotics used will depend on the organisms commonly isolated in that particular nursery. Changes in antibiotics can be made once the culture and sensitivity results are available. However, it needs to be borne in mind that the antibiotics used will have adverse effects on the resident bacterial flora in a neonatal unit. Thus, data on the aetiology of sepsis in the nursery need to be periodically reviewed to revise the antibiotic policy (Anwer, 2000). The diagnoses need to be reviewed at different stages of treatment, so that antimicrobial therapy is administered to only those neonates requiring them. This will also minimise the development of antibiotic resistant organisms. Apart from this, failure to respond to antimicrobials could imply either a non-infectious cause of illness or poor supportive management (Musoke, & Revathi, 2000).

Decisions to start antibiotics also need to be evaluated carefully. Thus, for example, fever in neonates needs to be evaluated carefully to avoid unnecessary empirical antibiotic therapy as it was found that even Hep B vaccination may cause an unexplained fever in neonates (Linder *et al*, 1999). A study evaluating newborns weighing more than 2 kg. for sepsis, found that the risk of bacterial infection in the asymptomatic infant is low. However, there was increased risk of infection with chorioamnionitis, low absolute neutrophil count and meconium-stained liquor (Escobar *et al*, 2000).

The appropriate antibiotics for the treatment of infections in neonates would vary from centre to centre as would the organisms causing the various infections. In Taiwan, it was found that Group B streptococcus had taken over E. Coli as being the leading cause of meningitis since 1991, and consequently, strategies to prevent such infections was recommended to be developed. (Chang Chien *et al*, 2000). On the other hand, in North Colombo, it was found that most late onset septicaemia was caused by nosocomial infections due to *Klebsiella* and *Staph. aureus* (Karunasekara & Pathirana, 1999). A Nigerian study found a high prevalence of neonatal bacterial sepsis, *L. monocytogenes* and a preponderance of multiple resistant organisms among neonates early in life (Ako Nal & Adejuyigbe, 1999).

In Malaysia, the most common organisms in late onset infections in very low birth weight infants were *Klebsiella* (38.3%), followed by coagulase-negative *Staphylococcus* (17.6%). The mortality rates were high in *Klebsiella* infections (46.9 %) (Jacqueline Ho, 2001)

## 4. METHODOLOGY

### 4.1 Febrile Neutropenia

An electronic search of PUBMED database using various keywords and limits was carried out as follows.

- (a) Keywords: "febrile neutropenia AND antibacterial antibiotics"  
Limits: 1997-2001  
Results: 156 citations, 42 relevant.
- (b) Keywords: "febrile neutropenia AND antifungals"  
Limits: 1997-2001  
Results: 32 citations; 6 relevant
- (c) Keywords: "febrile neutropenia AND antivirals"  
Limits: 1997-2001  
Results: 12 citations; none relevant

In addition, OVID full text search was carried out as follows:

- (a) Keywords: "febrile neutropenia AND antibiotics"  
Results: 207 citations; 26 relevant
- (b) Keywords: "febrile neutropenia".  
Limits: English, Human, 1997-2001  
Results: 497 citations; 28 relevant.

### 4.2 Meningitis and Encephalitis

An electronic search of PUBMED database using various keywords and limits was carried out as follows.

- (a) Keywords : "Bacterial meningitis AND children"  
Limits: 1997-2001, preschool, 6-12 years English  
1997-2001, child, 6-12 years English  
1997-2001, infants, 1-23 months English  
Results: 434, 478, 475 citations
- (b) Keywords: Meningoencephalitis AND children  
Limits: Infant, 1-23 months, 1997-2001, English, Human  
Preschool, 2-5 years, 1997-2001, English, Human  
Child, 6 to 12 years, 1997-2001, English, Human  
Results: 30, 43, 86 citations
- (c) Keywords: Encephalitis AND children  
Limits: Preschool, 2-5 years, 1997-2001, English, Human  
Child, 6-12 years, 1997-2001, English, Human

- Results: 460, 630 citations
- (d) Keywords: Herpes Encephalitis AND children  
 Limits: Child, 6-12 years, 1997-2001, English, Human  
 Preschool, 2-5 years, 1997 –2001, English, Human  
 Results: 21, 20 citations

### 4.3 Pneumonia

An electronic search of PUBMED database using various keywords and limits was carried out as follows.

- Keywords: Pneumonia  
 Limits: All children 0-18yrs, 1997-2001, English  
 Results: 1082 title - 198 relevant, 19 abstracts and full papers reviewed

In addition, manual searches of the references of the 19 articles were made:

- No. of references: 568 (1997 – 2001)  
 7 relevant titles, 2 abstracts reviewed and used

### 4.4 Sepsis in Children

An electronic search of PUBMED and COCHRANE Library databases using various keywords and limits was carried out as follows.

- Limits: last 5 years  
*Inclusion criteria* for selection of titles and abstracts:  
 - studies/papers on immuno-competent hospital in-patients or Paediatric Intensive Care Unit settings  
*Exclusion criteria*: papers on immuno-compromised patients, high-risk patients like HIV, cancer and post-splenectomy patients, individual organism studies, specific antibiotic trials and catheter-related infections, and fungal infections were excluded.

## PUBMED

- (a) Keywords: Sepsis OR Septicemia AND antibiotics  
 Limits: 1 month to 23 months; 2 years - 5 years; 6 years - 12 years, 1997-2001, English, Human  
 Results: 197 citations, 104 relevant titles, 46 relevant abstracts, 5 articles used;  
 49 citations, 20 relevant titles, 11 relevant abstracts, 3 articles used  
 56 citations & relevant titles, 13 relevant abstracts, 2 articles used.
- (b) Keywords: Bacteremia OR sepsis-syndrome AND antibiotics  
 Limits: 1 month to 23 months; 2 years - 5 years; 6 years -12 years; 1997-2001, English, Human  
 Results: 46 citations, 6 relevant titles, 5 relevant abstracts, 0 articles used  
 52 citations, 13 relevant titles, 9 relevant abstracts, 0 article used

49 citations, 38 relevant titles, 26 relevant abstracts, 0 article used.

- (c) Keywords: Bacteraemia AND antibiotics  
Limits: 1 month-23 months; 2 years - 5 years; 6 years - 12 years; 1997-2001, Human, English  
Results: 20 citations, 0 relevant title.  
19 citations, 1 relevant title, 1 relevant abstract, 0 article used  
20 citations, 18 titles, 12 relevant abstracts, 1 article used.
- (d) Keywords: Septicemia AND antibiotics  
Limits: 1 month-23 months; 2 years - 5 years; 6 years - 12 years; 1997-2001, Human, English  
Results: 20 citations, 1 relevant title, 0 relevant abstract.  
9 citations, 0 relevant title  
12 citations, 0 relevant title.
- (e) Keywords: Antibiotics AND pediatric intensive care  
Limits: 1 month - 18 years, 1997-2001, Human, English, 44 citation, 34 relevant title, 4 relevant abstract, 3 article used.

**COCHRANE Library:**

- (a) Keywords: Sepsis AND antibiotic  
Results: 25 relevant hits, 0 relevant title
- (b) Keyword: Antibiotic AND pediatric intensive care  
Results: 25 most relevant hits, 0 relevant title.
- (c) Keyword: Sepsis  
Results: 25 relevant hits, 1 relevant title, 1 relevant abstract, 1 article used

Note: *Though the term septicemia is obsolete, it was used in this search so as not to miss any article with this term*

**4.5 Infection in neonates**

An electronic search of PUBMED database using various keywords and limits of human, English, infants, newborns, 1997 -2001 was carried out as follows:

- (a) Keywords: Neonates AND sepsis AND antibiotics  
Results: 253 citations, 17 relevant titles, 3 paper reviews and 8 abstracts used.
- (b) Keywords: Neonate\* AND antibiotic\*  
Results: 1060 citations, 43 relevant titles, 10 abstracts used.
- (c) Keywords: Neonates OR neonate AND antibiotics OR antibiotic  
Results: 1239 citations, 186 relevant titles, 66 relevant abstracts, 11 papers and 44 abstracts used

- (d) Keywords: Neonates OR neonate AND antibiotics OR antibiotic AND septicemia OR septicaemia AND bacteremia OR bacteraemia  
Results: 170 citations, 0 relevant titles
- (e) Keywords: neonates OR neonate AND antibiotics OR antibiotics AND therapeutics  
Results: 219 citations, 27 relevant titles, 5 abstracts used
- (i) Keywords: neonates OR neonate AND antibiotic OR antibiotics AND meningitis OR encephalitis OR encephalomyelitis  
Results: 90 citations, 60 relevant titles, 6 abstracts used
- (j) Keywords: neonates OR neonate AND antibiotic OR antibiotics AND pneumonia  
Results: 25 citations, 9 relevant titles, 0 relevant abstract
- (k) Keywords: neonates OR neonate AND antibiotic OR antibiotics AND safety  
Results: 3 citations, 0 relevant title.
- (m) Keywords: neonates AND necrotising AND enterocolitis  
Results: 16 citations, 1 irrelevant title, 1 abstract reviewed.
- (n) Keywords: necrotising enterocolitis AND antibiotics  
Results: 3 citations, 0 relevant title
- (o) Keywords: acyclovir  
Results: 28 citations, 10 relevant titles, 9 abstracts reviewed
- (p) Keywords: neonate AND viral AND infection  
Results: 37 citations, 3 relevant titles
- (q) Keywords: viral AND infection NOT HIV  
Results: 228 citations, 15 relevant titles, 3 abstracts reviewed
- (r) Keywords: ribavirin  
Results: 13 citations, 8 relevant titles, 5 abstracts reviewed
- (s) Keywords: ganciclovir  
Results: 9 citations, 2 relevant titles, 2 abstracts reviewed
- (t) Keywords: CMV OR cytomegalovirus  
Results: 209 citations, 11 relevant titles, 1 abstract reviewed
- (u) Keywords: varicella zoster  
Results: 48 citations, 7 relevant titles, 4 abstracts reviewed

- (v) Keywords: rubella  
Results: 2 citations, 0 relevant title.
- (w) Keywords: herpes  
Results: 100 citations, 12 relevant titles, 4 abstracts reviewed.

The relevant articles were appraised, and the strength of the evidence was graded according to the Catalan agency for HTA (CAHTA).

## 5. RESULTS

### 5.1 Febrile Neutropenia

#### 5.1.1 Effectiveness

##### (a) Antimicrobial agents

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 cancer patients with fever (Viscoli *et al*, 1998; Gaya, 1998; Hughes *et al*, 1997).

The choice of initial empirical antibiotics, however, remains controversial (Duzova *et al*, 2001; Fleischack *et al*, 2001; Kebudi *et al*, 2001; Furno *et al*, 2000, Petrilli *et al*, 2000). However, Vancomycin is not recommended as initial empirical treatment (Feld, 1999).

Monotherapy with antibiotics like Cefepime, Ceftriaxone, Ceftazidime and Meropenem have been found to be equally efficacious and safe compared to combination chemotherapy with antipseudomonal beta-lactams and aminoglycosides. (Mustafa *et al*, 2001; Kebudi *et al*, 2001; Duzova *et al*, 2001; Fleischack *et al*, 2001; Ariffin *et al*, 2001; Sidi *et al*, 2000; Furno *et al*, 2000; Ramphal, 1999; Tomlinson *et al*, 1999; Freifeld *et al*, 1999; Karthaus *et al*, 1998). A prospective study found that Piperacilin-Tazobactam to be as effective as monotherapy for initial empirical antimicrobial therapy in febrile neutropenia patients (Bohme *et al*, 1998). A daily dose of Amikacin has been recommended for immunocompromised paediatric patients with fever (Krivoy *et al*, 1998). A subset of low risk patients with febrile neutropenia may be discharged and treated with oral Ciprofloxacin or Cefixime (Shenep *et al*, 2001; Aqino *et al*, 2000; Klaassen *et al*, 2000; Paganini *et al*, 2000; Petrilli *et al*, 2000; Mullen *et al*, 1999).

##### (b) Antifungals

Antifungal therapy is warranted for febrile neutropenic patients who do not respond to a week's course of antibiotic therapy, since close to 33% cases will develop systemic fungal infections like *Candida* or *Aspergillus* after that period. However, there is no good evidence in the literature to support routine antifungal or antiviral therapy at the onset of febrile neutropenia (Viscoli *et al*, 1998; Hughes *et al*, 1997).

### 5.1.2 Cost

Ceftriaxone plus aminoglycosides was found to be less expensive than other empiric antibiotic regimens for febrile neutropenia in children (Castaglonola *et al*, 1998).

## 5.2 Meningitis and Encephalitis

### 5.2.1 Effectiveness of antibiotic use

#### (a) *Haemophilus influenzae meningitis*

In the treatment of *Haemophilus influenzae meningitis*, Cefotaxime, Ceftriaxone, Ampicillin and Chloramphenicol are all thought to cross the blood brain barrier during acute inflammation in concentrations adequate to render them effective. With respect to sensitivity, a study in Poland found that all isolates were sensitive to third generation Cephalosporin and Chloramphenicol (Skocynska *et al*, 2000), while a study in Saudi Arabia had observed an isolate resistant to Ampicillin (Uduman *et al*, 2000)

#### (b) *Streptococcus pneumoniae meningitis*

Penicillin, a cheap and safe antibiotic has been the treatment of choice for *Streptococcus pneumoniae meningitis*. However, the incidence of relative and complete penicillin resistance, and multiple drug resistance has increased in the last decade (Greenwood, 1999). The incidence of Penicillin resistance has been reported to be 1% in a study in Holland ([Spanjaard@amc.uva.nl](mailto:Spanjaard@amc.uva.nl)), while studies in Italy and Sweden observed penicillin resistance of up to 0.2 - 10.2% and 11% respectively (Eriksson *et al*, 2000, Principi, 2000). In a three-year multi-centre surveillance study in USA, 19.3% of isolates were intermediate or resistant to Penicillin, while 7.2% were intermediate or resistant to Ceftriaxone (Arditi *et al*, 1998). In Malaysia too, an increasing trend in penicillin resistance has been seen from 2.4 - 7% in 1978-1988 to 8% in 1995-1996. Serotypes 23F, 6B, 34, 14, 19, 23 were implicated in Malaysia, while two *Pneumococcal* isolates were resistant to Erythromycin, Chloramphenicol, Cefotaxime and Ceftriaxone (Farida, 1997). Consequently, third generation cephalosporins such as Ceftriaxone and Cefotaxime are the next antibiotic of choice. It has been found that Chloramphenicol is not effective when administered alone, due to a lack of autolysins in penicillin resistant isolates (Farida, 1997). In hospitals with a high prevalence of Penicillin resistance, the recommended empiric therapy is a combination of Vancomycin and a third generation cephalosporin. (Arditi *et al*, 1998; Stanek *et al*, 1999). The Committee of Infectious Diseases of the American Academy of Paediatrics has recommended the above regime for all children older than 1 month of age with probable or definite bacterial meningitis (American Academy of Pediatrics).

#### (c) *Neisseria meningitidis meningitis*

Intravenous Penicillin remains the drug of choice for *Meningococcal Meningitis*, although rare resistant isolates have been reported. Chloramphenicol provides effective treatment for patients allergic to Penicillin. Both Cefotaxime and Ceftriaxone are also effective empirical therapy.

(d) *Encephalitis*

For Viral Encephalitis infections, no specific therapy is available (McMinn *et al*, 2001). Pleconoril is an attractive option but has been used on a limited basis (Rotbart *et al*, 2001; Hsiung & Wary 2000). Acyclovir remains the mainstay of treatment for *Herpes* Encephalitis (Utley & Oigden, 1997; McGrath *et al*, 1997).

**5.2.2. Adjuvant Dexamethasone administration in bacterial meningitis**

A meta-analysis supported the use of Dexamethasone only for *Haemophilus influenza* meningitis, given before or after administration of antibiotics. It was found that those received Dexamethasone had less hearing deficit episodes, although the reduction in the incidence of neurological deficits was not statistically significant (McIntyre *et al*, 1997). However, a study in USA reported no benefit of Dexamethasone in reducing incidence of either hearing loss or neurological deficits for *Streptococcus pneumonia* (Arditi *et al*, 1998). In addition, two other reports also revealed that Dexamethasone was not beneficial (Coyle [PK@neuro.som.sunny.edu](mailto:PK@neuro.som.sunny.edu); Shembesh *et al*, 1997).

**5.3 Community Acquired Pneumonia**

**5.3.1 Effectiveness**

(a) *Empirical treatment*

A review found that oral Amoxicillin and Erythromycin were effective for children aged 5 years or less, and older children or adolescents respectively (Grant & Ingram, 2000). Another review recommends Macrolides as the first choice antibiotic for outpatients, depending on the clinical picture and severity of illness, while penicillin G, macrolides or Cefuroxime plus macrolides are recommended for hospitalized patients (Ruuskanen & Mertsola, 1999)

(b) *Pneumonia due to Pneumococcus/Streptococcus / Haemophilus*

A study of pneumonia patients treated with either Azithromycin suspension or Amoxicillin-Clavulanate (for those less than 5 years) or Erythromycin estolate (for those aged 5 years or more), found the clinical response to therapy was similar, including those with bacterial infections. In this study only 43% of presumed etiology was identified (Wubbel *et al*, 1999).

A comparison of one injection of Benzathine Penicillin to a 7- day Procaine Penicillin regimen found no significant difference in the cure rates, with the former having the added advantages of lower cost, better compliance and low rates of adverse reactions (Camargos *et al*, 1997). A prospective, randomized blinded clinical trial of pediatric patients with presumed bacterial pneumonia found no significant difference between oral Amoxicillin and Procaine Penicillin G treatment (Tsarouhas *et al*, 1998).

In Pakistan, a large RCT found Co-trimoxazole to be effective therapy in non-severe pneumonia, while for severe, life-threatening pneumonia, it was less effective than Amoxicillin (Straus *et al*, 1998)

The US and British Thoracic Societies have recommended Cefuroxime as treatment for community-acquired pneumonia (Olivier, 2000).

A review of *Pneumococcal* infections in the developing world found that it could be treated effectively with penicillin (Greenwood, 1999). This was supported by another review recommending Penicillin and Amoxicillin as drugs of choice for pneumococcal infections (Grimwood *et al*, 1997). A study of children with non severe pneumonia found that they responded on the third day of administration of a 5-day treatment of Amoxicillin (Awasthi, 2000).

(c) *Penicillin resistant Streptococcus pneumoniae*

Penicillin resistant *Streptococcus pneumoniae* is a growing concern because of the importance of this pathogen in the infections of the respiratory tract. A study in Singapore found that 17% of the *Streptococcus pneumoniae* infections patients were penicillin resistance (Chong *et al*, 1997). A cross sectional survey in Central Africa, found 8.8 % *Streptococcus pneumoniae* resistant to Penicillin, and 6.3% to Trimethoprim–Sulfamethoxazole, with higher resistance rates among inpatients (Rowe *et al*, 2000).

The effect of treatment of community acquired pneumonia with combinations of antibiotics did not differ significantly between patients with penicillin-susceptible versus those with non-susceptible isolates of *S pneumoniae* (Tan *et al*, 1998).

In Central Africa, resistance rates to Ampicillin, Trimethoprim-Sulfamethoxazole, and Chloramphenicol were 1.4, 12.3 and 0%, respectively (Rowe *et al*, 2000). In Singapore, 5% of the *H. influenzae* had multiple resistance to Erythromycin, Trimethoprim-Sulfamethoxazole and Chloramphenicol (Chong *et al*, 1997).

(d) *Mycoplasma Pneumoniae and Chlamydia Pneumoniae*

A RCT comparing Azithromycin and Amoxicillin/Clavulanate in children aged 5 years or less and Erythromycin estolate in those more than 5 years old, found that microbiologic eradication of *C. pneumoniae* and *M. pneumoniae* was better with Azithromycin (Harris *et al*, 1998). Clarithromycin was also found to be efficacious in treating infants and children with *C. pneumoniae* (Numazaki *et al*, 2000).

It has been recommended that macrolides be considered as empirical antimicrobial treatment since *C pneumoniae* is an important cause of community acquired pneumonia in schoolchildren (Heiskanen-Kosma *et al*, 1999)

### 5.3.2 Safety

Treatment-related adverse events occurred less with Azithromycin compared to Amoxicillin/Clavulanate or Erythromycin group (Harris, 1998).

### 5.3.3 Costing

A study using sequential antimicrobial therapy found patients had a shorter length of hospital stay, shorter duration of inpatient antimicrobial therapy, and shorter of IV therapy, resulting in reduction of total healthcare costs (Al-Eidan *et al*, 1999).

### 5.3.4 Local situation

There is lack of local data on etiology for pneumonia in children, as well as on the pattern of antibiotic utilization for pneumonia in children. The current local prices of the commonly used antibiotics at hospital level are indicated in Appendix 1.

## 5.4 Sepsis in Children

### 5.4.1 Community acquired bacterial sepsis in previously healthy children

- (ii) Sepsis with no obvious source or with respiratory, 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.

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

Though the commonly used antibiotics are Cloxacillin/Vancomycin, a third generation Cephalosporin/Gentamycin and Metronidazole, no evidence could be obtained related to their use.

### 5.4.2 Nosocomial sepsis

A surveillance study found that the pattern of blood stream infections in Paediatric ICU is partly determined by the type of patient treated, and that the use of broad- spectrum empiric antibiotics not only risks promoting further antibiotic resistance, but may also not improve patient outcome (Gray, 2001). However, a prospective cohort study found that appropriate empirical antibiotics treatment was associated with a significant reduction in fatality in patients with bloodstream infection (Leibovici, 1998).

A cohort study showed that ruling out suspected ventilator-associated pneumonia, and curtailing extended prophylaxis would assist in reduction in antibiotic use (Fisher, 2000).

It has been found that four agents - Cefuroxime, Metronidazole, Gentamycin and Ampicillin accounted for half of all antimicrobials used, involving 20% of expenditure. Further, although 53% of antimicrobials surveyed were restricted, they accounted for only 29% of all antimicrobial courses (Raveh, 2001). A retrospective study on hospital acquired Candidaemia in a developing country found no significant difference between patients treated with Amphotericin B and Fluconazole (Al Soub & Estinoso, 1997). Another study found that 60% of Gram negative rods were Ampicillin resistant, although sensitive to third generation empirical antibiotics like Cefotaxime and Gentamicin (Sadow, 1999).

