Management of community-acquired pneumonia in children: South African thoracic society guidelines (part 3)

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G Reubenson,[1] FCPaed (SA); **T Avenant,**[2] FCPaed (SA); **D P Moore,**[3] PhD; **G Itzikowitz,**[4] MSc; **S Andronikou,**[4,5] PhD; **C Cohen,**[6] PhD; **R J Green,**[2] PhD; **P Jeena,**[7] FCPaed (SA); **R Masekela,**[7] PhD; **M P Nicol,**[8] PhD; **A Pillay,**[7] Cert ID Paed (SA); **S A Madhi,**[9,10] PhD; **H J Zar,**[4,11] PhD; **A C Argent,**[4] MD (Paediatrics)

[1] *Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Pretoria, South Africa*
[3] *Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa*
[4] *Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and Faculty of Health Sciences, University of Cape Town, South Africa*
[5] *Department of Pediatric Radiology, Perelman School of Medicine, University of Pennsylvania, and Children's Hospital of Philadelphia, PA, USA*
[6] *Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa*
[7] *Department of Paediatrics and Child Health, Nelson R Mandela School of Medicine, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa*
[8] *Division of Medical Microbiology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, South Africa; and Division of Infection and Immunity, School of Biomedical Sciences, University of Western Australia, Perth, Australia*
[9] *South African Medical Research Council Vaccine and Infectious Diseases Analytics Unit, University of the Witwatersrand, Johannesburg, South Africa*
[10] *Department of Science and Technology/National Research Foundation: South African Research Chair in Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[11] *South African Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, South Africa*

Corresponding author: *G Reubenson (gary.reubenson@wits.ac.za)*

Background. Pneumococcal conjugate vaccine (PCV) administration and other advances have been associated with a shift in the aetiological spectrum of community-acquired pneumonia, necessitating reconsideration of empiric antibiotic treatment guidelines. Management strategies have also evolved in the last decade.
Objectives. To produce revised guidelines for the treatment of pneumonia in South African (SA) children, including ambulatory, hospital and intensive care management.
Methods. An expert subgroup, reviewing evidence on the management of childhood pneumonia, was convened as part of a broader group revising SA guidelines. Evidence was graded using the British Thoracic Society (BTS) grading system and recommendations were made.
Results. Antibiotic treatment depends on the child's age, possible aetiology, antimicrobial resistance patterns, previous treatment, as well as factors affecting host susceptibility, including HIV, and nutritional and vaccination status. All children with signs of severe pneumonia should receive antibiotics. Children <1 month of age with pneumonia should be hospitalised and treated with ampicillin and an aminoglycoside. For treatment of ambulatory children >1 month of age, high-dose amoxicillin remains the preferred antibiotic. For severe pneumonia in this age group, hospitalisation and empiric treatment with amoxicillin-clavulanate orally is recommended; if oral therapy is not tolerated, intravenous therapy is recommended. Generally, 5 days of therapy is proposed, but longer duration may be needed in cases of severe or complicated disease. A macrolide antibiotic should be used if pertussis, mycoplasma or chlamydia pneumonia is suspected. Most hypoxic children can receive oxygen via nasal cannulae, but respiratory support should be individualised and extends to non-invasive and invasive ventilation in some cases. Children should be fed enterally; if this is not possible, administer intravenous isotonic fluids at <80% of maintenance, with monitoring of sodium levels. Empiric antibiotic treatment is the same in HIV-infected, HIV-exposed uninfected and HIV-uninfected children, although treatment for pneumocystis pneumonia and/or cytomegalovirus pneumonia should be considered in HIV-infected infants, especially in the absence of combination antiretroviral therapy.
Conclusions. Updated guidelines optimise the management of childhood pneumonia in the context of changing epidemiology, improvements in HIV prevention and new evidence on management.

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Changes in the epidemiology and aetiology of childhood pneumonia have necessitated a revision of management strategies. Pneumococcal and *Haemophilus influenzae* type b (Hib) conjugate vaccines have resulted in a shift in bacterial aetiology, with non-typable *H. influenzae* and *Staphylococcus aureus* causing a greater proportion of radiologically confirmed severe pneumonia in hospitalised children.

Improvements in diagnostic methods have further contributed to recognising causative pathogens. Furthermore, management

strategies of children with pneumonia continue to evolve and improve.