A study on predominant *Staphylococci* in an intensive care unit found that while susceptible to Vancomycin, 97% were resistant to Methicillin and 30% resistant to Mupirocin. However, *S epidermidis* was susceptible to Amoxicillin, Clavulanic acid and Cephalosporin ( Sewczyk, 2000).

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).

#### **5.4.3 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).

### **5.5 Neonatal Sepsis**

#### **5.5.1 Use of antimicrobials**

A study on bacterial infections in infants aged 60 days where *Listeria* was not isolated, it was found that 60% of the gram-negative rods were Ampicillin resistant. However, third generation cephalosporins with or without Gentamicin were useful (Sadow *et al*, 1999). In babies at risk of sepsis, empirical coverage for asymptomatic newborns need not include Gentamicin because although it improved the coverage of Ampicillin alone, it exposed infants to the side-effects of Gentamicin (Johnson, 1998). Another study found that in early onset sepsis, gram-negative bacilli predominated, with gram-positive cocci in late onset sepsis, and the third generation cephalosporins were found to be effective (Kaushik & Parmer, 1998). For infants who develop sepsis in the first week of life, since empirical therapy should cover Group B *Streptococcus*, *Enterobacteriaceae* and *Listeria*, as well as hospital acquired pathogens like *Staphylococcus*, *Enterococci*, and *Pseudomonas aeruginosa*, Penicillin or Ampicillin, and an Aminoglycoside are recommended. Cephalosporins are not recommended for the initial therapy of suspected sepsis (Yurdakok, 1998)

For suspected blood stream infection, a combination of Ampicillin and Gentamicin is recommended for early onset and Vancomycin and Gentamycin for late onset. Apart from this, a controlled antibiotic programme and periodic evaluation is needed (Cordero & Sandnes, 1999).

In skin infections, anti-*Staphylococcal* or anti-*Pseudomonal* agents like Netilmicin or Amikacin need to be used (Yurdakok, 1998).

In Israel, a policy of highly selective Vancomycin usage is supported as only one case of blood-borne Vancomycin resistant gram positive organism was observed during the period of the study (Matral-Kovalskis *et al*, 1998). A study found that policies regarding the empirical use of antibiotics affected the emergence of antimicrobial resistance, in that avoiding Amoxicillin and Cefotaxime restricted the emergence of resistant bacteria especially *Enterobacter cloacae* (de Man & Verhoevn, 2000).

### **5.5.2. Dosing of antibiotics**

#### **(i) Gentamicin**

Once daily dosing has been found to be as effective as twice daily therapy, more effective in premature and term infants (Solomon *et al*, 1999; Mureen *et al*, 1999). A once daily dose also has logistic and monetary benefits in addition to the pharmacokinetic advantage (Krishnan & George, 1997). An initial Gentamicin dosage interval of 12 hrs. in infants of any gestation age or of 24 hrs in infants less than thirty weeks gestational age, leads to most having toxic trough serum Gentamicin (SGM) levels. Conversely, most infants at thirty weeks gestational age or more, have safe non-toxic trough SGM levels if started on a dosage interval of 24hrs. (Davies & Cartwright, 1998). Although a loading dose, followed by once daily dosing resulted in safe and therapeutic range of drug levels in all term neonates, in low birth weight neonates, delaying the initiation of maintenance once daily dosing until 36-48 hours after loading, would result in a higher incidence of initial trough serum drug levels within the target range for such babies (Lundergan *et al*, 1999).

#### **(ii) Vancomycin**

A dosage of 30mg per day in 3 divided doses irrespective of age leads to adequate Vancomycin trough serum concentration and peak concentration without a need for routine monitoring of peak serum concentration. (De Hoog M *et al*, 2000).

#### **(iii) Amikacin**

In full term neonatal patients, a once daily dosing of Amikacin is no more toxic than the twice-daily dosing regime with regards to renal impairment (Kotze A *et al*, 1999).

### **5.5.3. Duration of antibiotics**

In neonates with pneumonia or sepsis, antibiotics should not be stopped although cultures show no growth, a duration of 10-14 days being recommended (Yurdakok, 1998). However, another study found that duration of antibiotics may be reduced in selected patients with neonatal pneumonia from 7 days to 4 days. Thus, additional studies are needed to assess safety and benefits (Burton *et al*, 2000)

### **5.5.4. Prophylactic antibiotics**

#### **(i) Vancomycin**

It has been found that in subgroups of infants at high risk of infection, like those less than 1 kg and on steroids, the benefits of prophylactic Vancomycin may outweigh concerns over potential emergence of bacterial resistance (Baier *et al*, 1998). Prophylaxis with intermittent low dose Vancomycin infusions may help reduce recurrent coagulase-negative *Staphylococcus aureus* bacteremia in very low birth weight infants receiving parenteral nutrition (Cooke *et al*, 1997). In preterm babies receiving parenteral nutrition over 1 year, prophylactic Vancomycin reduced the incidence of gram-positive infections (Ocete *et al*, 1998). The incidence of Vancomycin sensitive blood stream infections was decreased when Vancomycin was used at the time of catheter placement. Concerns regarding the emergence of Vancomycin resistant organisms preclude support of its use as a prophylactic agent (Falllat & Gallinaro, 1998).

**(ii) Penicillin**

The routine use of postnatal Penicillin prophylaxis appears to be effective in reducing the incidence of clinical sepsis and death from sepsis in neonates ( Patel *et al*, 1999)

**(iii) Teicoplanin**

Teicoplanin has been found to be as good as Vancomycin in preventing coagulase-negative *Staphylococcus aureus* sepsis (Moller *et.al*, 1997).

**5.5.5. Prophylaxis in specific conditions**

**(i) Necrotising Entero-Colitis (NEC)**

It has been found that there is no place for the use of enteral antibiotics for NEC in clinical practice (Bury & Tudhope, 2000)

**(ii) Airway colonisation**

Systemic antibiotics failed to eradicate gram-negative bacilli colonisation in airways in 97% of cases, and hence, empirical use for the prophylaxis or treatment of airway colonisation is discouraged (Cordero, 2000)

**(iii) Parenteral Nutrition**

Prophylactic intermittent low dose of Vancomycin infusions may help reduce recurrent coagulase-negative *Staphylococcus aureus* bacteremia in very low birth weight infants receiving pretermal nutrition (Cooke *et al*, 1997). Prophylactic Vancomycin also reduced the incidence of gram-positive infections in preterm babies receiving parenteral nutrition over a period of a year (Ocete *et al*, 1998).

**(iv) Catheter placement**

The incidence of Vancomycin sensitivity was also decreased when Vancomycin was given at the time of catheter placement ( Fallat & Gallinaro, 1998)

**5.5.6. Antibiotics of choice in specific conditions**

**(i) Fulminant sepsis**

The frequency of fulminant sepsis was found to be highest for *Pseudomonas* species and lowest for coagulase negative *Staphylococci*. Thus, although empiric antibiotic treatment of suspected sepsis in infants more than 3 days old need to effectively treat gram negative pathogens particularly *Pseudomonas* species, avoiding empirical Vancomycin therapy is a reasonable approach to late onset sepsis (Karlłowicz *et al*, 2000). One study found that Imipenam/Cilastin was effective therapy in premature infants and newborns with serious nosocomial infections even after failure of other broad-spectrum antibiotics (Boswald *et al*, 1999).

**(ii) Sepsis in Tetanus**

The common organisms causing sepsis in neonates that develop tetanus, were found to be *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Staph aureus*. While the antimicrobial susceptibility favoured Oflaxacin, a Cloxacillin/Gentamicin combination was recommended. Ceftazidime was the favoured cephalosporin with about 60 % susceptibility ( Egri Okwaji & Iroha,1998).

**(iii) Staphylococcus**

The blanket use of Mupirocin ointment was found to be an effective method of controlling Multiple Resistant *Staphylococcal aureus* in neonate intensive care units when outbreaks could not be managed by conventional measures ( Hitomi et al, 2000). Another study recommended Penicillinase-resistant Penicillins like Oxacillin, Nafcillin and Methicillin for *Staphylococcus*, and Vancomycin for resistant strains (Yurdakok, 1998).

**(iv) Group B Streptococcus**

Penicillin has been found to be the drug of choice for group B *Streptococcus* infections. In Penicillin intolerance, choice of an alternative antibiotic should be guided by contemporary resistance patterns (Lin *et al*, 2000). It was also found that Group B *Streptococcus* was sensitive to Penicillin G, Cefotaxime, Ampicillin with no high levels of resistance to Gentamicin being noted. (Aitmhand, 2000). Group B *Streptococcus* has been found to have overtaken *E coli* in one centre as the leading cause of meningitis, highlighting the importance of developing strategies to prevent these group B *Streptococcus* infections (Chang Chien *et al*, 2000).

**(v) Gram negative bacteria**

A study on neonatal sepsis found that among gram-negative bacteremia, with increased resistance to extended spectrum for Cephalosporins, Piperacillin, and Gentamicin, a combination of Ampicillin and Sulbactam with Amikacin, or Ampicillin and Sulbactam with Ciproflox was found to be effective (Joshi *et al*, 2000).

Increased resistance to Gentamicin, Amoxicillin/Ampicillin Ceftazidime, and Cefuroxime has been found to be due to non-investigation of infants put on antibiotics, unjustified and prolonged use of antibiotics, lack of utilisation of laboratory investigations when these were carried out, and delay in obtaining laboratory results at the ward level (Musoke & Revathi, 2000).

The use of third generation Cephalosporin and Amikacin in the treatment of gram-negative bacterial meningitis has also found support (Dellagrammaticas & Christodoulou, 2000). Other agents recommended for resistant gram-negative bacteria are Carbapenems, Aztreonam, Quinolones and Isepamicin (Yurdakok, 1998). Ciprofloxacin has also been found to be useful in the treatment of preterm/low birth weight infants infected with *Enterobacter cloaca*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* resistant to other antibiotics ( Van den Vever & Vers teegh, 1998)

**(vi) Enterobacter cloacae**

It has been found that highly antibiotic resistant *E cloacae* may emerge during an outbreak, although sensitive to Imipenem /Ciproxin ( Peters et al, 2000). In highly B lactam resistant *Enterobacter cloacae*, replacing Ampicillin plus Cefotaxime as standard empirical therapy with Penicillin G and Netilmicin, and consequent cohorting of newborns and staff had been effective in halting outbreaks (Finnstrom & Isksson ,1998)

**(vii) Klebsiella pneumonia**

Imipenem has been found to be a good alternative for neonatal *Klebsiella pneumonia*, although there is increased risk of *C. albicans* infection ( Oral, 1998). For multi-drug resistant *Klebsiella*, the use of Ciprofloxacin and Gentamicin has been found to be a good alternative (Khaneja & Naprawa, 1999). However, it has also been found that Gentamicin failed to sterilise the infants' blood and body fluids, and hence a combination of an Aminoglycoside and a third generation Cephalosporin such as Cefotaxime is necessary ( Traub *et al*, 2000). One study found all *Klebsiella pneumonia* isolated were resistant to Aminoglycosides, third generation Cephalosporins and Aztreonam, but were sensitive to Imipenem and Ciprofloxacin. (Roilides & Kyriakides, 2000).

In outbreaks of *Klebsiella*, Gentamicin resistant *K. pneumonia* were associated with low gestational age, low birth weight and increased length of stay. However, replacing Gentamicin with Amikacin stopped these outbreaks ( Van der zwet & Parlexliet, 1999). In Australia, an ESBL *Klebsiella pneumonia* outbreak was controlled by altered empiric antibiotic treatment for late onset sepsis like Imipenem/Vancomycin over Vancomycin and Gentamicin, and prevention of cross infection by strict attention to hand washing (Royle *et al*,1999). In Nigeria, it was found that all strains of *Klebsiella* were sensitive to most antibiotics but resistant to Ampicillin (Akindele & Rotilu,1997).

**(viii) Bacillus cereus**

A combination of Vancomycin and Gentamicin was found to be appropriate for meningitis or systemic infections of most *Bacillus cereus* species in Australia ( Tuladhar *et al*, 2000)

**(ix) Strenotrophonomas maltophilia**

A *Strenotrophonomas maltophilia* infection was found to be successfully treated by Amikacin ( Ozkan *et al*,1999)

**(x) Morganella morganii**

In *Morganella morganii* infections, since Gentamicin failed to sterilize the infants' blood and body fluids, a combination of Aminoglycoside and a third generation Cephalosporin such as Cefotaxime was found to be necessary ( Ranu *et al*, 1999)

**(xi) Salmonella typhi**

Quinolone resistant strains of *Salmonella typhi* or *paratyphi* have been reported from the Indian sub-continent (Bhutta, 1997). Newborns with *Salmonella meningitis* who relapsed after 4 weeks of Cefotaxime treatment were cured with Imipenem/Cilastin therapy ( Koc *et al*, 1997)

**(xii) Flavobacterium meningosepticum**

For *F meningosepticum*, synergy was observed between Rifampicin and Vancomycin especially in neonatal meningitis, while a combination of Meropenem and Vancomycin was antagonistic. Combinations of Vancomycin, Ciprofloxacin and Linezolid showed additive effect against all isolates. However, combinations of Ciprofloxacin with newer Quinolones or Linezolid need further study (Di Pentima *et al*, 1998)

**(xiii) Enterococci**

It has been found that the high level Aminoglycoside resistant *Enterococci* were sensitive to Vancomycin, while for Gentamicin sensitive strains of *E. Fecium*, Gentamicin and Ampicillin were recommended (Bhat *et al*, 1997). Combinations of Penicillin, Ampicillin or Vancomycin and an Aminoglycoside were also found to be effective (Yurdakok, 1998).

**(xiv) Pseudomonas**

Piperacillin and Azlocillin, Cefoperazone and Ceftazidime were most active against *Pseudomonas* (Yurdakok, 1998)

**(xv) Ureaplasma urealyticum**

*U. urealyticum* is a common isolate in the endo-tracheal tube aspirates of infants with respiratory distress in Malaysia. While Erythromycin was an effective antibiotic, however there was resistance to Lincomycin and Sulphamethaxazole Trimethoprim ( Tay *et al*, 1997). Erythromycin was also found to be effective in reducing colonization, but did not reduce the length of time infants needed supplemental oxygen (Jonson *et al*, 1998).

**(xvi) Candidiasis**

Candidiasis is common in patients exposed to systemic steroids, antibiotics (especially third generation Cephalosporins), catecholamine infusions and mechanical ventilation. Thus, these were used as a basis by clinicians to initiate empirical Amphotericin B in neonates at risk (Benjamin, 2000). It has been found that if blood cultures are positive prompt treatment with Amphotericin B, although these infants also need further evaluation (Rowen & Tate, 1998). Liposomal Amphotericin B has been found to be effective and safe for treatment of fungal infections (Scarcella & Pasquariello, 1998). Very low birth weight infants with *Candida* infections were successfully treated with Amphotericin B with no nephrotoxicity (Weitkamp & Poets, 1998).

**(xvii) Aspergillosis**

The predisposing factors in most cases with Aspergillosis were prematurity, Chronic Granulomatous Disease, complex diarrhoea, malnutrition, corticosteroid administration and invasive bacterial infections. The current therapeutic approach for treatment is high dose Amphotericin B and appropriate surgical interventions (Groll & Jauger, 1998)

**5.5.7. Use of Anti-virals**

**(i) Respiratory syncytial virus infection**

Ribavirin inhalation therapy has been suggested for high-risk infants with clinical symptoms indicating serious Respiratory syncytial virus (RSV) infection (Swedish Consensus Group, 2001). However, there is no place for Ribavirin in routine treatment of lower respiratory tract infection (Van Woensel *et al*, 2001; Greenough, 2001; Rodriguez, 1999)

**(ii) Cytomegalovirus infection**

Ganciclovir administration has been found to decrease the excretion of *Cytomegalovirus* (CMV) in urine, but recurred on cessation of therapy (Whitley *et al*, 1997). It has also

been found that antimicrobial treatment for CMV is unsatisfactory (Brown & Abernathy, 1998).

### **(iii) Herpes Simplex Virus Infection**

Newer anti-herpes agents like Valaciclovir, Famciclovir and Vidarabine have been found to offer no advantage over Acyclovir, and are thus not recommended for neonatal Herpes Simplex Virus (HSV) infection (Jacobs, 1998; Kesson, 2001). Acyclovir shortens the duration of clinical illness and viral shedding, and reduces morbidity and mortality (Kesson, 1998). The use of high dose acyclovir for the management of acute neonatal HSV disease has reduced mortality rates to the lowest level (Kimberlin, 2001). Patients with disseminated HSV treated with high dose Acyclovir had higher survival rates compared with those on standard doses (Kimberlin *et al*, 2001). Oral Acyclovir was demonstrated to prevent cutaneous recurrences of HSV after neonatal skin, ear and mouth infections (Jacobs, 1998). Thus, it has been recommended for patients with non-life threatening illness who may still have significant symptoms (Kesson, 1998). However, care must be taken as a case of Acyclovir-resistant neurocutaneous HSV infection has been reported (Oram *et al*, 2000).

Antiviral therapy for skin, eye, and mouth herpes infection was found to be cost effective, although treatment of the central nervous system or disseminated antiviral therapy saved more lives at an increased cost (Oram *et al*, 2000).

### **(iv) Varicella Zoster**

Intravenous Acyclovir has been suggested to be given to unwell babies with chicken pox (Heuchan & Isaacs, 2001). Acyclovir has also been found to be beneficial in treatment of neonatal Varicella (Singalavanija *et al*, 1999; Ogilvie, 1998). A combination of intravenous Immunoglobulin and Acyclovir has been found to effectively prevent perinatal Varicella. (Huang *et al*, 2001).

### **(v) Sepsis**

Comprehensive therapy including antimicrobials and anti-virals should be initiated in toxic newborns presenting with fever, lethargy, irritability, where it is important to consider a diagnosis of meningitis, until a cause is identified (Norris *et al*, 1999). For neonates with sepsis coverage for viral infections especially HSV, Acyclovir/Vidarabine has been found to be effective if started in early stages. Antivirals are also recommended for neonates whose mothers have a history of sexually transmitted disease to prevent the sequelae of untreated or inadequately treated HSV (D'Andrea & Ferrera, 1998).

#### **5.5.8. Safety**

There were not many references with regard to safety of antibiotics specifically in neonates. The use of Teicoplanin in the treatment of staphylococcal infections has been reported to have not produced any apparent toxicity (Degrease & Bemoan, 1998)

#### **5.5.9. Local situation**

The local sensitivity pattern of common organisms would need to be taken into account in decisions relating to appropriate antimicrobial therapy.

### 5.5.10. Cost

Several strategies have been recommended to attempt to save costs in use of antibiotics. Home antibiotic therapy as an alternative to hospital care has been suggested for patients with rapid recovery from infection, and meeting early discharge criteria, (Wagner et al, 2000). Early discharge may also be possible with reduced cost of treatment if sepsis could be ruled out by a combination of tests (Anwer & Mustafa, 2000). It has been also found that the largest reduction in antibiotic treatment in the ICU setting would be from measures to rule out suspected ventilator associated pneumonia (Fischer et al, 2000). A once daily dose of Gentamicin has also been found to be more cost effective (Krishnan & George 1997; Solomon et al, 1999).

The prices of some of the commonly used antibiotics in the Ministry of Health hospitals are provided in Appendix 2 for reference.

## 6. CONCLUSIONS

### 6.1 Febrile Neutropenias

There is sufficient evidence to support the use of either monotherapy or combination therapy antibiotics, using a third or fourth generation Cephalosporin, and Beta-lactam agent and an Aminoglycoside respectively.

There is scanty data regarding utility of empiric antifungal therapy in neutropenic children with cancer.

There is no good evidence to support the practice of routine antiviral therapy for febrile neutropenia

There is limited data regarding cost-effectiveness of different antibiotic regimens in the treatment of febrile neutropenia.

### 6.2 Meningitis & Encephalitis

There is sufficient evidence of the effectiveness of third generation Cephalosporins to treat *Haemophilus influenza meningitis type b* and *Streptococcus meningitis*

There is no evidence of effectiveness of antibiotics in viral encephalitis, except the use of Acyclovir in *Herpes* encephalitis.

There is evidence that Dexamethasone used with antibiotics reduces hearing loss in *Haemophilus influenza meningitis*.

### 6.3 Community Acquired Pneumonia

There is inadequate data on the effectiveness of various different antibiotics but there is some evidence to support the use of Azithromycin, Amoxicillin, Clavulanate, Erythromycin, Cefuroxime, Macrolides and Penicillin in the treatment of pneumonia.

There is inadequate data on adverse effects and costing

#### **6.4 Sepsis in children**

There is no evidence to support the use of specific antibiotics for sepsis in children, although the commonly used antibiotics were found to be Cefuroxime, Metronidazole, Gentamycin and Ampicillin

There is good evidence to support the use of Polyclonal Intravenous Immunoglobulin as adjuvant treatment for sepsis and septic shock.

#### **6.5 Neonatal Sepsis**

There is evidence to support the use of Penicillin, Ampicillin, Aminoglycosides, Cephalosporins and Vancomycin in the treatment of neonatal sepsis.

There is evidence to support the effectiveness of Liposomal Amphotericin B in Candidiasis

There is also evidence of effectiveness of once daily dose of Gentamicin, but inconclusive evidence on the appropriate duration of antibiotics.

There is evidence to support the use of Vancomycin, and some evidence on the use of Penicillin and Teicoplanin in prophylaxis. There is insufficient evidence on the use of prophylaxis in specific conditions.

There is also insufficient evidence on antibiotics of choice in specific conditions.

There is insufficient evidence to support the use of antiviral agent in various conditions, except for evidence of effectiveness of Acyclovir in Herpes simplex infection and neonatal *Varicella* infection

There insufficient evidence with regards to safety and cost effectiveness of antibiotics in neonates

### **7. RECOMMENDATIONS**

#### **7.1 Febrile Neutropenia**

- (i) Antibiotic therapy in patients with febrile neutropenia can be either with monotherapy or combination therapy.
- (ii) Monotherapy can be initiated with a third or fourth generation Cephalosporin, while combination therapy can be initiated using a Beta-lactam agent and an Aminoglycoside.
- (iii) Routine antifungal or antiviral therapy at the onset of febrile neutropenia are not recommended.

## **7.2 Meningitis & Encephalitis**

- (i) Third generation Cephalosporins should be used to treat meningitis due to *Haemophilus influenza meningitis type b* and *Streptococcus*.
- (ii) Dexamethasone is recommended to be used with antibiotics to reduce the possibility of hearing loss in *Haemophilus influenza meningitis*.
- (iii) Antibiotics are not recommended in viral encephalitis except for the use of Acyclovir in *Herpes* encephalitis.

## **7.3 Community Acquired Pneumonia**

- (i) Oral antibiotics like Azithromycin, Amoxicillin-Clavulanate, Erythromycin Estolate, Amoxicillin, and Co-Trimoxazole may be used in the outpatient treatment of pneumonia.
- (ii) The macrolides may have a role in the older child.
- (iii) For the treatment inpatient of Pseudomonas Community Acquired Pneumonia the Penicillin group of drugs may be used.

## **7.4 Sepsis in children**

- (i) Antibiotics like Cefuroxime, Metronidazole, Gentamycin and Ampicillin can be used to treat sepsis in children.
- (ii) Polyclonal Intravenous Immunoglobulin can be used as an adjuvant treatment for sepsis and septic shock.

## **7.5 Neonatal sepsis**

- (i) Ampicillin, Aminoglycosides, Cephalosporins and Vancomycin can be used in the treatment of neonatal sepsis while Penicillin is recommended for Group B *Streptococcus*
- (ii) Liposomal Amphotericin B is recommended in Candidiasis
- (iii) Gentamycin can be given on a once daily dose where indicated.
- (iv) Vancomycin, Penicillin and Teicoplanin can be used for prophylaxis
- (v) Acyclovir is recommended in Herpes simplex infection and neonatal *Varicella* infection

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**Appendix 1***Current local prices of commonly used antibiotics*

<b>No</b>	<b>Antibiotic</b>	<b>Cost (RM)/ unit</b>
1.	Cap. Azithromycin Dihydrate 250mg	3.97/cap
2.	Cap Amoxicillin 250mg	0.10/tab
3.	Tab Amoxicillin+ Clavulanic Acid 375mg	1.39/tab
4.	Tab Erythromycin ethylsuccinate 400mg	0.26/tab
5.	Tab Cotrimoxazole (Sulphamethoxazole 400mg & Trimethoprim 80mg)	0.043/tab
6.	Syr. Azithromycin Dihydrate 200/5ml	0.73/ml
7.	Syr. Amoxicillin + Clavulanic acid 228mg/5ml	0.23/ml
8.	Susp. Erythromycin Ethylsuccinate 200mg/5ml	0.04/ml
9.	Syr. Amoxicillin Trihydrate 125mg/5ml 125mg/5ml	0.02/ml
10.	Inj Crystalline Penicillin 1 MU	1.28/vial
11.	Inj Crystalline Penicillin 5 MU	3.07/vial

**Appendix 2***Prices of commonly used antibiotics in the Ministry of Health hospitals*

<b>Name</b>	<b>Price/unit (Rm)</b>
IV GENTAMICIN 80 MG	RM 0.43
IV VANCOMYCIN 500 MG	RM 16.82
IV AMIKACIN 200 MG	RM 8.19
IV AMIKACIN 500 MG	RM 14.04
IVPENG 1 MEGA	RM 1.33
IV PEN G 5MEGA	RM 3.28
IV PEN G 2.4 MEGA	RM 3.07
IV IMIPENAM 250 MG	RM 40.50
IV IMIPENAM 500 MG	RM 56.70
IV FORTUM 1 GM	RM 18.33
IV FORTUM 2G	RM 33.99
IV MUPIROCIN 0.7 G	No record
IV CLOXACILLIN 500 MG	RM 1.06
IV AMIPICILLIN 500 MG	RM 0.64
IV CEFOTAXIM I G	RM 11.09
IV CEFOTAXIIM 2 G	RM 26.91
IV UNASYN	RM 13.28
IV CIPROBAY	RM 44.10
IV ZINACEF 750 MG	RM 8.24
IV AMPHOTERISIN B	RM 74.60
IV ZOVIRAX	RM 32.76
IV PIPERACILLIN 2 G	RM 14.13
IV PIPERACILLIN 4 G	RM 23.19
IV CEFOPERAZON / CEFOBID	RM 9.64

**LEVELS OF EVIDENCE SCALE**

<b>Level</b>	<b>Strength of Evidence</b>	<b>Study Design</b>
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of 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*

**EVIDENCE TABLE**

**FEBRILE NEUTROPENIA**

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
1	<p>Charnas R, Luthi AR, Ruch W.</p> <p>Once daily ceftriaxone plus amikacin vs three times daily ceftazidime plus amikacin for treatment of febrile neutropenic children with cancer. Writing Committee for the International Collaboration on Antimicrobial Treatment of Febrile Neutropenia in Children.</p> <p><i>Pediatr Infect Dis J</i> 1997; 16:346-53.</p>	<p>Open, prospective randomised multinational study.</p> <p>N=265 pts with 468 episodes.</p>	<p>Complete response: 66% (119/181) in ceftriaxone-amikacin vs 66%(121/183) in ceftazone-amikacin. Failure: 4% (7/181) in ceftriax.-amik vs 5% (9/183) in ceftaz-amikacin.</p> <p>Safety profiles similar but acquisition &amp; administration costs lower for ceftriax-amikacin group.</p>	<p>Good</p> <p>Moderate sample size.</p> <p>Industry-sponsored study may have an element of bias.</p>
2	<p>Freifeld A,Pizzo P.</p> <p>Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients.</p> <p><i>Pediatr Infect Dis J</i> 1997;16: 140-5.</p>	<p>Review paper focussing on ciprofloxacin &amp; ofloxacin.</p>	<p>Potential benefit for oral quinolones among low risk febrile neutropenic pts.</p> <p>Joint complaints minimal &amp; reversible &amp; thought unrelated to cipro.</p>	<p>Poor</p> <p>Further data needed.</p>
3	<p>Mustafa MM, Carlson L, Tkaczewski I, McCracken GH, Buchanan GR</p> <p>Comparative study of cefepime versus ceftazidime in the empiric treatment of pediatric cancer patients with fever and neutropenia.</p> <p><i>Pediatr Infect Dis J</i> 2001,20; pp.362-9.</p>	<p>Randomised, open label study.</p> <p>N=104 pts</p>	<p>74% (26/35) efficacy in cefepime vs 70%(23/33) of ceftazidime-Rx group.</p> <p>Adverse events comparable in both groups.</p> <p>Cefepime appears safe and effective compared to ceftazidime</p>	<p>Good to fair</p> <p>Small sample size precludes statistical analysis.</p>

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
4	Duzova A, Kutluk T, Kanra G, Buyukpamukcu M, Akyuz C, Secmeer G et al.  Monotherapy with meropenem versus combination therapy with piperacillin plus amikacin as empiric therapy for neutropenic fever in children with lymphoma and solid tumors.  <i>Turk J Pediatr</i> 2001, 43; pp. 105-9.	Randomised trial.  N=90 febrile neutropenic episodes in children with lymphoma and solid tumors.	Success with meropenem comparable with pip./amik.(76.6% vs 64.6%,p=0.25) No serious drug-related adverse event. Meropenem monotherapy as effective as combin. With pip. + amikacin	Good to fair Small sample size. Single center.
5	Fleischack G, Hartmann C, Simon A, Wulff B, Havers W, Marklein G et al.  Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer.  <i>J Antimicrob Chemother.</i> 2001; 47: pp.841-53	Prospective randomised trial.  Mer (n=172 febrile neutropenic episodes) vs ceftaz(n=170)	Gram + bacteremias predominate. Success rate: 55.8% (Mer) vs 40%(ceftaz)(p=0.003 for FUIO but not significant for documented infections. Longer duration of fever(median 5 vs 4d,p=0.022) & A/M Rx(7 vs 6 in ceftaz. arm(p=0.009). Minimal side effects in both arms. Both drugs are useful as empirical monotherapy.	Good
6	Kebudi R, Gorgun O, Ayan I, Gurler N, Akia F, Torea K. Randomized comparison of cefepime versus ceftazidime monotherapy for fever and neutropenia in children with solid tumors.  <i>Med Pediatr Onco</i> 2001; 36, pp. 434-41.	Randomised trial.  N=63 febrile episodes(.N=32 Cefepime vs N=31ceftaz).	Success rate 62.5% cefepime vs 61.3% ceftaz No major adverse effects in both arms. Cefepime as effective and safe as ceftazidime	Good to fair Small sample size.

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
7	<p>Ariffin H, Arasu A, Mahfuzah M, Ariffin WA, Chan LL et al.</p> <p>Single-daily ceftriaxone plus amikacin versus thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropenia in children with cancer.</p> <p><i>J Paed Child Health</i>, 2001;37, pp.38-43.</p>	<p>Open-label ,randomised.</p> <p>N=128 pts</p>	<p>Success rate==55%, (ceftriax) vs 51.2%(ceftaz)</p> <p>Mean time to defervescence was 4.2d(ceftriax) vs 4.3d(ceftaz), Daily cost of once daily regimen was RM42 less vs thrice-daily regime.</p> <p>Convenience &amp; substantial cost benefit of daily Rx. No significant adverse events in either group.</p>	<p>Good to fair</p> <p>Moderate sample size.</p> <p>Single center study needs validation.</p>
8	<p>Shenep JL, Flynn PM, Baker DK, Hetherington SV, Hudson MM, Hughes WT et al.</p> <p>Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer</p> <p><i>Clin Infect Dis</i> 2001,32, pp.36-43..</p>	<p>Randomised cohort.</p> <p>N=156 pts</p>	<p>Rx failures similar in both groups: IV(27%) vs cefixime (28%)</p> <p>Safety of oral cefixime confirmed.</p>	<p>Good to fair</p> <p>Moderate sample size.</p> <p>Single center study require validation.</p>
9	<p>Sidi V, Roilides E, Bibashi E, Gompakis N, Tsakiri A, Kolioukas D.</p> <p>Comparison of efficacy and safety of teicoplanin and vancomycin in children with antineoplastic therapy-associated febrile neutropenia and gram-positive bacteremia.</p> <p><i>J Chemother.</i> 2000; 12, pp.326-31.</p>	<p>Randomised trial.</p> <p>N=32 pts &amp; 52 gram + bacteremias.</p> <p>25 episodes treated with teicoplanin &amp; 21 with vancomycin plus ceftazidime &amp; netilmicin.</p>	<p>Defervescence on 3<sup>rd</sup>-4<sup>th</sup> day occurred in 29/31(93.5%) teicoplanin Rx vs 18/21(85.7%) vancomycin Rx.</p> <p>All 12 teicoplanin Rx &amp; 13/13 vancomycin Rx showed microbiologic response.</p> <p>Mild renal insufficiency in 5 vancomycin Rx pts. But self-correctable.</p> <p>Both exhibit clinical &amp; microbiologic efficacy but teicoplanin less likely to induce allergic rxn or nephrotoxicity.</p>	<p>Good to fair</p> <p>Small sample size precludes accurate deduction.</p>

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
10	Furno P, Dionisi MS, Bucaneve G, Menichetti F, Del Favero A.  Ceftriaxone versus beta-lactams with antipseudomonal activity for empirical, combined antibiotic therapy in febrile neutropenia: a meta-analysis.  Supportive Care in Cancer. 2000; 8, pp.293-301.	Meta-analysis  N=1,537 febrile episodes.	256/782(32.7%) Rx failures with ceftriax-comb. vs 243/755(32.1%) with antipseudomonal beta-lactams. Pooled OR of death for ceftriax =0.84 54/782(6.9%) vs 62/755(8.2%) with antipseudomonal beta-lactams. Ceftriax. Comb are as effective as those antipseudo. beta-lactams.	Good Good study. However, prevalence of pseudomonas sepsis in all the trials not known.
11	Aquino VM, Herrera L, Sandler ES, Buchanan GR.  Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer.  <i>Cancer</i> . 2000; 88; pp. 1710-4.	Cohort study.  N=32 children with 45 febrile episodes.	40/45(89%) pts Rx successfully in outpatient. Lower 95% CI for successful Rx=70%	Good to Fair Small sample size.
12	Paganini HR, Sarkis CM, De Martino MG, Zubizarreta PA, Casimir L, Fernandez C et al.  Oral administration of cefixime to lower risk febrile neutropenic children with cancer.  <i>Cancer</i> 2000; 88:2848-52.	Randomised trial.  N=128 children. 154 febrile episodes.	Favourable outcome comparable in both groups (98.6% GpA vs 97.5% GpB)	Good Moderate sample size. Safe & cost-saving.

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
13	<p>Arrifin H, Navaratnam P, Mohamed M, Arasu A, Abdullah WA, Lee CL.</p> <p>Ceftazidime-resistant <i>Klebsiella pneumoniae</i> bloodstream infection in children with febrile neutropenia.</p> <p><i>Int J Infect Dis.</i> 2000; 4, pp. 21-5.</p>	<p>Prospective prevalence study.</p>	<p>CRKP seen in 51.6% of all isolates. Prolonged hospital stay (&gt;2weeks) &amp; prior use of Ceph3 are at high risk of CRKP bacteremia. Sepsis-related mortality higher in CKRP group(50% vs 13.3%;p=0.02)</p>	<p>Poor Single center study. Local epidemiology may vary. Importance of CKRP in the local setting emphasised.</p>
14	<p>Klaassen RJ, Allen U, Doyle JJ.</p> <p>Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia.</p> <p><i>J Pediatr Hematol Oncol.</i> 2000; 22(5): pp. 405-11.</p>	<p>Randomised placebo-controlled trial.</p> <p>N=73 pts (N=37 on oral cloxa &amp; cefixime &amp; N=36 on placebos)</p>	<p>5(14%) pts in A/B arm and 2(6%) in placebo arm were readmitted to hospital with recurrent fever while still neutropenic . All readmissions were uneventful and no fatalities.</p>	<p>Good to fair Small sample size. Supports discontinuation of A/B in low-risk patients with neutropenia on d/c.</p>
15	<p>Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A.</p> <p>Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients:randomized prospective trial.</p> <p><i>Med Pediatr Oncol</i> 2000 Feb;;34(2):87-91</p>	<p>Randomised prospective trial.</p> <p>Low-risk patients (N = 70) with episodes of fever and neutropenia (N = 116) were randomized to receive either oral ciprofloxacin or intravenous ceftriaxone as outpatients.</p>	<p>The mean duration of neutropenia was 5 vs. 6 days. Fever persisted for 1-9 days (mean 2 vs. 3 days). Therapy was successful with no modifications in 83% vs. 75% of the episodes. Patients were admitted in 7% vs. 4% of the episodes. No bone or joint side effects were seen in either group. All patients survived. Outpatient therapy with either oral ciprofloxacin or intravenous ceftriaxone for fever and neutropenia is effective and safe in pediatric patients with solid tumors and stage I/II non-Hodgkin lymphoma (low-risk patients).</p>	<p>Good to fair Small sample size.</p>

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
16	Ramphal R.  Is monotherapy for febrile neutropenia still a viable alternative?  <i>Clin Infect Dis</i> 1999 ; 29 :508-14.	Review	MonoRx is effective & less costly. Cefepime/ceftazidime/meropenem monoRx is a viable therapeutic approach.	Poor
17	Feld R.  Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons.  <i>Clin Infect Dis</i> 1999; 29:503-7	Review	no need to add vancomycin, in initial empirical Rx. Most experts recommend vancomycin not be part of initial empirical Rx.	Poor
18	Tomlinson RJ, Ronghe M, Goodbourne C, Price C, Lilleyman JS, Das S et al.  Once daily ceftriaxone and gentamicin for the treatment of febrile neutropenia.  <i>Arch Dis Child</i> 1999; 80:125-31.	N=59 pts with 113 febrile episodes	86/113(76%) episodes settled with first line antibiotic regimen. No failure of Rx in organisms sensitive to gentamycin. No vestibular toxicity, 3/30(10%) children underwent PTA reported high frequency hearing loss in one ear. OD gentamycin can be used safely & effectively. When used for short periods (<5d), in children not receiving other nephrotoxic drugs & who have normal serum creatinine, serum gentamycin. Estimations are unnecessary.	Fair  Small sample size.

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
19	<p>Freifeld A, Marchigiani D, Walsh T, Chanock S, Lewis L, Hiemenz J, Hiemenz S, Hicks JE, Gill V, Steinberg SM, Pizzo PA.</p> <p>A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy.</p> <p><i>N Engl J Med</i> 1999 Jul 29;341(5):305-11</p>	<p>Randomised trial.</p> <p>N=116 episodes (84 patients in the oral-therapy group and 79 patients in the intravenous-therapy group).</p>	<p>Treatment was successful without the need for modifications in 71 percent of episodes in the oral-therapy group and 67 percent of episodes in the intravenous-therapy group (difference between groups, 3 percent; 95 percent confidence interval, -8 percent to 15 percent;</p> <p>Inability to tolerate the regimen in 16 percent and 1 percent of episodes, respectively</p> <p>Incidence of intolerance of the oral antibiotics was 16 percent, as compared with 8 percent for placebo</p> <p>In hospitalised low-risk patients who have fever and neutropenia during cancer chemotherapy, empirical therapy with oral ciprofloxacin and amoxicillin-clavulanate is safe and effective.</p>	Good
20	<p>Mullen CA, Petropoulos D, Roberts WM, Rytting M, Zipf T, Chan KW, Culbert SJ, Danielson M, Jeha SS, Kuttesch JF, Rolston KV.</p> <p>Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients.</p> <p><i>Cancer</i> 1999 Jul 1; 86(1):126-34</p>	<p>Randomised study.</p> <p>Patients were evaluated, received a single dose of intravenous ceftazidime, and were observed for 3-16 hours.</p>	<p>Seventy-three episodes of F&amp;N in 41 patients 31 of 33 episodes in the ceftazidime arm, the patients remained outpatients, compared with 32 of 40 in the ciprofloxacin arm; this difference was not statistically significant.</p> <p>Carefully selected low risk children with fever and neutropenia can be treated safely as outpatients.</p>	Good to Fair Small sample size.
21	<p>Castaglonola E, Paola D, Giacchino R, Rossi R, Viscoli C.</p> <p>Economic aspects of empiric antibiotic therapy for febrile neutropenia in children.</p> <p><i>Supportive Care in Cancer</i> 1998; 6: 524-8.</p>	<p>Acquisition costs of various drugs calculated.</p>	<p>Ceftriax. + aminoglyco are less expensive compared to other regimens eg. Mono Rx with Cephalosporins or carbapenems.</p>	Poor Acquisition costs may vary locally.

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
22	Karthus M, Egerer G, Kullmann KH, Ritter J, Jurgens H.  Ceftriaxone in the outpatient treatment of cancer patients with fever and neutropenia.  <i>Eur J Clin Micro Infect Dis</i> 1998;17: 501-4.	N=120 pts with 126 febrile episodes.	Initial Rx with ceftriaxone alone or in combination, successful in 99 episodes (78%). 95 episodes (76%) successfully Rx in outpatient. No infection-related death.	Good to Fair Mono Rx is an option in low-risk febrile neutropenia.
23	Gaya H.  Empirical therapy of infections in neutropenic patients.  <i>British J Haematol</i> 1998; 101(1S):5-9.	Review.	Empiric antibiotic therapy for febrile neutropenia is standard practice. Carbapenem monotherapy may be as effective as combination with beta-lactam and aminoglycoside. Low risk patients may be treated on an ambulatory basis. Broad coverage for gram-negative pathogens is essential. Antibiotic resistance pattern should be considered.	Poor Expert review.
24	Viscoli C, Castagnola E.  Planned progressive antimicrobial therapy in neutropenic patients.  <i>Br J Haematol</i> 1998; 102:879-88.	Review	Empiric antibiotic therapy should be started for febrile neutropenia. Specific composition of the empirical therapy remains controversial. Monotherapy versus combination therapy controversial. Factors to consider: results of clinical trials, local antibiotic policies, bacteriological statistics, resistance pattern, antibiotic toxicity & cost, patient-related factors. Empiric antifungal therapy may be considered for patients with febrile neutropenia until the 5 <sup>th</sup> or 7 <sup>th</sup> day of appropriate antibiotics.	Poor Expert review.