Treatment of childhood pneumonia

Antibiotic treatment

Choice of empiric antibiotic treatment depends on the child's age, possible aetiology, antimicrobial resistance patterns, previous treatment, as well as factors affecting host susceptibility, including HIV, nutritional and vaccination status. All children with signs of pneumonia or severe pneumonia should receive antibiotics (evidence level Ib).[1,2]

Adaptation of guidance to address antibiotic resistance

Substantial (>80%) reductions in the incidence of invasive pneumococcal disease were observed within 4 years of pneumococcal conjugate vaccine (PCV) introduction.[3] High-dose amoxicillin is effective against pneumococci with low- and intermediate-level penicillin non-susceptibility causing pneumonia. Empiric therapy for hospitalised children with community-acquired pneumonia (CAP) should cover non-typable *H. influenzae* and *S. aureus*.[4,5]

Which empiric antibiotic?

For severe pneumonia in children >1 month of age, amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component) is recommended. Oral therapy (45 mg/kg/day 12-hourly of amoxicillin component) is preferable, but intravenous therapy (30 mg/kg/dose of intravemous amoxicillin component 8-hourly) should be initiated in children who are unable to tolerate oral medications, if there is a concern about oral absorption, or if the child is severely ill.

For children <1 month of age, initial therapy should be intravenous ampicillin (40 mg/kg/dose 6-hourly) and gentamicin (7.5 mg/kg/dose daily) to cover common neonatal pathogens, including Listeria spp. (evidence level II). Group B Streptococcus, *S. aureus*, *Chlamydia trachomatis* and viruses should also be considered as causes of neonatal pneumonia. Consideration should be given to broadening cover if there is no clinical improvement within 48 hours of initiation of therapy.

A macrolide should be included when 'atypical' pathogens (e.g. Mycoplasma spp., Chlamydophila spp., pertussis) are suspected (evidence level IVa).

For ambulatory treatment of pneumonia, amoxicillin (45 mg/kg/dose 12-hourly) remains the preferred antibiotic for children >1 month old. Outpatient management should not be considered for infants <1 month of age (Table 1).

HIV infection or exposure influences investigation and management of children with pneumonia (see below: Special circumstances: HIV infection or exposure).

Route of administration

Oral therapy is preferable; however, parenteral antibiotics should be used for children requiring intensive care unit (ICU) admission or for those too ill to tolerate oral medication. There are, however, risks and costs associated with intravenous use, and oral de-escalation is recommended as soon as feasible (evidence level IIIa).[6,7]

Duration of antimicrobial therapy

In general, 5 days of antibiotic therapy is recommended, but longer duration may be needed in children with severe or complicated disease, if there is a poor response to therapy, or as informed by microbiology results.

Bacteraemic staphylococcal pneumonia should be treated for 14 - 28 days, dependent on complications and response to treatment.[8] Uncomplicated presumed staphylococcal pneumonia (i.e. blood culture negative, but with suggestive clinical or chest X-ray (CXR) features) may be appropriately managed with a 7 - 10-day course of targeted antibiotic therapy, depending on clinical response (evidence level IVa).[9]

Management of a child who is not responding to therapy

A poor response to treatment has many possible explanations. Consider infection with *Mycobacterium tuberculosis*, viruses, fungi or atypical organisms. Evaluate for the presence of a foreign body, empyema, heart disease or underlying immunodeficiency.[10]

Change to amoxicillin-clavulanate if there is a poor clinical response or deterioration in a child treated with amoxicillin. For children initially treated with amoxicillin-clavulanate, change to ceftriaxone (evidence level IVa).[2] Where laboratory support is available, it is strongly recommended to repeat a microbiological work-up, including blood culture, before changing antibiotics.

Summary: Antibiotic therapy for community-acquired pneumonia

1. Oral amoxicillin is recommended for children >1 month of age who do not require hospitalisation (evidence level Ia).
   - Treatment duration should be 5 days, with review after 3 days to evaluate response.
   - Switch to amoxicillin-clavulanate if there is clinical deterioration, and consider referral for further investigation.
2. Children <1 month of age should be hospitalised and treated with ampicillin and an aminoglycoside (evidence level Ib).
3. Amoxicillin-clavulanate (intravenously or orally) is recommended for treatment of hospitalised children >1 month of age with severe pneumonia (evidence level IVa).
   - Treatment duration should be 5 days.
   - If there is clinical deterioration, switch to ceftriaxone or cefotaxime for 5 days (evidence level IVa).
4. Treatment duration should be prolonged for severe or complicated disease, and depend on microbiology testing.
   - Bacteraemic *S. aureus* pneumonia may require 14 - 28 days of antibiotic therapy, depending on clinical response (evidence level IVa).
5. Macrolide antibiotics should be used if pertussis, mycoplasma or chlamydia is suspected (evidence level IVa).