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
25	<p>Bohme A, Shah PM, Stille W, Hoelzer D.</p> <p>Piperacilin-tazobactam versus cefepime as initial empirical antimicrobial therapy in febrile neutropenic patients: a prospective randomized study.</p> <p><i>Eur J Med Research</i> 1998;3:324-30.</p>	<p>Prospective randomised study.</p> <p>N=102 febrile episodes.</p>	<p>Response rate similar in both groups : Piperacillin-tazobactam 22/51 (43%) vs cefepime 19/49 (39%). Piperacillin-tazobactam. &amp; cefepime might be sufficient initial mono Rx.</p>	<p>Good</p> <p>Small sample size needs validation.</p>
26	<p>Krivoy N, Postovsky S, Elhasid R, Ben Arush MW.</p> <p>Pharmacokinetic analysis of amikacin twice and single daily dosage in immunocompromised pediatric patients.</p> <p><i>Infection</i> 1998 Nov-Dec; 26(6):396-8</p>	<p>Ten children received amikacin twice daily and 13 were treated using the single daily protocol.</p>	<p>A single daily dose of amikacin had a significantly longer elimination half-life, lower clearance, higher peak concentration and lower trough concentration in comparison to the twice-daily schedule. The use of amikacin 20 mg/kg daily delivered in a single daily dose is recommended for immunocompromised pediatric patients with fever and neutropenia, in spite of the measured pharmacokinetic differences.</p>	<p>Fair</p> <p>Small sample size.</p>
27	<p>Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R et al.</p> <p>1997 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever.</p> <p><i>Clin Infect Dis</i> 1997; 25:551-73.</p>	<p>Evidence-based practice guidelines from IDSA</p>	<p>One of three regimens for initial antibiotic therapy:  If vancomycin needed: vanco.+ceftaz.  If vancomycin not needed:  a. Monotherapy with ceftazidime/imipenem/cefepime /meropenem  b. Aminoglycoside + antipseudomonal beta-lactam  If febrile on days 5-7,add amphotericin B with or without antibiotic changes.  Use of antiviral agents not routine, Use of colony-stimulating factors not routine.  Antibiotic prophylaxis for afebrile neutropenic patients not routine except for PCP prophylaxis.</p>	<p>Good</p> <p>Good evidence-based guidelines developed by experts</p>

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and & Comments
28	<p>Viscoli C, Paesmans M, Sanz M, Castagnola E, Klastersky J, Martino P, Glauser M.</p> <p>Association between antifungal prophylaxis and rate of documented bacteremia in febrile neutropenic cancer patients.</p> <p><i>Clin Infect Dis</i> 2001 Jun 1;32(11):1532-7</p>	<p>Retrospective analysis.</p> <p>N=3002 febrile neutropenic patients</p> <p>F/up : 1986-1994.</p>	<p>Globally, 1322 patients (44%) did not receive antifungal prophylaxis; 835 (28%) received poorly absorbable antifungal agents and 845 (28%) received absorbable antifungal agents.</p> <p>The rates of bacteremia for these groups were 20%, 26%, and 27%, respectively In a multivariate model without including antifungal prophylaxis, factors associated with bacteremia were: age, duration of hospitalisation, duration of neutropenia before enrollment, underlying disease, presence of an intravenous catheter, shock, antibacterial prophylaxis, temperature, and granulocyte count at onset of fever. When antifungal prophylaxis was included, the adjustment quality of the model improved slightly, with an odds ratio of 1.19 for patients receiving nonabsorbable and 1.42 for those who were receiving absorbable antifungal agents.</p> <p>Antifungal prophylaxis with absorbable agents might have an impact on the rate of documented bacteremia in febrile neutropenia.</p>	Fair

## MENINGITIS

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
1	Dawson KG, Emerson JC, Burns JL  15 years of experience with bacterial meningitis  <i>Pediatr Infect Dis J</i> 1999 Sept; 18(9): 816-22	Retrospective study  N=806 cases  F/U- 1981-1995	Commonest cause of bacterial meningitis was H influenza, Strep pneumonia and N meningitides  Changing pattern of meningitis was observed after introduction of the unconjugated and conjugated vaccines. H influenza was the commonest organism for the first 2 periods. Dropped to third place in the 3 <sup>rd</sup> 5 <sup>th</sup> period. No cases caused by Streptococcus pneumonia and Neisseria meningitides have remained steady	Poor
2	Kuruvilla KA, Thomas N  Neonatal group B streptococcal bacteremia in India : 10 years experience  <i>Acta Pediatric</i> 1999 Sep: 88(9): 1031-2	Observational	In perinatal center in India with 60,119 live births between 1988-1997, GBS isolated from blood C&S of 10 babies. (incidence 0.17/1000 LB)  No cases of late onset disease. Low incidence could be due to low rate of colonization & high prevalence of protective antibody in mothers.	Poor
3	Lee HJ  Epidemiology of systemic Haemophilus influenza diseases in Korean children  <i>Pediatr Infect Dis J</i> 1998 Sep 17 (Suppl 9) S185-189	Epidemiology	48 H influenza infections 25 meningitis 44% < 1 year old 92% < 5 years old	Poor
4	Hussein Imam, Sofiah Ali, Ong LC  Haemophilus influenza meningitis in Malaysia  <i>Pediatr Infect Dis J</i> 1998, Sep 17( Suppl 9) S 189-90	Retrospective cCross sectional  N=435 patients	Overall incidence in first 5 years of life: 76.6/100 000 per year Haemophilus influenza meningitis accounted for 48% of all bacteriological proven cases	Poor

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
5	Sung RY, Senok AC, Oppenheimer SJ, Davies DP Meningitis in Hong Kong children with special reference to the infrequency of haemophilus influenza and the meningococcal infection  <i>J Paediatr Child Health</i> 1997 Aug; 33 (4): 296-9	Retrospective N= 85 children F/U -9 year period	Mycobacterium bacteria was the commonest aetiological agent for meningitis in Hong Kong -15.3% The incidence of Haemophilus influenza and meningococcal meningitis was very low. Annual incidence rate of bacterial meningitis not including TB In children<5 years old : 5.2/100 000 For children >5 but > 15 years old : 1.6/100 000 Meningococcal disease <5 years of age: 13/100 000.All occurred in Vietnamese children	Poor .
6	Almuneef M, Memish Z, Khan Y et al  Childhood bacterial meningitis in Saudi Arabia  <i>J Infect</i> 1998,36(2): 157-60	Retrospective study  N= 70 children over a 11 years study period	Causative organisms: Haemophilus influenza 66%, Strep pneumonia 24%, N meningitides 4%, Gp B Strep 4%, Staph aureus:2%, Only I case resistant to penicillin Haemophilus influenza meningitis is the predominant meningitis.	Poor The Hib vaccine was not available during the study period
7	McIntyre PB, Berkey CS,King SM et al  Dexamethasone as adjunctive therapy in bacterial meningitis A meta-analysis of randomized clinical trials since 1988  JAMA 1997 Sep 17, 278(11): 925-31	Meta analysis	Adjunctive dexamethasone therapy reduced severe hearing loss for H influenza type b meningitis whether dexamethasone was given before or with antibiotics. For strep pneumonia meningitis, there was a suggested protection against hearing loss only if given earlier. For all organisms combined the pooled odds ratio suggested protection against neurological deficits other than hearing loss but this is not significant. Limiting dexamethasone to 2 days may be optimal	Good

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
8	<p>Arditi M; Mason EO, Bradley JS et al</p> <p>Three year multicenter surveillance of pneumococcal meningitis in children, clinical characteristics and outcome related to penicillin susceptibility and dexamethasone use</p> <p><i>Pediatrics</i> 1998 Nov; 102(5): 1087-97</p>	<p>Retrospective chart review</p> <p>N=180</p> <p>F/up: 3 year period -Sept 1993 to August 1996</p>	<p>Results-7.7% deaths, 25% neurological deficits 32% unilateral and bilateral hearing deficits at discharge. 12.7% and 6.6% pneumococcal isolates have intermediate and complete resistance to penicillin respectively. 4.4% have intermediate resistance to ceftriaxone. 40% of children were given Dexamethasone. Dexamethasone had no beneficial effect to reduce disease severity. Incidence of moderate to severe hearing loss was higher in the dexamethasone group (46% vs 23%). incidence of neurological deficits including hearing loss was also higher in the dexamethasone group (55% vs 33%)</p>	Poor
9	<p>Stanek RJ, Mufson MA</p> <p>A 20- year epidemiology study of pneumococcal meningitis</p> <p><i>Clin Inf Dis</i> 1999 Jun;28 (6) 1265-72</p>	<p>Retrospective study</p> <p>N=55 Strep pneumonia meningitis (adult and child)</p> <p>F/up:1978-1997</p>	<p>14 (36.8%) of 38 adults died, 2(11.8%) of 17 children died due, serotypes 6,23,13,18 were predominant, serotype 19(1), serotype 23(2), The above serotypes have moderate to high resistance to penicillin Multidrug resistance emerged during this period Due to emergence of penicillin non-susceptible pneumonia treatment regimens now include cephalosporins and vancomycin</p>	Poor
10	<p>Coyle PK</p> <p>Glucocorticoids in Central Nervous System bacterial infections</p> <p>pcoyle@ neuro.som.sunny.edu</p>	<p>Review</p>	<p>To evaluate mortality and morbidity rates on adjuvant dexamethasone therapy in CNS bacterial meningitis including TB meningitis</p> <p>Conclusive only for H influenza meningitis Optimal duration for dexamethasone 2 vs 4 days is still not known</p>	Good to Fair

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
11	Greenwood B  The epidemiology of pneumococcal infections in children in the developing world  <i>Philo Trans R Soc Land B Biol Sc</i> 1999 April 29 1384: 777-85	Review	100 000 to 500 000 deaths from bacterial meningitis. Sickle cell disease and perinatally acquired HIV infections play a role as predisposing factors. Pneumococci infections could be treated with penicillin, a cheap and safe antibiotic. Pneumococci that are resistant to penicillin is becoming prevalent	Poor
12	Gold R  Epidemiology of bacterial meningitis  <i>Infect Dis Clin North Am</i> 1999 Sep 13 (3) 515 -25	Epidemiology study	Bacterial meningitis caused by Haemophilus influenza type b has almost disappeared in USA, Canada and other countries after implementation of routine vaccination. Overall incidence of meningitis has decreased by 50% Clusters of meningococcal disease in school children (serotype 2a) Age of susceptibility has shifted to adult patients	Poor
13	Limcangco MR, Salole EG, Armour CL  Epidemiology of Haemophilus influenza type b meningitis in Manila, Phillipines 1994-1996  <i>Pediatr Infect Dis J</i> 2000 Jan: 19(1) 7-11	Cohort study  N= 415 992 children less than 5 years old is the study population  F/U- Jan 1994-Dec 96	Hib meningitis in central Manila is common. Confirmed cases of Hib meningitis in 118. Particularly high in <6/12months age group. 15 % sequelae, 1% case fatality rate Adverse neurological outcomes and high case fatality rates in children less than 1 year of age	Poor
14	Skoczynska A, Kriz P, Konradsen HB et al  Characteristics of the major aetiologic agents of bacterial meningitis isolated in Poland 97-98  <i>Microb Drug Resist</i> 2000 Summer; 6 (2): 147-53	N=220 isolates were sent to NRBCM  F/U- 1997-1998	N meningitis(40.9%), H influenza (26.4%), S pneumonia(20.9%). Of the meningococcal isolates, 88.9% were serogroup B and 10% were serogroup C.10% had reduced susceptibility to penicillin 90% of H influenza belonged to type b. All were sensitive to third generation cephalosporin and CMC. Amongst pneumococcal isolates, 13 % were not susceptible to penicillin	Poor

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
15	Shembesh NM, Elbargarthy SM, Kashbur IM  Dexamethasone as an adjunctive therapy of bacterial meningitis	N= 77 Libyan children with bacterial meningitis from the ages of 1 month to 10 years	CSF sugar, protein and PMNL were compared between both groups. Significant difference between the 2 groups Dexamethasone: decreased the duration of fever and had no changes on the neurological deficit or fatality rates	Good to Fair
16	Eriksson M, Henriques B, Ekdahl K  Epidemiology of pneumococcal infections in Swedish children  <i>Acta Paediatr Suppl</i> 2000 Dec; 89 (435): 35-39	Retrospective review of 10 year. Cases of meningitis in Northern Stockholm	Meningitis is the most severe manifestation. Prevalence: 10/100 000 in (0-2 years) age grp and 5.8/100 000 (0-5 years) Serotype 7,6,14,23. Decreasing order sensitivity to penicillin (0.2%-11%). Severe sequelae seen in 20%. Large proportion of serotype 7. At present 7-9 valent protein conjugated vaccine Heptavalent 4,6b,9v,18c,19f,23f, Converage 18% of resistant isolates	Poor
17	Spanjaard L, van der Ende A  Epidemiology of meningitis and bacteraemia due to Streptococcus pneumonia in the Netherlands The Netherlands ref lab for bacterial meningitis  spanjaard@amc.uva.nl	Cross sectional study	Pneumococcal meningitis incidence rate: 1/100 000 in 1990 to 1.5/100 000 in 1996 Highest incidence < 5 years (8.2/100 000 in 1999) Serotype 3,6b,9v,14,18c,19f,23f are prevalent Pneumococcal resistance to penicillin 1%	Poor
18	Uduman SA, Adeyani E, El Khadir A  H influenza type b meningitis still remains a leading cause of meningitis among unvaccinated children: Prospective CSF analysis study <a href="mailto:uduman@emirate.net.ae">uduman@emirate.net.ae</a>  <i>J Trop Paediatr</i> 2000 Dec 46 96) 331-4	Prospective hospital based CSF analysis.  N= 65 children with bacterial meningitis diagnosed on admission.	H influenza meningitis diagnosed by positive CSF C&S in 4 and by antigen detection in 9. Strep pneumonia meningitis diagnosed by positive CSF C&S in 1 and by antigen detection in 3. 42 children had normal CSF studies Leading cause of meningitis; Haem influenza. Incidence rate Hib meningitis; 31/100 000 children < 5	Poor

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
19	Principi N, Marhisio, P  Epidemiology of Streptococcus pneumonia in Italian children  <i>Acta Paediatr Suppl</i> 2000 Dec; 89 (435): 40-3	Cross sectional study	Incidence rate 1.1/100 000 0-4 years. Incidence of penicillin resistance is 10.2% Serotypes 14,6,23,1,4 in decreasing order resistant to penicillin. Incidence of macrolide resistance 25%	Poor
20	Rotbart HA,  Treatment of potentially life- threatening Enterovirus infections with pleconoril  <i>Clin Infect Dis</i> 2001 Jan 15;32 92) 228-35	Prospective cohort study  N=38. There were 15 patients $\leq$ 16 years old and 6 with neonatal enterovirus infections	Clinical response is (defined as diminishment of $\geq$ than 1 of the prominent presenting symptoms and signs)-28 of 36 had favorable response (78%). Virological response (defined as reversion from Enterovirus culture positive to Enterovirus culture negative)-12 out of 13 Laboratory responses (normalization or substantial improvement in a previously abnormal lab characteristic for the specific disease)-14 out of 16 Radiological responses (objective improvements in the findings of MRI or technetium-99 m bisicate brain scanning or CXR before and after therapy): 3 out of 5 Adverse effects: nausea, vomiting, fatigue weakness and others. 7 patients classified as severe, 23 as moderate and 11 as mild and 8 deaths.	Poor  Not all adverse effects was detailed in the paper
22	McMinn P, Stratov I, Nagarajan L  Neurological manifestations of EV 71 infection in children during an outbreak of hand, foot and mouth disease in Western Australia  <i>Clin Infect Dis</i> 2001; Jan 15:32 (2): 326-42	Feb 99 through Sept 99 EV outbreak in Perth, Western Australia involving 16 children 14 culture proven 9 (64%) had severe neurological disease Varied neurological disease These were: Aseptic meningitis Guillain barre syndrome Acute transverse myelitis Acute cerebellar ataxia	Clinically indistinguishable from Coxsackie virus a 16 infections, EV71 isolated from stool, nasopharynx, skin vesicle and CSF, Serology : Assay of EV71 specific antibodies in serum samples by microneutralization techniques during acute and convalescent phases No effective antiviral therapy, IV IG was administered in 4 patients: No benefit	Poor

No	Title, Author, Year	Type of Study, sample Size, follow up	Characteristics and Outcome	Grade and Comments
23	Mc Grath N, Anderson NE, Croxson MC, Powell KF  Herpes simplex encephalitis treatment with acyclovir; diagnosis and long term outcome  <i>J Neurol Neurosurg Psychiatry</i> 1997 Sept; 63 (3): 321-6	Prospective  N= 42 patients and all patients were given Acyclovir	Diagnosed via the following techniques: Herpes simplex virus culture from brain Increase in CSF HSV antibody titre Detection of HSV deoxyribonucleic acid in CSF Acyclovir decreased mortality in HSV encephalitis.30% of patients died or developed severe neurological deficits 70% regained independence in activities of daily living	Poor
24	Utley TF Oigden JA  The long term outcome of herpes neuropsychological outcome of herpes encephalitis in a series of unselected individuals  <i>Neuropsychiatry neuropsychol Behav neurol</i> 1997 July 10 (3) 180-9	22 adults confirmed HSE –acyclovir treated All under went neuropsychological assessment	Conclusion: better cognitive function found in participants where there was a short delay (<5/7) between onset of symptoms and acyclovir treatment	Poor
25	Hsiung GD, Wary JR  Enterovirus infections with special refence to EV 71 <i>J Microbiol Immuno Infect</i> 2000 Mar; 33(1): 1-8	Enteroviruses : large group of immunologically distinct serotypes Picornoviruses	Many cause infections EV 71 epidemiology in Taiwan in 98 was a fatal infection Polio V, Coxsackie A, Coxsackie B, ECHO Enteroviruse 68-71, Virus isolation : Best method of is CNS isolation : maybe by PCR, Final identification serotyping of enteroviruses using monoclonal antibody, pleconoril orally bioavailable	Poor
26	Farida Jamal  Emergence of antibiotic resistant Strerptococcus pneumonia in Malaysia  <i>M'sian J Childhealth</i> 1997; 9(2)::174-77	Review	1987 : 90 isolates, 4.7% penicillin resistant 1995 : 86 isolates, 8% penicillin resistant 996 : 300 isolates, 7.8% penicillin resistant	Poor

## PNEUMONIA

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
1	Toikka P, Juven T, Virkki R, Leinonen M, Mertsola J, Ruuskanen O  Streptococcus pneumoniae and Mycoplasma pneumoniae coinfection in community acquired pneumonia.  Arch Dis Child 2000 Nov;83(5):413-4	Case report  N=254 patients CAP	Evidence of Streptococcus pneumoniae and Mycoplasma pneumoniae coinfection in 9 patients are described. M pneumoniae was diagnosed in 17 patients.	Poor
2	Drummond P, Clark J, Wheeler J, Galloway A, Freeman R, Cant A  Community acquired pneumonia--a prospective UK study.  Arch Dis Child 2000 Nov;83(5):408-12	Prospective study  N=136 patients	19 (14%) a bacterium (7%) group A Streptococcus, 4% Streptococcus pneumoniae), Pneumococcal pneumonia was the most common bacterial cause of under 2 years but not in older children Fifty (37%) had a virus implicated (65% respiratory syncytial virus) Viral infection accounted for 71% of the cases	Poor
3	McCracken GH  Diagnosis and management of pneumonia in children.  Pediatr Infect Dis J 2000 Sep;19(9):924-8	Review	Streptococcus pneumoniae as the primary bacterial cause of pneumonia in infants and children. In developed countries S. pneumoniae. Probably accounts for 25 to 30% of cases of pediatric community-acquired pneumonia. Chlamydial infections become more prevalent with increasing age. Mycoplasma infections become more prevalent with increasing age. Viral etiologies become less prevalent with increasing age.	Poor
4	Clements H, Stephenson T, Gabriel V, Harrison T, Millar M, Smyth A, Tong W, Linton CJ  Rationalised prescribing for community acquired pneumonia: a closed loop audit  Arch Dis Child 2000 Oct; 83(4):320-4	Retrospective and prospective audit  N= 89 children	51 microbiological diagnoses were achieved in 48 children. Seven children had Streptococcus pneumoniae infection, 14 children had Mycoplasma infection 51 microbiological diagnoses were achieved in 48 children. Twenty-three children had a viral cause of which respiratory syncytial virus was commonest	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
5	Rowe AK, Deming MS, Schwartz B, Wasas A, Rolka D, Rolka H, Ndoyo J, Klugman KP  Antimicrobial resistance of nasopharyngeal isolates of <i>Streptococcus pneumoniae</i> and <i>Haemophilus influenzae</i> from children in the Central African Republic.  <i>Pediatr Infect Dis J</i> 2000 May;19(5):438-44	A cross-sectional survey  N=371 ill children	NPA cultures Out patients 272 SP 73 HI	Poor
6	Juven T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, Eskola J, Saikku P, Ruuskanen O  Etiology of community-acquired pneumonia in 254 hospitalized children.  <i>Pediatr Infect Dis J</i> 2000 Apr;19(4):293-8	Prospective study  N=254 children  F/up:3-year	A potential causative agent was detected in 215 (85%) of the 254 patients. 53% had bacterial infection. 30% had evidence of concomitant viral-bacterial infection. <i>Streptococcus pneumoniae</i> (37%), 1 out of 125 blood cultures were positive. A potential causative agent was detected in 215 (85%) of the 254 patients. Sixty-two percent of the patients had viral infection of which respiratory syncytial virus (29%) and rhinovirus (24%)	Poor
7	Levine OS, Liu G, Garman RL, Dowell SF, Yu S, Yang YH  <i>Haemophilus influenzae</i> type b and <i>Streptococcus pneumoniae</i> as causes of pneumonia among children in Beijing, China.  <i>Emerg Infect Dis</i> 2000 Mar-Apr; 6(2): 165-70	Non randomized control study  N=96 patients (214 age-matched control)	Pneumonia patients were more likely to be colonized <i>S. pneumoniae</i> than control patients	Good to fair

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
8	Ruuskanen O, Mertsola J  Childhood community-acquired pneumonia.  <i>Semin Respir Infect</i> 1999 Jun; 14(2): 163-72	Review	Streptococcus pneumoniae, Mycoplasma pneumoniae, and respiratory syncytial virus are the most common causative agents. Streptococcus pneumoniae, Mycoplasma pneumoniae, and respiratory syncytial virus are the most common causative agents. Streptococcus pneumoniae, Mycoplasma pneumoniae, and Respiratory syncytial virus are the most common causative agents.	Poor
9	Greenwood B  The epidemiology of pneumococcal infection in children in the developing world. Philos Trans R Soc Lond B  <i>Biol Sci</i> 1999 Apr 29; 354(1384):777-85	Review	Streptococcus pneumoniae (pneumococcus) is the most important bacterial cause of pneumonia in young children	Poor
10	Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, Abramo T, Leinonen M, McCracken GH  Etiology and treatment of community-acquired pneumonia in ambulatory children.  <i>Pediatr Infect Dis J</i> 1999 Feb; 18(2):98-104	Randomized controlled trial  N=174 patients, (68 of whom fulfilled protocol criteria for evaluation ) F/u: 6 months to 16 years	Etiologic agents were identified in 73 (43%) of 168 patients. Infection was attributed to S. pneumoniae in 27% (35 of 129)	Good to fair
11	Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, Juvonen H, Kallinen S, Sten M, Tarkiainen A, Ronnberg PR, Kleemola M, Makela PH, Leinonen M  Etiology of childhood pneumonia: serologic results of a prospective, population-based study.  <i>Pediatr Infect Dis J</i> 1998 Nov; 17(11): 986-91	Cohort studies prospective  N=201	Serologic evidence of specific microbial etiology was obtained in 133 (66%). Streptococcus pneumoniae was the most common agent (57 cases; 28%). S. pneumoniae is an important organism in the etiology of community-acquired pneumonia in children of all ages.	Fair

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
12	Tran TT, Le QT, Tran TN, Nguyen NT, Pedersen FK, Schlumberger M  The etiology of bacterial pneumonia and meningitis in Vietnam.  <i>Pediatr Infect Dis J</i> 1998 Sep; 17(9 Suppl): S192-4	Descriptive studies  N=213 bacteremic pneumonia cases	92.5% of blood cultures grew <i>Streptococcus pneumoniae</i> and only 1% grew Hib.	Poor
13	Yang Y, Shen X, Jiang Z, Liu X, Leng Z, Lu D, Rao J, Liu J, Chang L  Study on <i>Haemophilus influenzae</i> type b diseases in China: the past, present and future.  <i>Pediatr Infect Dis J</i> 1998 Sep ;17(9 Suppl):S159-65	Review	About one-fourth to one-third of cases of pneumonia in Chinese children is a result of Hib.	Poor
14	Vuori E, Peltola H, Kallio MJ, Leinonen M, Hedman K  Etiology of pneumonia and other common childhood infections requiring hospitalization and parenteral antimicrobial therapy. SE-TU Study Group  <i>Clin Infect Dis</i> 1998 Sep; 27(3): 566-72	Descriptive studies  N=170 children aged 3 months to 15	Pathogenic agent was identified in 62% of the cases. Bacteria were detected in 54%, and a pneumococcus was found in 59% of the cases. Pathogenic agent was identified in 62% of the cases. Bacteria were detected in 54%, and a Viruses were found in 15% overall.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
15	Gendrel D, Raymond J, Moulin F, Iniguez JL, Ravilly S, Habib F, Lebon P, Kalifa G  Etiology and response to antibiotic therapy of community-acquired pneumonia in French children  <i>Eur J Clin Microbiol Infect Dis</i> 1997 May; 16(5):388-91	Descriptive study  N=104 children ages 18 months to 13 years.	Potential respiratory pathogens were identified in 87 (85%) cases; Streptococcus pneumoniae seen in 14 cases Potential respiratory pathogens were identified in 87 (85%) cases; these included respiratory syncytial virus in ten, Streptococcus pneumoniae in 14 and Mycoplasma pneumoniae (diagnosed by serologic procedures) in 43. Respiratory pathogens were identified in 87 (85%) cases. These included Respiratory syncytial virus in ten, Streptococcus pneumoniae in 14 and Mycoplasma pneumoniae (diagnosed by serologic procedures) in 43	Poor
16	Martinez Tagle M, Kogan R, Rojas P, Rubilar L, Vidal R, Paya E  Diagnosis of Chlamydia pneumoniae in community-acquired pneumonia in children in Chile.  <i>Acta Paediatr</i> 2000 Jun; 89(6):650-3	Prospective  N=112 children aged 1 month to 14 years.	C. pneumoniae plays a minor role in the aetiology of pneumonia in children less than 9 y of age in Chile.	Poor
17	Chugh K  Pneumonia due to unusual organisms in children.  <i>Indian J Pediatr</i> 1999 Nov-Dec;66(6):929-36	Review	Chlamydia pneumoniae are common in school age children Chlamydia trachomatis occurs in early infancy.	Poor
18	Nelson JD  Community-acquired pneumonia in children: guidelines for treatment.  <i>Pediatr Infect Dis J</i> 2000 Mar; 19(3):251-3	Review	Mycoplasma and chlamydia infection are common in the school going age of 5-15yrs. Mycoplasma pneumoniae are common in school age children. Mycoplasma and chlamydia infections are common in the school going age of ages 5-15yrs. Adenovirus and parainfluenzae are common in infancy	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
19	<p>Heiskanen-Kosma T, Korppi M, Laurila A, Jokinen C, Kleemola M, Saikku P</p> <p>Chlamydia pneumoniae is an important cause of community-acquired pneumonia in school-aged children: serological results of a prospective, population-based study.</p> <p><i>Scand J Infect Dis</i> 1999; 31(3): 255-9</p>	<p>Cohort studies</p> <p>N= 8851 children in the area of 4 municipalities</p> <p>F/up:12 months</p>	<p>29 cases of Chlamydia, 9% of the cases was children aged 5-9 y and 31% for those aged 10 years or more. Our results indicate that C. pneumoniae is an important cause of community-acquired pneumonia in school-aged children</p>	Fair
20	<p>Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, Abramo T, Leinonen M, McCracken GH</p> <p>Etiology and treatment of community-acquired pneumonia in ambulatory children.</p> <p><i>Pediatr Infect Dis J</i> 1999 Feb; 18(2):98-104</p>	<p>Randomized controlled trial</p> <p>N=174 patients, 68 of whom fulfilled protocol criteria for evaluation</p> <p>F/u:6 months to 16 years</p>	<p>Etiologic agents were identified in 73 (43%) of 168 patients, C. pneumoniae in 6% (10 of 168), Etiologic agents were identified in 73 (43%) of 168 patients. Infection was attributed to M. pneumoniae in 7% (12 of 168), None of the swab specimens from 75 healthy control children was positive for C. pneumoniae or M. pneumoniae.</p>	Good to fair
21	<p>Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, Juvonen H, Kallinen S, Sten M, Tarkiainen A, Ronnberg PR, Kleemola M, Makela PH, Leinonen M</p> <p>Etiology of childhood pneumonia: serologic results of a prospective, population-based study.</p> <p><i>Pediatr Infect Dis J</i> 1998 Nov; 17(11):986-91</p>	<p>Cohort studies prospective</p> <p>N= 201</p>	<p>Serologic evidence of specific microbial etiology was obtained in 133 (66%). Chlamydia spp. (29; 14%) Chlamydia infections in patients &gt; or =10 years of age. M. pneumoniae and Chlamydia pneumoniae are important from the age of 5 years onwards. Serologic evidence of specific microbial etiology was obtained in 133 (66%). Mycoplasma pneumoniae (44; 22%). Mycoplasma infections were seen mostly in patients &gt; or =5 years. M. pneumoniae are important from the age of 5 years onwards. Serologic evidence of specific microbial etiology was obtained in 133 (66%). Respiratory syncytial virus seen in 43; (21%) pneumonia in children of all ages.</p>	Fair

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
22	McCracken GH  Etiology and treatment of pneumonia.  <i>Pediatr Infect Dis J</i> 2000 Apr;19(4):373-7	Review	Mycoplasma pneumoniae occur commonly in older children. Viruses (mostly respiratory syncytial virus) are responsible for approximately 20% of cases.	Poor
23	Chaudhry R, Nazima N, Dhawan B, Kabra SK  Prevalence of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community acquired pneumonia.  <i>Indian J Pediatr</i> 1998 Sep-Oct;65(5):717-21	Prospective study  N=62 children  F/U-1 year study	70 (27.4%) were found to have serological evidence of M. pneumoniae infection. Results of this study indicate that M. Pneumoniae plays a significant role in CAP in infants and young children.	Poor
24	Sonoda S, Gotoh Y, Bann F, Nakayama T  Acute lower respiratory infections in hospitalized children over a 6 year period in Tokyo.  <i>Pediatr Int</i> 1999 Oct;41(5):519-24	Descriptive studies  N=1521 patients	Etiological agents were identified in 668 s (43.9%) by serological antibody responses, 75 (4.9%) with Mycoplasma pneumoniae; Influenza virus and M. pneumoniae were two main causative agents in patients with acute respiratory illness over 5 years of age .Etiological agents were identified in 668 s (43.9%), 240 (15.8%) with respiratory syncytial (RS) virus; 62 (4.1%) with influenza virus type A; 26 (1.7%). Respiratory syncytial (RS) virus was a main causative agent of respiratory infections in patients younger than 3 years of age.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
25	Heiskanen-Kosma T, Korppi M, Laurila A, Jokinen C, Kleemola M, Saikku P  Chlamydia pneumoniae is an important cause of community-acquired pneumonia in school-aged children: serological results of a prospective, population-based study.  <i>Scand J Infect Dis</i> 1999; 31(3):255-9	Cohort studies  N=8851 children in the area of 4 municipalities  F/up:12 months	Mycoplasma pneumoniae serology (CF) was positive in 44 patients (22%).	Fair
26	Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR  Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children.  <i>Pediatr Infect Dis J</i> 1998 Oct; 17(10):865-71	Multicenter trial  N= 456 patients 420 were evaluable	Evidence of infection was identified in 46% of 420 patients (1.9% bacteria, 29.5% M. pneumoniae and 15% C. pneumoniae).	Poor
27	Chong CY, Lim WH, Heng JT, Chay OM  The changing trend in the pattern of infective etiologies in childhood acute lower respiratory tract infection.  <i>Acta Paediatr Jpn</i> 1997 Jun; 39(3):317-21	Descriptive study  N= 397 children were admitted to acute LRTI compared to 240 children in 1988.  F/up: May 1994 to April 1995.	The most common bacteria infection was M. catarrhalis (34.7%) in 1995 followed by non-type B Haemophilus influenzae (33%). However in 1988, Mycoplasma (33%) was the predominant organism followed by H. influenzae (17%) Etiological agents were found in about 70% of patients in both studies. Viruses constituted 41.3% of the etiologic agents in 1995 but constituted only 28% in 1988.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
28	Miranda-Navales G, Solorzano-Santos F, Leanos-Miranda B, Vazquez-Rosales G, Palafox-Torres M, Guiscafre-Gallardo  Blood culture and respiratory syncytial virus identification in acute lower respiratory tract infection.  <i>H Indian J Pediatr</i> 1999 Nov-Dec;66(6):831-6	Descriptive studies  N=101 children under 5 years of age	The detection for RSV was positive in 24 patients (23.7%). RSV is a common cause of LRTI in children younger than five years old.	Poor
29	Aggarwal R  Lower airway disease caused by respiratory syncytial virus  <i>Indian J Pediatr</i> 1998 May- Jun;65(3):355-62	Review	Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease in infants and young children.	Poor
30	Chan PW, Goh AY, Chua KB, Kharullah NS, Hooi PS  Viral aetiology of lower respiratory tract infection in young Malaysian children.  <i>J Paediatr Child Health</i> 1999 Jun;35(3):287-90	Descriptive retrospective studies  N=5691 children	Young Malaysian children admitted with LRTI had a 22% viral isolation rate and RSV 84% was the commonest virus isolated.	Poor
31	Videla C, Carballal G, Misirlan A, Aguilar M  Acute lower respiratory infections due to respiratory syncytial virus and adenovirus among hospitalized children from Argentina  <i>Clin Diagn Virol</i> 1998 May 1;10(1):17-23	Descriptive studies  N=168 children under 2 years of age hospitalized due to ALRI	RSV was detected in 36.3% and adenoviruses in 14.3% of the cases (P < 0.0001).	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
32	Hijazi Z, Pacsa A, el-Gharbawy F, Chugh TD, Essa S, el Shazli A, Abd el-Salam R  Acute lower respiratory tract infections in children in Kuwait.  <i>Ann Trop Paediatr</i> 1997 Jun; 17(2):127-34	390 children with LRTI are described	Respiratory syncytial virus was the commonest cause of LRTI.	Poor

### **Pneumonia -Effectiveness**

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
1	Olivier C  Clinical use of cefuroxime in paediatric community-acquired pneumonia.  <i>Paediatr Drugs</i> 2000 Sep-Oct;2(5):331-43	Review	Cefuroxime has been recommended as a component of treatment for community-acquired pneumonia (CAP) in guidelines produced by several groups, including the US and British Thoracic Societies.	Poor
2	Grant CC, Ingram RJ  Outpatient treatment of pneumonia.  <i>N Z Med J</i> 2000 Feb 25;113(1104):58-62	Review	The antibiotic of choice for children < or = 5 years of age is oral amoxicillin and for older children and adolescents is oral erythromycin.	Poor
3	Ruuskanen O, Mertsola J Childhood community-acquired pneumonia. <i>Semin Respir Infect</i> 1999 Jun;14(2):163-72	Review	Macrolides as the first choice in outpatients depending on the clinical picture and severity of the illness.  Penicillin G, macrolide or cefuroxime plus macrolide in hospitalized patients.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
4	Tsarouhas N, Shaw KN, Hodinka RL, Bell LM Effectiveness of intramuscular penicillin versus oral amoxicillin in the early treatment of outpatient pediatric pneumonia. <i>Pediatr Emerg Care</i> 1998 Oct;14(5):338-41	Prospective, randomized blinded, trial. N= 170 patients	There does not appear to be a significant difference between PO amoxicillin and IM penicillin treatment of pediatric patients with presumed bacterial pneumonia.	Good
5	Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B  Co-trimoxazole Study Group. Pakistan Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxycillin for pneumonia among children in Pakistan: randomised controlled trial.  <i>Lancet</i> 1998 Jul 25;352(9124):270-4	Randomized controlled trial in 2 centers.  N=595 children, aged 2-59 months, randomly assigned on a 2:1 basis co-trimoxazole (n=398) or amoxycillin (n=197)	Co-trimoxazole provided effective therapy in non-severe pneumonia. For severe, life-threatening pneumonia, however, co-trimoxazole is less likely than amoxycillin to be effective.	Good Large RCT Excluded those who have taken antibiotic n the last 48 hours
6	Rowe AK, Deming MS, Schwartz B, Wasas A, Rolka D, Rolka H, Ndoyo J, Klugman KP  Antimicrobial resistance of nasopharyngeal isolates of <i>Streptococcus pneumoniae</i> and <i>Haemophilus influenzae</i> from children in the Central African Republic.  <i>Pediatr Infect Dis J</i> 2000 May;19(5):438-44	A cross-sectional survey  N=371 ill children	SP resistance rates to penicillin, trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline and chloramphenicol were 8.8, 6.3, 42.3 and 9.2%, respectively. HI resistance rates to ampicillin, TMP-SMX and chloramphenicol were 1.4, 12.3 and 0%, respectively. The study recommended that TMP-SMX as the first line treatment for pneumonia in CAR	Poor
7	Greenwood B  The epidemiology of pneumococcal infection in children in the developing world. <i>Philos Trans R Soc Lond B</i>  <i>Biol Sci</i> 1999 Apr 29;354(1384):777-85	Review	Until recently, pneumococcal infections could be treated effectively with penicillin, a cheap and safe antibiotic. However, pneumococci that are resistant to penicillin are becoming prevalent in many countries.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
8.	Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, Abramo T, Leinonen M, McCracken GH  Etiology and treatment of community-acquired pneumonia in ambulatory children.  <i>Pediatr Infect Dis J</i> 1999 Feb; 18(2):98-104	Randomized control trial N=174 patients	Clinical response to therapy was similar for the three antibiotic regimens evaluated, including those with infection attributed to bacterial agents. There were no differences in the clinical responses of patients to the antimicrobial regimens studied. Out of the 168 cases, 21 were excluded for clinical evaluation 147 evaluated, 143 were classified as cure.	Good Large RCT
9	Tan TQ, Mason EO, Barson WJ, Wald ER, Schutze GE, Bradley JS, Arditi M, Givner LB, Yogev R, Kim KS, Kaplan SL  Clinical characteristics and outcome of children with pneumonia attributable to penicillin-susceptible and penicillin-nonsusceptible <i>Streptococcus pneumoniae</i> . <i>Pediatric Infectious Disease</i> , <i>Pediatrics</i> 1998 Dec;102(6):1369-75	Multicenter, prospective study.  N=254 children had 257 episodes of pneumococcal pneumonia	Of the 257 isolates, 22 (9%) were intermediate and 14 (6%) were resistant to penicillin.. 248 patients (97.6%) had a good response to therapy. Six patients died; however, only 1 of the deaths was related to the pneumococcal infection. The clinical presentation and outcome of therapy did not differ significantly between patients with penicillin-susceptible versus those with nonsusceptible isolates of <i>S pneumoniae</i> ..	Poor Varous combinations of antibiotics were used.
10	Camargos PA, Guimaraes MD, Ferreira CS  Benzathine penicillin for unilateral lobar or segmental infiltrates presumptively caused by <i>Streptococcus pneumoniae</i> in children 2-12 years old.  <i>J Trop Pediatr</i> 1997 Dec; 43(6):353-60	Randomised controlled trial  N=176 children	Evidence of total radiographic clearing was demonstrated for 92.3 and 95.1 per cent of the benzathine penicillin and procaine penicillin groups, respectively (P = 0.54). Benzathine penicillin may be considered an alternative to classic regimens for treating pneumonia due to sensitive strains of <i>S. pneumoniae</i> among children 2-12 years old. Other benefits are its lower cost, better compliance and low rates of adverse reactions.	Good Large RCT

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
11	Grimwood K, Collignon PJ, Currie BJ, Ferson MJ, Gilbert GL, Hogg GG, Isaacs D, McIntyre PB  Antibiotic management of pneumococcal infections in an era of increased resistance.  <i>J Paediatr Child Health</i> 1997 Aug;33(4):287-95	Review	At present, penicillin and amoxicillin remain the drugs of choice for pneumococcal infections.	Poor
12	Awasthi S.  Clinical response to two days of oral amoxycillin in children with non-severe pneumonia.  <i>Indian Pediatr</i> 2000 Mar;37(3):301-6	Descriptive study	Three-fourth cases of non-severe pneumonia in children between 2-59 months of age responded on the third day when administered 5 days treatment with amoxicillin.	Poor
13	Chong CY, Lim WH, Heng JT, Chay OM  The changing trend in the pattern of infective etiologies in childhood acute lower respiratory tract infection.  <i>Acta Paediatr Jpn</i> 1997 Jun;39(3):317-21	Descriptive study.  N=397 children  F/up: May 1994 to April 1995	No penicillin resistance was detected in 1988. However, in 1995, penicillin resistance was found in 17% of the <i>Streptococcus pneumoniae</i> , 38.5% of <i>H. influenzae</i> and 83% of <i>M. catarrhalis</i> . It was also found that 30% of the <i>S. pneumoniae</i> were also resistant to erythromycin, and 23% were resistant to sulfamethoxazole-trimethoprim. 5% of the <i>H. influenzae</i> had multiple resistance to erythromycin, sulfamethoxazole-trimethoprim and chloramphenicol.	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
14	<p>Numazaki K, Sakamoto Y, Umetsu M, Agatsuma Y, Yamanaka T, Kogasaka R, Hiraki M, Kuniya Y, Miua J, Ukae S, Ueda D, Sato T, Chiba S</p> <p>Int J Research Group of Sapporo for Pediatric Chlamydial Infections Therapeutic effect of clarithromycin for respiratory-tract infections in children caused by Chlamydia pneumoniae</p> <p><i>Antimicrob Agents</i> 2000 Jan; 13(3):219-22</p>	<p>Multicenter clinical trial</p> <p>N=21 infants and children</p>	<p>Overall clinical efficacy rate was 85.7% (18 of 21 cases). Clarithromycin was considered to be a suitable treatment for improving lower respiratory infections in infants and children caused by C. pneumoniae.</p>	Poor
15	<p>Heiskanen-Kosma T, Korppi M, Laurila A, Jokinen C, Kleemola M, Saikku P</p> <p>Chlamydia pneumoniae is an important cause of community-acquired pneumonia in school-aged children: serological results of a prospective, population-based <i>study</i>.</p> <p><i>Scand J Infect Dis</i> 1999; 31(3):255-9</p>	<p>Descriptive studies.</p> <p>N = 201</p> <p>F/up:12 months</p>	<p>C. pneumoniae is an important cause of community-acquired pneumonia in school-aged children. Macrolides should be considered as an empirical antimicrobial treatment for community-acquired pneumonia, especially in school-aged outpatients.</p>	Poor
16	<p>Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR</p> <p>Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children.</p> <p><i>Pediatr Infect Dis J</i> 1998 Oct;17(10):865-71</p>	<p>Multicenter, parallel group, double blind trial in which were randomized 2:1.</p> <p>N=420</p>	<p>Microbiologic eradication was 81% for C. pneumoniae in the azithromycin group vs. 100% in the comparator group. (amoxicillin/clavulanate if &lt; or =5 years of age or erythromycin estolate if &gt;5 years of age)</p>	Good Large RCT

**SAFETY**

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
1	Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR  Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children.  <i>Pediatr Infect Dis J</i> 1998 Oct; 17(10):865-71	Multicenter RCT double blind trial randomized  N= 456 patients 420 were evaluated	Microbiologic eradication was 100% for M.pneumoniae in the azithromycin group Azithromycin used once daily for 5 days produced a satisfactory therapeutic outcome similar to those of amoxicillin/clavulanate or erythromycin given three times a day for 10 days for treatment of community-acquired pneumonia.	Good Large RCT

**COST**

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome & Characteristics	Grade and Comments
1.	J Al-Eidan FA, McElnay JC, Scott MG, Kearney MP, Troughton KE, Jenkins J  Sequential antimicrobial therapy (SAT): treatment of severe lower respiratory tract infections in children.  <i>Antimicrob Chemother</i> 1999 Nov; 44(5):709-15	Descriptive studies  N=89 paediatric patients (44 control and 45 SAT)	The SAT patients had a shorter length of hospital stay (4.0 versus 8.3 days), shorter duration of inpatient antimicrobial therapy (4.0 versus 7.9 days) with the period of iv therapy being reduced from a mean of 5.6 to 1.7 days. The total healthcare costs were reduced by 52%.	Fair