Adjunctive therapies

Antiviral treatment

Oseltamivir is of limited benefit and is not recommended for routine use. Consider use during the influenza season in children at high risk for severe influenza, who present soon after symptom onset.[8,24-36]

Corticosteroid therapy

The role of corticosteroids remains unclear. They have a role in children with suspected or confirmed pneumocystis pneumonia (PCP) (see below: Special circumstances: HIV infection or exposure – Treatment), or in pulmonary tuberculosis with nodal airway compression and obstruction.[11,12]

Vitamin and micronutrient supplementation

Vitamin A. Vitamin A supplementation reduces severity of respiratory complications of measles,[13] but is not recommended for routine use.[14] Consider routine vitamin A supplementation for HIV-infected or malnourished children with CAP.[15]

Table 1. Empiric antibiotic therapy

Age	Outpatients	Inpatients
0 - 1 month	Children <1 month of age should be hospitalised	Ampicillin 50 mg/kg IV 6-hourly, or benzylpenicillin 50 000 U/kg IM/IV 6-hourly and gentamicin 7.5 mg/kg IM/IV daily If poor response Ceftriaxone 50 mg/kg IV 12-hourly × 5 d *or* Cefotaxime 50 mg/kg IV 8-hourly × 5 d If cultures are negative, switch to oral amoxicillin-clavulanate when clinically improving and taking well orally – complete a total antibiotic duration of 5 d If cultures are positive, use targeted therapy according to the organism's susceptibility pattern Step down to oral antibiotic therapy as soon as the patient is clinically stable Add Azithromycin 10 mg/kg daily orally × 5 d if *Chlamydia trachomatis* is suspected (alternative: clarithromycin 7.5 mg/kg/d orally 12-hourly × 5 d; erythromycin is contraindicated in this age group)
>1 month	Amoxicillin 45 mg/kg/dose 12-hourly orally × 5 d If poor response Amoxicillin-clavulanate 45 mg/kg/dose 12-hourly × 5 d Add Azithromycin 10 mg/kg orally daily × 5 d if *Mycoplasma pneumoniae, Chlamydia pneumoniae* or *C. trachomatis* suspected (alternatives: clarithromycin 7.5 mg/kg/d orally every 12 h for 10 d or erythromycin 50 mg/kg/d for 10 - 14 d)	Amoxicillin-clavulanate 30 mg/kg/dose (of amoxicillin component) 8-hourly IV × 5 d *or* Amoxicillin-clavulanate 45 mg/kg/dose orally 12-hourly × 5 d If cultures are positive, use targeted therapy according to the organism's susceptibility pattern Step down to oral antibiotic therapy as soon as the patient is clinically stable For susceptible *Staphylococcus aureus*, use flucloxacillin 50 mg/kg orally 6-hourly × 2 - 4 weeks If poor response Ceftriaxone 50 mg/kg IV 12-hourly × 5 d *or* Cefotaxime 50 mg/kg IV 8-hourly × 5 d Add Vancomycin 10 - 20 mg/kg/dose 6-hourly *or* Clindamycin for suspected CA-MRSA 1 month - 16 years: 20 - 40 mg/kg IV or IM/d, in 3 - 4 equally divided doses Use higher doses for treatment of more severe infections Add Azithromycin 10 mg/kg orally daily × 5 d if *M. pneumoniae*, *C. pneumoniae* or *C. trachomatis* suspected (alternative: clarithromycin or erythromycin)

IV = intravenous; IM = intramuscular; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*.

Vitamin D. Vitamin D supplementation does not appear to improve CAP outcomes and is not routinely recommended (evidence level Ia).[16-19]

Summary: Adjuvant therapies

1. Oseltamivir should be considered as early empiric therapy in children at risk of severe influenza-related pneumonia, who are hospitalised during the influenza season (evidence level II).
2. Routine use of corticosteroids for childhood CAP is discouraged (evidence level Ib).
3. Vitamin A is indicated for measles-associated pneumonia, or in those with vitamin A deficiency (evidence level Ib).
4. Do not routinely use vitamin D supplementation (evidence level Ia).