### SEPSIS IN CHILDREN

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
1	Oda K, Matsuo Y  Sepsis in Children  <i>Pediatr Int</i> 2000 Oct;42 (5): 528-33	Retrospective descriptive  N=366 episodes of sepsis 244 patients  F/U Jan 84 – Dec 98	20% of septic patients were under 1 year of age. 90% had underlying diseases; 55% hematologic disorders or neoplasm. 366 episodes of sepsis, 409 causative agents:, 7% polymicrobial infections, 68% gram positive, 18% staph. Aureus, 37 patients died of sepsis The causative agents of sepsis affected the outcome. GNR significantly higher mortality than gram positive bacteria (25% v 10%,)	Poor
2	Jamal WY, El-Din K  An analysis of hospital acquired bacteremia in intensive care unit patients in a university hospital in Kuwait  <i>J Hosp Infect.</i> 1999 Sep; 43(1): 49-56	Retrospective  N= 692 patients  F/u: 2years	Incidence of bacteremia: 127 (18.4%) 79 deaths, 52% attributable to nosocomial bacteremia Hospital acquired bacteremia in ICU carries a poor prognosis.	Poor Adult patients included in this study
3	Kempf, Volkhard AJ  Rapid Identification of pathogens in blood  <i>Ann. Intern Med.</i> 2000Feb 15, 132(4) :330-331	Letter	Rapid identification of the causative agents in septicaemia is crucial for selecting appropriate antimicrobial agents. Suggested FISH with ribosomal RNA targeted fluorescently labeled oligonucleotide probes for rapid detection and identification of pathogens, without cultivation and biotyping.	Poor
4	Fisher JE  Use of antibiotics in pediatric intensive care and potential savings  <i>Intensive Care Med.</i> 2000 Jul; 26(7): 959-66	Observational cohort study  N= 456 neonates & children  F/up: Sept 98 – March 99	258 (56.6%) received systemic antibiotics = 1815 exposure days (54.6%). 28% prophylaxis, 47% suspected pneumonia, 20% suspected sepsis. 40% had no infection or viral infection during treatment days. The largest reduction in antibiotic treatment would result from measures assisting suspected ventilator-associated pneumonia to be ruled out and from curtailing extended prophylaxis.	Fair prophylactic verses suspected infection only 20% sepsis

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
5	Leibovici L  The benefits of appropriate empirical antibiotics treatment in patients with blood stream infection  <i>J Intern Med.</i> 1998 Nov; 244 (5): 379-86	Prospective cohort  N=2158 patients  F/up: 1988 – 1994	In-hospital fatality rate: A-20%, B-34% , Length of hospitalization: A-9 days, B-11 days (survived); A-5, B-4 days (died). Appropriate empirical antibiotics treatment was associated with a significant reduction in fatality in patients with bloodstream infection.	Fair
6	Al Soub H, Estinoso W  Hospital-acquired candidaemia: experience from a developing country  <i>J Hosp. Infect.</i> 1997 Feb; 35 (2): 141-7	Retrospective study  N=37 episodes	Mortality 48.6% , C albicans 56.8%, C. tropicalis 13.5%. No significant difference between patients treated with amphotericin B and those treated with fluconazole.	Poor
7	Raveh D.  Longitudinal surveillance of antibiotics use in the hospital  <i>QJM</i> 2001 Mar; 94 (3): 141 – 52	Prospective Comparative  N= 2306 patients  F/up: 3-4 months	62%± 22% received antibiotics with a range of 4-100% per department. 47% community community acquired infection, 34% hospital, 9% nursing home, prophylaxis 9%.,11% sepsis. Half of all antimicrobial use consisted of 4 agents cefuroxime, metronidazole, gentamicin ampicillin = 20 % of expenditure. 53% of antimicrobials surveyed was restricted and accounted for only 29% of all antimicrobial courses.	Poor
8	Sadow KB  Bacterial infections in infants 60 days and younger: epidemiology, resistance, and implications for treatment  <i>Arch Pediatr Adolesc Med</i> 1999 Jun; 153(6): 611-4	Retrospective  F/U- 1/1/94 – 31/12/97	All positive urine, blood and CSF cultures 367 pathogens, 51% NICU, 41.7% ED, 5.4% ward, 1.9% PICU. 121 pathogens, 77.7% urine, 13.2% blood, 3.3% CSF, 2.5% blood & CSF, 3.3% blood & urine 8 Organisms, 11.6% GBS, 79.3% GNRs – 60% ,ampicillin resistant, (all sensitive to cefotaxime & gentamicin). 0 Listeria. 5.8% Enterococcus. 2.5% Strept pneumoniae. 0.8% Neisseria meningitides. 0 Haemophilus . 0 Staphy aureus.60% GNRs ampicillin resistant.No Listeria isolated. Recommended empiric antibiotics – third generation cephalosporin & gentamicin.	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
9	Szewczyk E M  Predominant Staphylococci in the intensive care unit of a pediatric hospital  <i>J. Hosp Infect.</i> 2000 Jun ;45(2): 145-54	Review  F/up: 6 months	Isolates mainly <i>S. cohnii</i> , 97% resistant to methicillin, 72 from infants – MRSA mainly <i>S. epidermidis</i> . <i>S. epidermidis</i> relatively susceptible to amoxicillin-clavulanic acid & cephalosporin All susceptible to vancomycin, 30% resistant to mupirocin	Poor
10	Gray J  Three year survey of bacteremia and fungemia in a PICU  <i>Pediatr Infect Dis J.</i> 2001 Apr; 20(4): 416-21	Surveillance  F/up:3 years	131 episodes of BSI. Incidence of BSI 39.0/1000 admissions, 10.6 per 1000 bed days. 84 (64.1%) episodes were ICU acquired, 27 (20.6%) community acquired. 143 isolates of which 62.2% gram positive – Staphy, 30.8% gram negative - <i>Neisseria meningitidis</i> , 1.4% anaerobic, 5.6% yeast. Pattern of BSI in PICUs is partly determined by type of patient treated	
11	Blanc P.  Economic impact of a rational use of antibiotics in intensive care  <i>Intensive Care Med.</i> 1999 Dec; 25(12) 1407 – 12	Comparative Retrospective and prospective study	The exposures for antibiotic drugs decreased by 19% in 1995 and 22% in 1996. A positive economic impact seen after the implementation of a rational policy in antibiotic therapy.	Poor
12	Alejandria MM, Lansang MA, Dans LF, Mantaring JBV  Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review)  <a href="#">The Cochrane Library, Issue 4, 2001</a> . Prepared and published by <a href="#">Update Software Ltd</a> .	Randomised control trial.	Twenty-seven out of 55 studies met our inclusion criteria. Pooled analysis of all types of IVIG preparations revealed a significant trend toward reduction of mortality Overall mortality was reduced in patients who received polyclonal IVIG. Mortality was not reduced among patients who received monoclonal antibodies such as anti-endotoxins or anti-cytokines (n=4,318 in 4 good quality studies; RR=0.93; 95% CI 0.86 to 1.01). Polyclonal IVIG significantly reduces mortality and can be used as an adjuvant treatment for sepsis and septic shock.	Good Adjuvant therapy

### NEONATAL SEPSIS

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
1	Karlowicz MG, Buescher ES, Surlear A/E  Fulminant late onset sepsis in a neonatal ICU and the impact of avoiding empiric vancomycin therapy  <i>Pediatrics</i> 2000 Dec; 106(6): 1387-90	Retrospective study N=536 infants F/up:over 10 years 1988-1997	Frequency of fulminant sepsis was highest for Ps.sp. and lowest for coagulase negative staphylococci (1 %). 1% = 4 patients, 2 had polymicrobial sepsis, multiple major malformation, thrombus. Actual incidence is 0.7%. Substitution of oxacillin for vancomycin as the empiric antibiotic for gram positive sepsis had no impact on frequency of fulminant sepsis. Empiric antibiotics for treatment of suspected sepsis in infants > 3 days need to effectively treat gm (-) ve pathogens particularly Ps.sp. Avoiding empiric vancomycin therapy is reasonable approach to late onset sepsis.	Fair
2	Fischer JE Ramser M; Fanconi S, (Swizertant)  Use of antibiotics in PICU & potential savings  <i>Intensive Care Med</i> 2000 Jul; 26(7): 959-66	Observational study  N=2 456 newborn & children	1 258 patients received systemic antibiotics – 1815 exposure days during 3322 hospitalization days. 512 (28 %) were prescribed as prophylaxis and 1303 for suspected infection. Out of this 47 % of 1303 treatment days were for suspected ventilator associated pneumonia. 552 treatment days –(40%) patients had no infection or viral infection. Largest reduction in antibiotic treatment would result from measures assisting suspected ventilator associated pneumonia to be ruled out.	Fair
3	Benjamin OK; Ross K; Mc Kinney RE  When to suspect fungal infection in neonates: A clinical comparison of <i>Candida albicans</i> & <i>C. parapsilosis</i> fungemia with coagulase negative staphylococcal bacteremia  <i>Pediatrics</i> 2000 Oct; 106 (4): 712-8	Retrospective review  N= 51 patients	Candidemic patients had greater exposure to systemic steroids; antibiotics (29 out of 32 treated with 3 rd generation cephalosporins), catecholamine infusions, mechanical ventilation, less likely to tolerate enteral feeds. Above key features used by clinicians to initiate empiric amphotericin B in neonates at risk.	Fair

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
4	Wagner CL; Wagstaff P; Cox TH; Annibale DJ  Early discharge with home antibiotic therapy in the treatment of neonatal infection  <i>J.Perinatology</i> 2000 Sep; 20(6): 346-50	Prospective cohort study  N= 95 infants in UH  F/up: 6 months	Aim: determine feasibility and cost of home antibiotic treatment for a select group of neonates. Infants diagnosed with sepsis, presumed sepsis (62 %) pneumonia (25 %) or uncomplicated meningitis included. Have met prior established criteria for home antibiotic therapy. Mean BW 3160 gm, Mean GA 38.4 weeks Ampicillin/gentamicin prescribed for 56 % of the cohort, ceftriaxone for 21 % of cohort. Mean age of discharge was 5.2 days. No serious complications or treatment failures, fewer costs of continued inpatient treatment. Savings up to 41200-2250.	Fair
5	Solomon R, Kuruvilla KA Job V, Selvakumar R, eyaseelan L, Kanagasabapatry AS, Jana AK  Randomized controlled trial of once vs twice daily gentamicin therapy in newborn  <i>Indian Pediatric</i> 1999 Feb; 36(2) 133-7	Randomised control trial  N=73 neonates of GA > 32/52 at risk or with clinical features of sepsis	Patients were randomised to receive single daily dose 4mg/kg or a twice daily dose (2.5mg/kg) of injection iv In preterm & term babies mean peak & trough gentamicin levels were comparable in 2 regimes Once daily gentamicin administration is as effective as twice daily therapy & more cost effective.	Good to fair
6	Patel DM, Rhodes PG, Le Blanc MH, Graes GR, Glich C, Morrison J  Role of postnatal penicillin prophylaxis in prevention of neonatal group B streptococcus infection  <i>Acta Pediatric</i> 1999 Aug; 88(8): 874-9	Prospective  N=10,998 infants	The use of penicillin prophylaxis reduced the incidence: a. Clinical sepsis (1.7 % vs. 2.5 % NPP) b. GBS infection 0.4 % PP vs. 0.9 % NPP) c. death from sepsis (0.1 % PP vs 0.3 % NPP) Routine use of postnatal penicillin prophylaxis appears to be effective in reducing the incidence of clinical sepsis and death from sepsis in neonates.	Fair

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
7	Mureen PJ, Reiter PD, Gessores A, Stolpman NM  Once versus twice daily gentamicin dosing in neonates $\geq$ 34 weeks gestation; cost effectiveness analysis.  <i>Pediatrics</i> 1999 Mar; 103(3): 594 – 8	Prospective Study  N= 56 (27 neonates in ODD group. 28 neonates in TDD group).	57 % of SGC in TDD group were outside the target concentration range versus 7 % in the OPD group. Based on cost effectiveness analysis ODD was the dominant dosing strategy in all categories analyzed. ODD of gentamicin at 4 mg / kg in neonates $\geq$ 34 weeks gestation is the preferable. Treatment strategy based on: a. Significantly improved SGC performance compared with TDD. b. Elimination of the need for routine SGC. c. Hospital cost savings.	Fair
8	Jonsson B, Rylander M, Faxelius G  Urea plasma urealyticum erythromycin and respiratory morbidity in high-risk preterm neonates.  <i>Acta Pediatric</i> 1998 Oct; 87 (10): 1079-84	Case series  N = 155 preterm ventilated infants mean GA 26 weeks	Colonised infants were randomly assigned to treatment with erythromycin 40mg/k/d iv or orally. In the colonised infants PROM (48% vs 12%), chorioamnionitis (46% vs 17%) and vaginal delivery (71% vs 29%). Colonised infants needed supplemental O <sub>2</sub> at 36 postconceptual age (p<0.05) Rate of colonization 19 %. Erythromycin was effective in reducing colonization with negative control cultures in (86%) of treated infants but did not reduce the length of time infants needed supplemental oxygen.	Poor
9	Baier RJ, Bocchini JA, Brown EG  Selective use of vancomycin to prevent coagulase negative staphylococcal nosocomial bacteremia in high risk very LBW infants  <i>Pediatric Infect Dis J</i> 1998 Mar; 17(3) : 179-83	Double blind randomised controlled study  N=38 infants with/without CVC randomised to receive no medication or 25 ug/ml VM added to PN (VLBW infants receiving PN in a tertiary NICU	Addition of 25ug/ml of VM to PN prevented bacteremia in VLBW infants receiving PN The total no of hospital days 108 vs 76 were reduced Infants with BW < 1 kg who received corticosteroid for treatment of CLD benefited most – confirmed by multiple logistic regression Prophylactic treatment with Vancomycin effectively prevented CoNS bacteremia under conditions of study. ( p = 0.037)Its use was most effective in infants with BW < 1 KG No VM resistant CONS / enterococci detected	Good to Fair

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
10	Cooke RW, Nycyk JA, Okuonghae H  Low dose VM prophylaxis reduces CoNS bacteremia in VLBW infants  <i>J. Hosp. Infect</i> 1997 Dec; 37 (4): 297-303	Randomised control trial  N=72 infants (37 were randomised to VM and 35 to control group)	In VM group 11 had 1 more episodes of CoNS bacteremia compared with 17 in control group. 2 babies in treatment group had more than one episode of CoNS bacteremia cf 9 in control group (p=0.02) 13 episodes of CoNS bacteremia in the VM group cf with 29 in control group Prophylaxis with intermittent low dose VM infusions may help reduce recurrent CoNS bacteremia in VLBW infants receiving PN	Good to Fair
11	Moller JC, Nelskamp I, Jensen R  Comparison of VM and teicoplanin for prophylaxis of sepsis with CoNS in VLBW infants  <i>J. Perinatal Med</i> 1997; 25 (4): 361-7	Prospective randomised study  N=55 infants	Infants after 4 <sup>th</sup> day of life or after eventual therapy of early onset sepsis were included 27 were given VM and 28 were given teicoplanin. There were no cases of blood C&S positive sepsis cf CoNS sepsis rate of 24% in institution . Teicoplanin is preventing CoNS sepsis as well as VM	Good to Fair
12	Burton KM, Pritchard MA, Frawley WH  Neonatal pneumonia: comparison of 4 Vs 7 days of antibiotic therapy in term and near term infants  <i>J. Perinatol</i> 2000 Oct-Nov; 20(7): 421-6	Prospective control  N= 73	4 days of antibiotic therapy plus a 24 hour observation for selected cases of neonatal pneumonia comparable to 7 days of therapy. Recommended additional studies to assess the safety and benefits.	Good to Fair
13	Tay ST, Boo NY, Khoo TB  Prevalence and antibiotic susceptibility of <i>Ureaplasma urealyticum</i> in Malaysian neonates with respiratory distress  <i>Med J Malaysia</i> 1997 Dec 52(4) 409-411	Cohort study  N=182 infants	<i>U. urealyticum</i> was isolated from ET aspirates of 39 (21.4%) of 182 infants with RDS requiring ventilator support. All organisms were sensitive to erythromycin but resistant to lincomycin and sulphamethaxazole trimethoprim. All except 1 were sensitive to tetracycline and minocycline. <i>U urealyticum</i> is a common isolate in the ET aspirates of infants with respiratory distress	Fair

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
14	<p>Cordero L, Sananes M, Ayers LW</p> <p>Failure of systemic antibiotics to eradicate gram -ve bacilli from the airway of mechanically ventilated very LBW infants</p> <p><i>Am. J. Infect Control</i> 2000 Aug; 28 (4): 286-90</p>	<p>Controlled prospective study</p> <p>N=106 infants</p>	<p>GNB airway colonization is associated with morbidity and mortality. 64 other infants GNB bloodstream infection as antibiotic treatment outcome group. Gentamicin alone or with ceftazidime, ceftazidime, piperacillin in combination with tazobactem or tobramycin and tobramycin in combination with ampicillin/sulbactem or mezlocillin. Systemic antibiotics failed to eradicate GNB colonization in 97% of cases. Its empirical use for the prophylaxis or treatment of airway colonization discouraged</p>	Fair
15	<p>Joshi SG; Ghole VS; Niphadkar KB</p> <p>Neonatal gram negative bacteremia</p> <p><i>Indian Journal of Pediatrics</i> 2000 Jan; 67 (1): 27-32</p>	<p>Prospective study</p> <p>N=1326 cases</p> <p>F/up: 22 month</p>	<p>In 67.8 % cases of gram negative bacteremia – the predominant were <i>Ps. aeruginosa</i> (38.3%), <i>Klebsiella pneumoniae</i>, <i>E. Coli</i> (15.6%) and <i>Acinetobacter</i> (7.8%) 59 % were inborn babies prematurity and LBW in 60% of the neonates mortality was 32% Increased resistance to extended spectrum cephalosporins (25%-75%), piperacillin (68-78%) and gentamicin (23-69%) Combination of ampicillin and sulbactam with amikacin or ampi and sulbactam and ciproflox is most effective</p>	Poor
16	<p>Musoke RN, Revathi G</p> <p>Emergence of multidrug resistant gram negative organisms in a neonatal unit and the therapeutic implications</p> <p><i>J. Tropical Pediatrics</i> 2000 Apr; 46 (2): 86-91</p>	<p>Observational</p> <p>N= 192 infants with sepsis</p>	<p>16.7 % had positive blood cultures of which 73.6 % were gram negative organisms. <i>Klebsiella</i> was the predominant organism -31%. The case fatality rate was 41 %. Resistance to gentamicin was 20 %, CMXC was 23.6 %, amoxicillin/ampicillin 66.3 %. Ceftazidime 19.1%, cefuroxime 21.3%. Contributory factors to increased resistance include non ix of infants put on antibiotics (50%) prolonged (73%) unjustified (41%) non utilisation of ix when these are done(52%) and delay in getting results in ward (6 days)</p>	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
17	<p>Oral R; Akisu M; Kultursay N</p> <p>Neonatal Klebsiella pneumonia sepsis and imipenem/cilastin</p> <p><i>Indian J Pediatrics</i> 1998 Jan –Feb 65(1): 121-9</p>	<p>Observational</p> <p>N=44 infants</p>	<p>Efficacy and safety of imipenem/cilastin in neonatal Klebsiella pneumonia sepsis was investigated in 45 infants cf 39 control infants on conventional antibiotic regime. Sensitivity to imipenem 94%, cephoxitin (88%) quinolones (80%) amikacin (52%). 5 vs 27 infants were unresponsive to treatment and died the cure rates were 73% AND 28% respectively. The most common adverse effect of imipenem/cilastin were Candida albicans superinfection (20%). Imipenem is a good alternative for neonatal Klebsiella pneumonia however there is an increased risk of C. albicans infection</p>	Poor
18	<p>De Man P; Verhoevan BA</p> <p>An antibiotic policy to prevent emergence of resistant bacilli</p> <p><i>Lancet</i> 2000 mar 18; 355 (9208):973-8</p>	<p>Prospective study</p> <p>N=436, 218 in each NICU(2 NICU were assigned different empiric antibiotic regimes unit A Pen G and tobramycin for early onset sepsis; flucloxacillin and tobramycin for late onset septicemia).</p>	<p>Unit B iv amoxicillin with cefotaxime used. After 6 months the regimes were interchanged. 3 neonates with Pen tobramycin regimen were colonised with bacilli resistant to empirical therapy vs 41 neonates in amox cefotaxime group. Enterobacter cloacae predominant bacilli in amox cefotaxime group. E.coli predominant bacilli in pen tobra group. Policies regarding the empiric use of antibiotics do matter in the control of antimicrobial resistance. a regime avoiding amoxicillin and cefotaxime restricts the resistance problem</p>	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
19	Dellagrammaticas HD Christodoulou C  Treatment of gram negative bacterial meningitis in term neonates with third generation cephalosporin plus amikacin  <i>Biol Neonate</i> 2000 mar 77(3): 139-46	Retrospective uncontrolled study  N=72 infants  F/up: 6 months	All isolates were sensitive to cefotaxime or ceftazidime and amikacin. Predominant organism was E.coli (68%) . Survival at discharge was 97.2 % at discharge. Ventriculitis in 10% infants, 1.3% developed hydrocephalus , 1.3 % with P.mirabilis developed brain abscess with relapse of meningitis. 91.1% of the infants were normal at 6 months. 92.3% of the infants were normal at 6 years. Strongly support the use of 3 <sup>rd</sup> generation cephalosporin and amikacin for treatment of Gm –ve bacterial meningitis	Poor
20	Khaneja M, Naprawa J  Successful treatment of late onset infection due to resistant Klebsiella pneumonia in an extremely LBW infant using ciprofloxacin  <i>J. Perinatology</i> 1999 Jun 19 (4): 311-4	Clinical case report	Infant sepsis and meningitis from multidrug resistant K. Pneumonia. Treated with cipro and gent Risk to damage to cartilage occurs rarely if at all in peds patients. Concl: Use restricted to treatment of serious infection for which an alternative antibiotic is not available	Poor
21	Hitomi S, Kubota M, Mori N  Control of MRSA outbreak in 9 neonatal ICU by unselective use of mupirocin ointment  <i>J. Hosp Infect</i> 2000 Oct; 46(2): 123-9	Case series  F/U – 10 years	Carrier patients at any sites – intranasal ointment 3X daily for 3 days (eradication); 3X weekly (prophylactic). Administration executed for a month. Weekly nasal swabs was taken till end of December. MRSA undetectable in all but 1 intubated inpatient. Conc- as neither an increase in MIC nor adverse reaction noted, this procedure is an effective method of controlling MRSA in NICU when outbreak cannot be managed with conventional measures.	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
22	Roiledes E, Kyriakides G  Septicemia due to multiresistant Klebsiella pneumonia in a neonatal unit. A case control study.  <i>Am J. Perinatal</i> 2000; 17(1) 35-9	Case control study	Neonates with septicemia due to K. Pneumonia were matched 1:1 with neonates without septicemia (31) pairs or with neonates with septicemia due to other organism (8) pairs according to birthe weight & time of admission. All Klebsiella p isolated were resistant to aminoglycosides , 3 <sup>rd</sup> generation cephalosporins and atreonam but sensitive to impenem and ciprofloxacin. Factors associated with septicemia a. Mechanical ventilation, b. Parenteral nutrition Enhanced infection control measures and a temporary change of antibiotic policy reduced this serious complication.	Poor
23	Tuladhar R, Patole SK, Koh TH  Refractory Bacillus cereus infection in a neonate  <i>Int. J. Clin Pract</i> 2000 Jun; 54 (5) 345-7	Case report	Neonate (24 week gestation) with B. cereus infection with positive blood and bone marrow culture despite treatment with vancomycin, gentamycin, imipenem, clindamycin, ciprofol, 1 g and gest over 49 days died. Combination of vancomycin and gentamycin is appropriate for meningitis/ severe systemic infections of most bacillus series.	Poor
24	Chang Chien HY, Chiu NC, Li WC  Characteristics of neonatal bacterial meningitis in teaching hospitals in Taiwan from 1984-1997  <i>J. Microbial Immunol Infection</i> 2000 Jun; 33(2):100-4	Case series  N=85 patients, ages 1-28 days.	Most common organism was GBS (31.8%), E.coli (20%). Proteus mirabilis (7.1%), Enterobacter cloacae (5.9%), other strep including excluding S. pneumonia (5.9%), Chyrseobacterium meningosepticum (5.9%), enterococci (4.7%), K pneumonia (3.5%). Ampicillin/ cefotamime were most commonly used antibiotics. Since 1991, GBS has over taken E coli as leading cause of meningitis. The results highlight the importance of developing strategies to prevent group B strep infection.	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
25	Escobar GJ, Li DK, Armstrong MA  Neonatal sepsis workups in infants $\geq$ 2000gm at birth. A population based study  <i>Pediatrics</i> 2000 Aug; 106 (2 pt 1): 256-63	Retrospective cohort study  N=2758  F/U: 1/52	The risk of bacterial infection in the asymptomatic infant is low. Evidence based observation & treatment protocols could be defined based on limited set of predictors- maternal fever, chorioamnionitis, initial neonatal examination and absolute neutrophil count.	Fair
26	Lin FY, Mureen PJ, Azimi PH, Weisman LE, Philips JB, Regan J  Antibiotics susceptibility profiles for group B streptococci isolated from neonates 1995-1998.  <i>Clin. Infect. Disc</i> 2000 Jul; 31(1) 76-9	Observational	Antibiotic susceptibility profiles were analysed for 119 invasive & 227 colonising strains of group B streptococci isolated from neonates at 6 academic centers. All strains susceptible to penicillin, vancomycin, chloramphenicol and cefotaxime. Rate of resistance to erythromycin (20.2%), clindamycin (6.9%). Type V strains more resistant erythro than type 1a	Poor
27	Akindele JA, Rotilu IO  Outbreak of neonatal Klebsiella septicemia a review of antimicrobial sensitivities  <i>Afr. J. Med.Sci</i> 1997 Mar-Jun; 26 (1-2):51-3	Prospective observational study	K. Pneumonia (46.2%), K. Aerogenes (43.6%), K. Edwardsii (7.7%), K. Oxytoca (2.5%). All strains sensitive to ciprofloxacin and ofloxacin but resistant to ampicillin. Sensitivities: 41% ceftazidime, 36% cefotaxime, 31% ceftriazone, 23% cefuroxime, 21% gentamycin, 15% kanamycin	Poor
28	Boswald M, Dobig C, Kandler C  Pharmacokinetic & clinical evaluation of serious infections in premature & newborn infants under therapy with impenam and cilastatin  <i>Infection</i> 1999; 27 (4-5): 299-304	Retrospective case series  N=104 premature and newborn	A total daily dose of 50 mg/kg for premature and newborn infant divided into 2 doses led to impenem peak concentrations of 17.7mg/&#9.2mg/&(range 1.95-38.05) trough 2.35mg/&#1.02 (range 2.34-10.8) in premature peak 20.6#10.8 (range 0.16-0.94) in newborn. Seizures in 8.9% patient cf 5.8% of premature & NB with serious nosocomial infection even after failure of other broad spectrum antibiotics.	Poor
29	Aitmand R, Moustou N  Serotypes & antimicrobial susceptibility of	Observational	Serotypes and level of antibiotic resistance of 59-streptococcus agalactiae isolates from Feb 1992 to July 1997 studied. All strains susceptible to pen G,	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	group B streptococcus isolated from neonates in Casablanca  <i>Scand .J Infect Dis</i> 2000; 32(3) 339-40		cefotaxime, ampicillin, 1 strain resistant to erythromycin. No high level resistance to gentamicin The antibiotic susceptibility patterns support the recommended treatment & prophylaxis of invasive group B streptococcal.	
30	De Hoog M, Schoemaker RC, Mouton JW  Vancomycin population pharmacokinetics in neonates  <i>Clin Pharmacol Ther.</i> 2000 Apr; 67(4): 360-7	Retrospective study with prospective validation (? Case series)  N=108 infants	108 newborns with suspected central line related septicemia during the first month of life-received 30mg/kg/day of vancomycin divided into 2 doses regardless of gestation/ postconceptual age. Trough & peak vancomycin S. conc determined before & after 3 <sup>rd</sup> dose. 34.3 % of measured trough concentrations and 17.6 % of peak concentrations were outside therapeutic range. Simulation of various dosing schemes, schedule of 30 mg/kg/d irrespective of G.A in doses was optimal. This was prospectively tested. This lead to adequate vancomycin trough S.conc. & peak concentration and there is no need for routine monitoring of peak serum conc.	?8
31	Anwer SK, Mustafa S  Rapid identification of neonatal sepsis  <i>J.Pak. Med Assoc</i> 2000 Mar; 50(3) 94-8	Observational study  N=50 NN	5 tests – total leucocyte count, absolute neutrophil count, immature/Total neutrophil ratio, platelet count, C reactive protein were used. CRP & absolute neutrophil count had a sensitivity of over 60 % with a specificity of 50 %. WBC had a specificity of 93 % but sensitivity of 14 %. Conc: None reliable alone. In combination, 5 tests may help to diagnose sepsis within a few hours. If high negative predictive value, neonates discharged early, stopping antibiotics hence reducing cost of treatment & anxiety of family.	8
32	Anwer SK, Mustafa S, Pariyani S  Neonatal sepsis an etiological study	Prospective, Observational	In early onset gm (-) ve & gm+ve organism were 33 and 35. Among gram (-)ve organisms, most of them were Klebsiella sp. Enterococcus was commonest gram	8

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	<i>J.Pak.Med</i> 2000 Mar; 50(3): 91-4	N=50 neonates	+ve organism. In late onset group, majority of infections were due to gm + ve organisms (30 out of 41) staph aureus and <i>S. epidermidis</i> were commonest. Organisms were least sensitive to ampicillin (<20 %) and highly sensitive to Amikacin (90-100%), cefotaxime (84-89%). Conc: Gram +ve organisms were main cause of neonatal sepsis. <i>Klebsiella</i> sp is still commonest organism causing early onset sepsis. Data periodically review and ab policy revised	
33	Ozkan H; Pasaoglu G,Olacac N  Stenotrophomonas maltophilia pneumonia in a premature infant  <i>Turk J. Pediatric</i> 1999 Apr-Jun; 41(2): 283-6	Case report	Patients compromised by debilitating illnesses, surgical procedures/indwelling vascular catheters are prone to <i>S.maltophilia</i> infections. 1st case of <i>S.maltophilia</i> in a premature infants of 31 weeks of gestational age. Patient successfully treated by amikacin.	Poor
34	Peters SM; Bryan J Cole MF  Enterobacterial repetitive intergenic consensus PCR typing of isolates of <i>Enterobacter cloacae</i> from an outbreak of infection in a NICU  <i>Am.J.infect Control</i> 2000Apr; 28(2): 123-7	Observational  N=17 patients	RIC PCR was used to examine 111 <i>E. cloacae</i> isolates from 17 patients including 81 from surveillance cultures, 23 from E.T.T, 3 from eyes, 1 each from blood, urine skin, throat. 1161 isolates were susceptible to imipenam/cipro 50 isolates susceptible to all antibiotics accept for aminopenicillin & 1 <sup>st</sup> generation cephalosporin. Highly antibiotic resistant <i>E cloacae</i> may emerge during an outbreak.	Poor
35	Ranu SS, Valencia GB, Piecuch S  Fatal early onset infection in an extremely low infant due to <i>Morganella morganii</i>  <i>J.Perinatol</i> 1999 Oct-Nov; 19(7) 533-5	Case report	Chorionamnionitis due to <i>M.m.</i> in a mother who presented with ruptured membranes at 24 weeks gestation and was treated with dexamethasone and prophylactic ampicillin. Infant developed severe early onset neutropenia, thrombocytopenia and severe acidosis and expired. Patient was on GM to which the organism was sensitive.	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
			Gentamicin failed to sterilize the infants blood / body fluids hence a combination of aminoglycoside and a 3rd generation cephalosporin such as cefotaxime is necessary.	
36	Pauli I, Shekhawat P, Kehl S  Early detection of bacteremia in the neonatal ICU using BACTEC system  <i>J. Perinatal</i> 1999,Mar; 19(2):,127-31	Retrospective Review Observational  N=25 infants	15 % were positive cultures out of these, 64 % were coag. (-) ve staphy, 14 % viridans, strept, 8 % E. coli, 40 % Enterococcus, 4% Ps. Sp, 2 % enterobacter sp, 2 % Klebsiella sp, 20 % c. albicans. 54 % of cultures were detected positive at 18 hrs, 71 % at 24 hrs 100% by 30 hrs.. BACTEC helps with early identification of neonatal bacteremia (in 24-30 hrs) with gm (-) ve organism detected earlier than Gram +ve organism, This will allow earlier diagnosis, appropriate treatment of the potentially bacteremic & bacteremic infant.	Poor
37	Traub WH; Schwarze 1 Bayer D  Nosocomial outbreak of cross infection due to multiple antibiotic resistant Klebsiella pneumonia Characterization of the strain & antibiotic susceptibility studies. <i>Chemotherapy</i> 2000 J-Feb ; 46(1) 1-14	Observational	Multiple antibiotic resistant(MAR) strain of Klebsiella pneumonia colonized neonates of 2 words with several cases of systemic infection.. Organism resistant cefotaxime, ceftazidime, aminoglycoside including amikacin. The isolates were identical & susceptible to carbapenem (meropenem more effective than imipenem) fluoroquinolones (ciprofloxacin & trovafloxacin) and polymixin B	Poor
38	Karunasekera KA; Pathirana D  A preliminary study on neonatal septicemia in a 3 ' referral Paediatric Unit  <i>Ceylon Med J.</i> 1999 Jun; 44(2): 81-6	Cross sectional study  N=98	98 babies had septicemia, Incidence 24.4 /1000 LB CFR 11.2 % , Incidence higher in preterm, LBW, instrumental delivery. 21.4 % developed septicemia D1, 74.5 % D2.7;4.1 % after W1. Common bacteria- Klebsiella 26.5 %; Staph aureus 15.3 %.coliform bacilli 9.2 %, spore forming bacilli 9.2 %, Common sensitive antibiotics amikacin 88.9 %, amoxy & clavulonic acid 83%, ceftriaxone 78.1 % and netilmicin 63 %. Concl : Septicemia an important cause of morbidity particularly preterm babies, LBW,	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
			instrumental delivery. High incidence of late onset septicemia together with klebsiella/staph aureus as common & resistant pathogens for septicemia indicate that the majority were nosocomial infections.	
39	Linder N, Raz M Sirota L  Unexplained fever in neonates may be associated with hepatitis B vaccine  <i>Arch. Dis Child Fetal Neonatal</i> Ed. 1999 Nov 81(3): F 206-7	Review	The increase in no of cases of unexplained neonatal fever seems to be associated with the introduction of routine hep B vaccination in D1 .A controlled study needed to confirm this finding.	Poor
40	Van der zwet, MC; Parlexliet GA  Nosocomial outbreak of gentamicin resistant Kleb.Pneumonia in a NICU controlled by a change in antibiotic policy.  <i>J Hosp infect</i> 1999 Aug; 42(4): 295-302	Case control study	13 neonates were colonized and 3 of them because infected. Care control study conducted to identify risk factors associated with acquisition of gentamicin resistant K. pneumonia. Risk factors were low GA, BW (need more care and handling) increased length of stay Outbreak stopped by replacing gentamicin by amikacin as the antibiotic of first choice whenever the use of aminoglycoside was indicated.	Poor
41	Kotze.A, Bartel PR,Sommers OK  Once VS twice daily amikacin in neonates a prospective study on toxicity  <i>J. Pediatric Child Health</i> 1999,Jun; 35(3): 283-6	A controlled randomized prospective study  N=40	15 patients in once daily group and 12 patients in b.d group showed at least one period of renal function impairment (decline of less than 50 % of expected physiological drop in S.creatinine over time) while in hospital. This decreased to 5/16 and 4/10 during follow up. Differences not statistically significant. BSE potential did not find signs of ototoxicity at any time. In full term neonatal patients once daily dosing of amikacin is no more toxic than the twice daily regime.	Good to Fair
42	Ako Nal AK, Adejuyigbe EA  Bacteriology of neonatal septicemia in Ile lfe	Observational	Incidence of septicemia among neonates as being at high risk was 55 % in Ile lfe Nigeria. Gram (+) ve organisms ( <i>S. aureus</i> specifically) were	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	Nigeria.  <i>J. Trop Pediatric</i> . 1999 Jun 45(3): 146-51		predominant – 33.8 % others: a) coag neg. staphylococcus 21 % b) L.Monocytogenes 8.4 % c) P. aeruginosa 3 % d) S.epidermidis 5 % e) E coli 7 % f) Enterobacter aerogenes 5 % g) Citrobacter freundii 2 % h) Salmonella sp 2 % i) Proteus sp 2 % j) K. pneumonia 14 % Isolates, were relatively resistant to antibiotics traditionally employed to treat cases of septicemia. High prevalence of neonatal bacterial sepsis and emergency role of L. monocytogenes. Preponderance of multiple antibiotic resistant organism among neonates early in life.	
43	Royle J, Halasz S, Eagles G,  Royal Alexandra Hospital for children, Australia Outbreak of extended spectrum B lactamase producing Klebsiella Pneumonia in a NNU  <i>Arch. Dis Child Fetal Neonatal Ed</i> 1999 Jan; 80(1) : F64-8	Case series	Outbreak & ESBL Klebsiella in NNU – 7 cases with 2 deaths. Control of outbreak was achieved by altered empiric antibiotic treatment for late onset sepsis ie imipenem/vancomycin over vancomycin and gentamicin and prevention of cross infection by strict attention to hand washing. No further episodes of sepsis occurred.	Poor
44	Sadow KB, Derr R, Teach SJ  Bacterial infections in infants 60 days and younger: epidemiology, resistance and implications for treatment.  <i>Arch.Pediatric Adolesc. Med</i> 1999 Jun 153 (6): 611-4	Retrospective case series All positive blood/urine, CSF cultures in children 60 days or younger from 1.1.94-31.12.97 from inpatients and patients initially evaluated in ED	1) GNR (79.3 %), group B strept (11.6%) enterococcus (5.8%), S. pneumonia (2.5%), N. meningitis (0.8%). No listeria was isolated. Of the GNR, 62.5 % were ampicillin resistant. All sensitive to gentamicin & cefotaxime. Conc: 1) No listeria 2) GNR-60 % ampicillin resistant. Empiric use of ampicillin as part of combination for presumed bacterial infection in patients 60 days or younger neither necessary nor	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
			beneficial. Consider 3 rd gen. Cephalosporin with/without gentamicin. This policy was beneficial because GNR was far most common organism. Cephalosporins also in vivo demonstrated clinical efficiency in GBS sepsis and meningitis	
45	Lundergan FS; Glasscock GF Kim EH  Once daily gentamicin dosing in newborn infants  <i>Pediatrics</i> 1999 Jun 103 (6 pt 1): 1228-34	Comparative Cohort study	In LBW neonates, the regime resulted in peak & trough SDL throughout therapy that were similar to those observed in the control group. Delaying the initiation of maintenance once daily dosing until 36-48 hours after loading dose would be expected to result in a higher incidence of initial trough SDL in target range for VLBW neonates.	Fair
46	Ocete E, Ruiz Extremera A, Golcochea A  Low dosage prophylactic vancomycin in central venous catheters for neonates  <i>Early Hum. Dev.</i> 1998 , Dec 53 Suppl (4 p t 1) 5181-6	Case series	Negative coagulase staphylococcus is the principal pathogen in most neonatal ICU. Efficacy of prophylactic use of vancomycin in preterm babies receiving parenteral nutrition evaluated period over 1 year. Prophylaxis reduced incidence of gram positive infections.	Poor
47	Kaushik SL, Parmer VR  Neonatal sepsis in hospital born babies  <i>J. Comm. Dis</i> 1998 Sep 30 (3) 147-52	Observational	Incidence of neonatal sepsis in a study in hospital born babies was 5.3 % (10.9%) higher in LBW cf normal B.W babies. Sepsis related mortality also exceeded in LBW babies. Positive cultures in 36.7 % of babies with sepsis. Organisms were. Staph pyogenes (40%), Ecoli (27.5%), Klebsiella sp ( 15%), Staph epidermidis ( 100%), Enterobacter sp ( 7.5%), Gram negative bacilli predominated in early onset (<72 hrs) & gram positive cocci in late onset., Isolates resistant to routinely used antibiotics (penicillin, ampicillin, and getamicin). 3 rd generation cephalosporin & aminoglycosides were found to be effective in treatment of neonatal sepsis.	Poor
48	Davies MW, Cartwright DW  Gentamicin dosage intervals in neonates: longer	Retrospective observational Study	Data collected on BW; gestation, gentamicin dose, trough level of gentamicin, s. creatinine & urine output. Trough serum gentamicin level of > or =1.5	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	<p>dosage interval – less toxicity</p> <p><i>J. Pediatr Child Health</i> 1998 Dec; 34 (6): 577-80</p>	<p>N=Neonates born between 1/7/95 – 31/12/95 who received gentamicin</p>	<p>mg/L was considered toxic. 21 infants in 24-29/52 gestation received Gm with a dosage interval of 24 hrs. 16 infants had toxic trough serum gentamicin level. (76%). In 30-34/52 – 8 infants had GM 12 hourly and all had toxic. Trough S.G.M levels – 14 infants had GM 18 hourly and 13 had toxic trough. (93%) SGM levels – 61 infants had GM 24 hrsly and 25 had toxic trough S.G.M (41%). In &gt; or=35/week, 29 infants had gm 12 hours and 25 had toxic trough SGM (86%). 6 had GM 18 hourly and 2 (33%) had toxic trough SGM levels. 31 infants had GM 24 hourly and 4 (13%) had toxic trough S.G.M levels. Concl: A starting gentamicin dosage interval of 12 h in infants of any gestational age or a starting dosage interval of 24 h for infants &lt; 30/52 GA, leads to most having toxic trough S.G.M levels. In infants 30/52 GA or greater most have safe non-toxic trough SGM levels if started on a dosage interval of 24 h.</p>	
49	<p>Rowen JL, Tate JM</p> <p>Management of neonatal candidiasis Neonatal candidiasis study Group</p> <p><i>Ped.Infect. Dis J.</i> 1998 Nov: 17(11) 1007-11</p>	<p>Consensus</p>	<p>95 % of respondents cared for an infant with systemic candidiasis in past 2 years. Flucanazole used to some extent by 90 % Liposomal amphotericins by 69 % . Single blood c+s positive for candida led to immediate treatment by 99 % . Amphotericin B was preferred therapy for candidemia (88%) in ill infants. &gt; 80 % would request for CSF, urine and repeat blood c+s, ophthalmologic examination in evaluation of candidemia. If CSF c+s were positive, 25 % would be amphotericin B alone 62 % would add flucytosine. If urine c+s was positive only 66% would use a single positive SPA as grounds for treatment, 3.No consensus or duration of therapy, amphotericin B test dose or mx of a central catheter during a candidemia. Con: Agreement that prompt therapy with amphotericin B is required if a blood cultures is positive for candida and</p>	<p>Poor</p>

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
			infants required additional evaluation.	
50	Finnstrom O, Isaksson B  Control of an outbreak of a highly B lactam resistant <i>Enterobacter cloacae</i> strain in a neonatal S.C.U  <i>Acta Paediatr</i> 1998 Oct 87- (10): 1070-4	Case Series  N= patients	2 outbreaks of colonisation and infection with <i>E. cloacae</i> resistant to 3 rd generation cephalosporins within 12 months. Replacing ampicillin plus cefotaxime as standard empiric therapy with pen G +t netilmicin and consequent cohorting of newborn and staff halted the outbreaks. The next 5 years no further outbreaks of CREC reported	Poor
51	Egri OkwajiMT; Iroha EO  Bacteria causing septicemia in neonates with tetanus.  <i>West Afr J Med</i> 1998 Jul-Sep; 17 (3): 136-9	Observational  N=105	Neonates admitted for tetanus were screened for sepsis. Presence of omphalitis/poor color, hypothermia and hypothermia were sensitive predictors of septicemia 50 pathogens isolated from 50 babies. <i>Klebsiella preum</i> (20.7%) <i>Enterobacter cloacae</i> (19%), <i>Staph aureus</i> 19.2 % Antimicrobial susceptibility favoured ofloxacin but combination of clox / gentamicin recommend., Ceftazidime with about 60 % susceptibility across board is the favoured cephalosporin.	Poor
52	Van den Vever HL; Vers teegh FG  Ciprofloxacin in preterm neonates: a case report & review of literature  <i>Eur J. Paediatr</i> 1998 Oct; 157 (10): 843-5	Case report	Ciprofloxacin treatment of preterm/LBW infants infected with <i>E cloaca</i> , <i>Ps aeruginosa</i> , <i>K. pneumoniae</i> resistant to other antibiotics.	Poor
53	Groll All, Jauger G  Invasive aspergillosis in a critically ill neonate: a case report & review of invasive aspergillosis during 1st 3 months of life.	Case report	11/44 – primary cutaneous aspergillosis 14/44- disseminated disease 10/44 – pulmonary aspergillosis Overall survival 73 %. Majority of underlying conditions were prematurity, CGD, complex diarrhoea, malnutrition and invasive bacterial infections. .41% of	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	<i>Clin Infect Dis</i> 1998 Sep; 27 (3) : 437-52		patients had been given corticosteroids before diagnosis. outcome was favourable with 73% survival in 22 patients receiving systemic antifungal treatment and or surgical treatment. Current therapeutic approach (lit review) Approaches high dose amphotericin B and appropriate surgical interventions.	
54	Fallat ME, Gallinaro RN  Central venous catheter blood stream infections in the NICU  <i>J. Pediatr Surg</i> 1998 Sep; 33(9): 1383-7	Retrospective cohort study  N=157	Factors that significantly decreased the incidence of CVC BSI were increasing G. Age at time of insertion , associated vancomycin at time of catheter placement, fewer days of catheter use. Concerns about emergence of vancomycin resistant organisms preclude support of its use as a prophylactic agent	Fair
55	Yurdakok M  Antibiotic use in neonatal sepsis  <i>Turk J.Pediatr</i> 1998 Jan-Mar; 40(1): 17-33		If neonates has pneumonia /sepsis antibiotic should not be stopped although cultures negative. Duration of therapy depends on initial response to antibiotics but should be 10-14 days in most infants with sepsis & minimal/absent focal infection. Infants who developed sepsis in 1st week of life empirical therapy must cover group B strept. Enterobacteriaceae (Esp. Ecoli) & Listeria monocytogenes. Penicillin or ampicillin and an aminoglycoside are usually effective. Empirical antibiotic therapy for infants who developed sepsis beyond the 1st days of life must cover the organisms with early onset sepsis as well as hospital acquired pathogens - Staphylococci, Enterococci, Ps. Aeruginosa. Pen/ampicillin and aminoglycoside may be used in nosocomial infections, netilmicin or amikacin preferred in cases with increased risk of staphylococcal infection (vascular catheter) or Pseudomonas infection (skin lesions) – antistaphylococcal or anti Ps. Agents used. 3 rd gen. Cephalosporins should not be used in initial therapy of suspected sepsis emergence of drug resistant	

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
			microorganisms, antagonistic interactions demonstrated when other lactam antibiotics (penicillin) combined with cephalosporins. Antipseudomonas activity – piperacillin & azlocillin most active Espectrum (extended spectrum) penicillins 3rd generation cephalosporin – cefoperazone & ceftazidime. New antibiotics for gram (-)ve bacteria resistant to other agents are carbapenems, aztreonam, quinolones & isepamicin . Enterococci – Penicillin, ampicillin or vancomycin and an aminoglycoside Staphylococci- penicillin resistant penicillin (oxacillin, nafcillin & methicillin) Resistant strains are sensitive to vancomycin.	
56	Krishnan L, George SA  Gentamicin therapy in preterm : a comparison of 2 dosage regimens  <i>Indian Pediatr</i> ,1997 Dec;34 (12) :1075-80	Randomised double blind study  N=18  F/up: Jan 1994-May 1994	Optimum therapeutic peak level after the 1st dose was achieved only with once daily gentamicin regimen Mean 5.88 Vs 3.88 ug/ml Mean peak levels were not significantly different in either regime. None of neonates showed nephrotoxicity. Once daily dose 4mg/kg of gentamicin has logistic & monetary benefits in addition to the obvious pharmacokinetic advantage.	Good to Fair
57	Matral- Kovalskis Y, Greenberg D,Shinwell ES  Positive blood culture for coagulase negative staphylococci in neonates: does highly selective vancomycin usage affect outcome  <i>Infection</i> 1998, Mar-April 26(2): 85-92	Retrospective & party prospective  N= 239 episodes  F/up: 1990-1996	VM administered in 22 episodes after identification of bacteria. Others mx without antibiotics or empiric antibiotic therapy (usually ceftazidime + ampicillin) for suspected sepsis. Severity of initially illness, subsequent morbidity and mortality were low regardless of treatment. Only 1 case of blood borne VR gram positive organism was observed during study period. Hence a policy of highly selective VM usage supported.	Fair
58	Weitkamp JH, Poets CF	N=21 VLBW	Systemic fungal infection occurs in 2-4.5 % VLBW	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
	<p>Candida infection in VLBW infants - outcome and nephrotoxicity of treatment with liposomal amphotericin B</p> <p><i>Infection</i> 1998 Jan-Feb 26 (1) : 11-5</p>		<p>infants &lt; 1.5 kg mean GA 25(23-31). Fatal 25- 54 %</p> <p>Candida sp major pathogen and amphotericin B the treatment of choice . To reduce SE and optimize drug action, formulation of amphotericin B encapsulated in liposomes (Am Bisome) introduced. All patients treated with Am Bisome eradicated fungi and recovered clinically No nephrotoxicity noted</p>	
59	<p>Scarcella A, Pasquariello MB</p> <p>Liposomal amphotericin B treatment for neonatal fungal infections</p> <p><i>Pediatr Infect Dis J.</i> 1998 Feb 17 (2); 146-8</p>	N=40 premature	<p>Liposomal encapsulated amphotericin B (Am Bisome) given to 40 premature (mean BW 1090-/ +313.6g, mean GA 28.35+2.13 weeks and 4 full term mean birth weight, 3080 +118g, mean gestational age 39 +0.7 weeks with severe fungal infections</p> <p>Candida Albicans most frequent fungus isolated (70%). Administration of ambisome effective in 72.7% of patients. 5 of 6 cases of meningitis recovered. 63</p>	Poor
60	<p>Ocete E, Ruiz - Extremera A</p> <p>Low dosage vancomycin in CV central venous catheters for neonates</p> <p><i>Early Human Dev</i> 1998 Dec 53 Suppl 5181 - 6</p>	Prospective control trial	<p>Negative coagulase staphylococcus is the principal pathogen in most NICU.</p> <p>Evaluate efficacy of prophylactic vancomycin administered via catheters significantly reduced incidence of Gram + ve infections.</p>	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
61	Falllat ME, Giallino RN  Central venous catheter blood stream infections in NICU  <i>J. Pediatr Surg</i> 1998, Sep 33 (9): 1383-7	Retrospective cohort study	268 lines placed in 157 NICU over 29 months. 65 lines (24%) had confirmed CVC BSI. Common symptoms - fever 49 %, pulmonary dysfunction 30 % S. Epidermidis most common organism. Factors significantly decreased the incidence of (VS BSI were increasing EGA associated vancomycin use at the time of catheter placement fever drip of catheter use Concerns regarding emergence of VR organisms preclude support of its use as a prophylactic agent.	Fair
62	Degrease PL, Bemoan GH  Use of teicoplanin in preterm neonates with staphylococcal late onset neonatal sepsis.  <i>Boil Neonate</i> 1998; 73(5) :287-94	Nonrandomised descriptive study  N= 23 preterm neonates	Subjects was suspected of late on set septicemia. 21 cultures proven to have septicemia. 20 were caused by staphylococci. Teicoplanin loading dose was 15 mg/kg iv. Followed by maintenance dose of 8 mg/kg every 24 hours. Iv gentamicin administered also pending blood culture. Peak & trough level averaged 27.8 & 12.3 mg/L. microbiological & clinical cure rates were 90 % in gram positive septicemia. No apparent toxicity was noted.	Poor
63	Bhutta ZA  Gunolove resistant S. paratyphi & meningitis in a newborn  <i>J. Infection</i> 1997; Nov 35 (3); 308-10	Case report	New reports of quinolone resistant strains of salmonella typhi or paratyphi from Indian subcontinent. Case report of newborn with meningitis due to a quinolone resistant strains of S. paratyphi B presenting to Aga Khan U.H	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
64	<p>Cordero L, Sandnes M</p> <p>Bloodstream infections in a neonatal ICU: 12 years experience with an antibiotic control program</p> <p><i>Infect Control Hosp Epid</i> 1999</p>	<p>Case review</p> <p>N=363 infants</p>	<p>Conc.: combination of ampi &amp; genta for suspected every onset BSI: VM and gentamicin for late onset BSI has been successful suggest controlled ab program and periodic evaluation based on individual unit advisable.</p>	Poor
65	<p>Jacqueline Judith Ho</p> <p>Late onset infection in very low birth weight infants in Malaysian level 3 nurseries</p> <p><i>Paed Infectious Journal</i> 2001 June 20 (60): 557-560</p>	<p>Observational study</p> <p>N=962 infants</p>	<p>Overall survival was 69%. Mortality 30.8%</p> <p>Rate of late onset infection 19.3%</p> <p>The most common infecting organism was <i>Klebsiella pneumoniae</i> – 38.3% of infections, and 46.9 % of deaths in neonates with infection. This was followed by coagulase negative staphylococci – 17.6% of infections and deaths 12.2%</p> <p>The risk factors for late onset gram negative compared to gram-positive infection were endotracheal infection at birth and blood transfusion. Hypoglycemia was associated with gram-positive infection.</p> <p>Conc.: the late onset infection in Malaysian low birth weight infants does not differ fro that reported for developed counties but the mortality is higher. This could be because of an excess of gram-negative infections.</p>	Poor

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66	<p>Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, de Sierra TM, Weller S, Soong SJ, Kiell J, Lakeman FD, Whitley RJ</p> <p>Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections.</p> <p><i>Pediatrics</i> 2001 Aug 108 920; 230-8</p>	<p>Cohort study</p> <p>N=88</p> <p>F/up: 4 years</p>	<p>1. 21 % of 29 HD acyclovir recipients experienced neutropenia</p> <p>2. Survival rate for patients with HD (high dose) acyclovir was higher cf previous study (NIAIDCASG) trial with SD (standard dose) acyclovir</p> <p>3. Survival rates for patients with CNS disease were similar in SD/MD group</p> <p>4. In recipients of HD acyclovir there was borderline significant decrease in morbidity</p> <p>Support use of 21 day HD IV acyclovir to treat neonatal CNS &amp; disseminated HSV disease. Serial ANC should be made at least twice weekly</p>	Fair
67	<p>Kimberlin DW.</p> <p>Advances in the treatment of neonatal herpes simplex infections.</p> <p><i>Rev. Med Virol</i> 2001 May-June 11 93 0 157-63</p>	Review	<p>Use of high dose acyclovir for the treatment of acute neonatal HSV disease has reduced mortality rates to their lowest level.</p> <p>Utilization of suppressive oral acyclovir following acute neonatal disease is another therapeutic option under investigation to improve morbidity outcome.</p>	Poor
68	<p>Huang YC, Lin TY, Lin YJ, Lien RI, Chou YH.</p> <p>Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella.</p> <p><i>Eur J Pediatr</i> 2001 Feb; 160 92 0: 91-4</p>	<p>N= 39(n= 24 newborn infants whose mother developed varicella rash within 14 days before &amp; after delivery and n=15 newborn whose mother's rash appeared within 7 days before &amp; 5 days after delivery (at risk group)</p>	<p>In the at risk group – received IVIG (500 mg/kg/ dose or with IV acyclovir (5 mg/kg 8 hourly) for 5 days.</p> <p>4 infants who received IVIG alone – 2 developed varicella</p> <p>None of 10 infants receiving both IVIG &amp; ACV contracted varicella:</p> <p>1 receiving ACV alone had no varicella.</p> <p>9 infants in not at risk group, 4 had undetectable varicella-zoster virus antibody on admission &amp; developed clinical varicella subsequently.</p> <p>Conc: Combination of IVIG &amp; prophylactic acyclovir can effectively prevent perinatal varicella</p>	Poor Small study

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69	<p>Oram RJ, Marcellino D, Strauss D, Gustafson E, Talarico CL, Root AK, Sharma PL, Thompson K, Fingerth JD, Crumpacker C, Herold</p> <p>Characterization of an acyclovir-resistant herpes simplex virus type 2 strain isolated from a premature neonate.</p> <p><i>Pediatric Infectious J Infect Dis</i> 2000 Apr;181(4):1458-61</p>	Case report	<p>A premature infant with neurocutaneous HSV infection was treated for 21 days with acyclovir. Disseminated disease recurred 8 days later. A recurrent isolate was resistant to acyclovir. Acyclovir resistant HSV 2 mutants can develop rapidly in neonatal infection &amp; cause clinical significant disease</p>	Poor
70	<p>Singalavanija S, Limpongsanurak W, Horpoapan S, Ratisawadi V.</p> <p>Neonatal Varicella: A report of 26 cases.</p> <p><i>J. Med. Assoc.Thai</i> 1999 Oct 82 910 0 957-62</p>	<p>Care series</p> <p>N= 26</p>	<p>12 cases had varicella from mothers infected between 6 days before delivery to 2 days after delivery. 14 cases were postnatal varicella IV acyclovir given in high risk &amp; severe cases (9 perinatal &amp; 3 postnatal) No deaths IV acyclovir was beneficial in treatment of neonatal varicella.</p>	Poor
71	<p>Ogilvie MM.</p> <p>Antiviral prophylaxis and treatment in chickenpox. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection.</p> <p><i>J Infect</i> 1998 Jan;36 Suppl 1:31-8</p>	Review	<p>.Iv acyclovir therapy for 5-10 days is effective for varicella in neonates &amp; immune compromised and for varicella pneumonia or other complications in adults &amp; children if begin early. Oral acyclovir is effective if begin within 24 hour of onset of rash. It is recommended for treatment of varicella in healthy adults &amp; adolescents but not for routine use in children &lt; 13 years unless they are sibling contacts/have other medical condition Acyclovir has high therapeutic index &amp; good safety profile</p>	Poor

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72	D'Andrea CC, Ferrera PC  Disseminated herpes simplex virus infection in a neonate.  <i>Am J Emerg Med</i> 1998 Jul;16(4):376-8	Case report	In neonates with sepsis, ampicillin with either an amino glycoside or cefotaxime are chosen. Coverage for viral esp. HSV rarely given in ED. (emergency Department). However, acyclovir/vidarabine has to be started in early stages to be effective. Broadening the indications for initiating antiviral therapy to include neonate whose mother has any history of STD may prevent sequelae of untreated or inadequately treated HSV	Poor
73	Norris CM, Danis PG, Gardner TD.  Aseptic meningitis in the newborn and young infant.  <i>Am Fam Physician</i> 1999 May 15;59(10):2761-70	Review	When toxic newborn/ young infant presents with fever and lethargy or irritability, meningitis should be considered. Initial CSF results many not conclusively differentiate aseptic from bacterial meningitis & antimicrobial therapy for all likely organisms should be instituted including antivirals. Etiologies of aseptic meningitis include viral/partially treated bacterial meningitis, congenital infection, drug reaction, post vaccination, systemic disease & malignancy. Prompt diagnosis & treatment are essential.	Poor
74	Kesson AM.  Use of acyclovir in herpes simplex virus infections.  <i>J Paediatr Child Health</i> 1998 Feb;34(1):9-13	Consensus	In most situations the use of acyclovir shortens duration of clinical illness & viral shedding & reduces morbidity & mortality. All life/sight threatening infections should be managed in inpatient hospital setting with intravenous therapy. Oral acyclovir is recommended in patients with non life threatening illness who may still have significant symptoms.	Poor

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75	<p>Swedish Consensus Group.</p> <p>Management of infections caused by respiratory syncytial virus.</p> <p><i>Scand J Infect Dis</i> 2001;33(5):323-8</p>	Comments	<p>Ribavirin inhalation treatment may be considered in high risk infants with clinical symptoms indicating a serious course of RSV infection.</p> <p>Treatment with ribavirin in combination with intravenous polyclonal immunoglobulin considered in patients who had received stem cell transplantation or organ transplantation with &gt; 1 episode of rejection treatment and who have mild/moderate RSV pneumonia.</p> <p>Evidence based documentation for treatment of other groups is lacking.</p>	Poor
76	<p>Van Woensel JB, Kimpfen JL, Brand PL.</p> <p>Respiratory tract infections caused by respiratory syncytial virus in children. Diagnosis and treatment.</p> <p><i>Minerva Pediatr</i> 2001 Apr;53(2):99-106</p>	Review	<p>Based on current available evidence there is no place of ribavirin in routine treatment of RSV LRT.</p> <p>Corticosteroids may be useful in more severe RSV LRTI.</p> <p>Immunoglobulin have no place in the treatment of RSV LRTI</p>	Poor
77	<p>Greenough A.</p> <p>Recent advances in the management and prophylaxis of respiratory syncytial virus infection.</p> <p><i>Acta Paediatr Suppl</i> 2001 Mar;90(436):11-4</p>	Review	<p>Overall the results of randomized trial do not support the use of bronchodilator corticosteroids or Ribavirin.</p> <p>Immuno prophylaxis should be reserved for infants at highest risk of severe RSV infection to be cost effective</p>	Poor
78	<p>Rodriguez WJ.</p> <p>Management strategies for respiratory syncytial virus infections in infants.</p> <p><i>J Pediatr</i> 1999 Aug;135(2 Pt 2):45-50</p>	Review	<p>Several recent studies suggest that ribavirin may have beneficial effect on sequela although other studies failed to demonstrate any benefit.</p> <p>Management of RSV LRTI in infants is predominantly supportive &amp; symptomatic.</p>	Poor

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79	Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, Dankner W, Spector SA, Starr S, Pass RF, Stagno S, Britt WJ, Alford C Jr, Soong S, Zhou XJ, Sherrill L, FitzGerald JM, Sommadossi JP.  Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group.  <i>J Infect Dis</i> 1997 May;175(5):1080-6	Case series  N=47	Doses of 8/12 mg/kg of ganciclovir were administered in divided doses at 12 hourly interval for 6 weeks. Thombocytopenia in 37 babies & neutropenia in 29 babies observed. Quantitative excretion of CMV in urine decreased but after cessation of therapy viruria returned. Therapy improvement or stabilization occurred in 5 babies at 6 months or later indicating efficacy.	Poor
80	Brown HL, Abernathy MP  Cytomegalovirus infection.  <i>Semin Perinatol</i> 1998 Aug; 22(4):260-6	Review	CMV results in severe injury to the fetus Mortality is 30 %. 80 % of survivors have severe neurological morbidity Antimicrobial therapy & immuno prophylaxis for CMV infection are unsatisfactory	Poor
81	Heuchan AM, Isaacs D.  The management of varicella-zoster virus exposure and infection in pregnancy and the newborn period. Australasian Subgroup in Paediatric Infectious Diseases of the Australasian Society for Infectious Diseases.  <i>Med J Aust</i> 2001 Mar, 19;174(6):288-92		ZIG Should be given to a baby whose mother develops chickenpox up to 7 days before delivery or up to 28 days after delivery. Iv acyclovir should be given to babies presenting unwell with chickenpox.	Poor

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82	<p>Kesson AM.</p> <p>Management of neonatal herpes simplex virus infection.</p> <p><i>Paediatr Drugs</i> 2001;3(2):81-90</p>	Review	<p>Treatment is recommended where diagnosis is confirmed or there is a high level of suspicion. The current recommendation is acyclovir 20 mg/kg 3 time daily by Iv Infusion.</p> <p>The newer anti herpes agents valacyclovir, famcyclovir after no advantage over acyclovir and are not recommended for neonatal HSV infection.</p>	Poor
83	<p>Bury RG Tudehope D</p> <p>Enteral antibiotics in preventing NEC in LBW or preterm infants</p> <p>Cohrance Database System Rev 2000; 2: CD00405</p>	Cochrance review	<p>There is insufficient evidence to support the use of enteral antibiotic prophylaxis for NEC in clinical practice. To address this question further, a large trial would be required with a sample size sufficient to examine all the important benefits and harms. Adverse outcomes associated with infection, particularly with resistant bacteria, should be evaluated.</p>	Good
84	<p>Koc E, Turkkyilmaz C, Atalay Y Sen E</p> <p>Imipenem for treatment of relapsing Salmonella meningitis in a newborn infant</p> <p><i>Acta Paediatric Jpn</i> 1997 Oct; 39 (5):624-5</p>	Case report	<p>Salmonella meningitis is a rare clinical entity that occurs mainly during early infancy. Treatment of Salmonella infections may be complicated by the bacteria's growing resistance to clinically important antimicrobial agents, especially third-generation cephalosporins. A report is presented of a newborn infant with Salmonella meningitis who relapsed after 4 weeks of cefotaxime treatment and was cured completely with imipenem cilastatin therapy</p>	Poor

No	Author, Title, Journal	Study design, Sample size, Follow-up	Outcome & characteristics	Grade and Comments
85	Bhat KG, Paul C, Bhat MG  Neonatal bacteremia due to high level aminoglycoside resistant (HLAR) enterococci  Indian j Paediatric 1997 Jul- Aug; 64(4):537-9	Case study  N= 41	85.4% were Enterococcus faecalis and 14.6% were Enterococcus faecium. A total of 8.6% strains of E. faecalis and 33.3% E. faecium strains showed high level aminoglycoside resistance (HLAR). None of the enterococci tested were vancomycin resistant. Drug resistance was more common among E. faecium strains. All clinically significant isolates of enterococci should be tested for their antibiotic sensitivity pattern including HLAR, and for treatment, antibiotics are selected based on in vitro antibiotic sensitivity test results.	Poor
86	Jacob RF  Neonatal herpes simplex virus infections  Semin Perinatol 1998 Feb; 22(1):64-71	Review	No differences in outcome were seen between neonates treated with vidarabine and acyclovir. More recently, administration of oral acyclovir has been demonstrated to prevent cutaneous recurrences of HSV after neonatal SEM disease. Although promising, this investigational protocol requires further evaluation before a routine recommendation for prophylactic therapy with oral acyclovir can be made. Oral acyclovir able to prevent recurrences of HSV after neonatal skin, ear and mouth infections	Fair to good
87	Di Pentima MC, Mason EO Jr, Kaplan SL  In vitro antibiotic synergy against Flavobacterium meningosepticum: implications for therapeutic options.  Clin Infect Dis 1998 May;26(5):1169-76	Review of case reports	Flavobacterium meningosepticum is an unusual, highly resistant, gram-negative bacillus that is associated with neonatal meningitis and nursery outbreaks of meningitis. These results support the clinical evidence that the combination of vancomycin and rifampin is an appropriate regimen for neonatal meningitis due to F. meningosepticum. The combination of meropenem and vancomycin was antagonistic. The clinical efficacy of combinations including ciprofloxacin, newer quinolones, or linezolid for treating F. meningosepticum meningitis deserves further study.	Poor