When can a hospitalised child be discharged?

Apyrexial children no longer requiring oxygen, with adequate oral intake and acceptable home circumstances, can generally be safely discharged (Table 2).[20]

General and supportive measures

Oxygen therapy

Assess oxygenation with regular pulse oximetry. If <92% at sea level (or <90% at altitude ≥1 800 m), administer oxygen via nasal cannula or face mask to maintain oxygen saturation 92 - 94% (evidence level II).[21] If pulse oximetry is unavailable, administer oxygen if there is central cyanosis, grunting, restlessness, inability to drink or feed, or if respiratory rate is ≥70/breaths per minute.[22]

Respiratory support

High-flow humidified nasal oxygen (HFHNO) or nasal continuous positive airway pressure (nCPAP) systems provide support to children with severe respiratory disease (see below: Care of the child

with pneumonia in the paediatric ICU or high care).[23,24] These can be safely provided in adequately staffed and equipped high-care areas and district hospitals.[24,25]

Blood transfusion

In general, children who are haemodynamically stable should not be transfused if the haemoglobin (Hb) level is ≥7 g/dL (evidence level Ib); if their Hb is <5 g/dL, then transfuse packed red cells to raise the Hb to above the transfusion threshold (i.e. not to 'normal ranges') (evidence level II). For children with Hb 5 - 7 g/dL, evaluate their overall clinical status when deciding whether to transfuse.

Fluids and electrolytes

Fluid overload is associated with worse outcomes in severe CAP, particularly in those undergoing mechanical ventilation.[26-28] Hyponatraemia is common secondary to high antidiuretic hormone secretion and is related to the severity of infection,[29-33] but is less likely with isotonic intravenous manintenance fluids.[34]

Generally, children should be fed enterally; if this is not possible, then intravenous isotonic fluids should be administered at <80% of maintenance, with monitoring of sodium levels.

Antipyretics and analgesia

Hospitalised children with pneumonia, who often have fever and may have chest pain, should receive treatment,[35,36] including:[37]

- paracetamol, orally (loading dose 20 mg/kg/dose, then 15 mg/kg/dose 4 - 6-hourly)
- ibuprofen, orally (10 mg/kg/dose 8-hourly) with meals
  - where an anti-inflammatory effect is required
  - can be used in combination with paracetamol or opioids
- tilidine (1 drop per 2.5 kg body weight, i.e. 1 mg/kg/dose)
  - intermediate-efficacy opioid.

Other measures

Over-the-counter cough medications are not effective in the management of CAP (evidence level Ia).[38]

Chest physiotherapy may be of benefit for children with lobar collapse,[39] or when used in conjunction with nebulisation;[40] however, routine chest physiotherapy is not recommended (evidence level Ia).[41,42]

Vaccination status should be reviewed and catch-up provided, including booster immunisation, as indicated.

Summary: Treatment of pneumonia – supportive measures

1. Children with room air oxygen saturations of <92% (at sea level) or <90% (at altitude ≥1 800 m) should be treated with oxygen (evidence level II).
2. Most children may receive oxygen via nasal cannula, but the route of oxygen administration should be individualised (evidence level IVa).
3. Children who are haemodynamically stable should not be transfused if their Hb is ≥7 g/dL (evidence level II).
4. Children should be fed enterally; if this is not possible, administer intravenous isotonic fluids at <80% of maintenance with monitoring of sodium levels (evidence level Ib/II).
5. Children with fever or chest pain should be treated with appropriate antipyretics or analgesics (evidence level IVa).
6. Over-the-counter cough medications are not recommended (evidence level Ia).
7. Chest physiotherapy may benefit children with lobar collapse (evidence level Ia).
8. Vaccination status should be reviewed and catch-up provided, including booster immunisation, as indicated (evidence level IVb).

Care of the child with pneumonia in the paediatric intensive care or high-care unit

Introduction

A proportion of hospitalised children with CAP require admission to high care or the paediatric ICU (PICU); many of them have comorbid disease or other underlying susceptibilities.

Admission criteria

Specific criteria for PICU admission depend on available resources and vary between institutions (Table 3).

Investigations

Microbiology

See 'Epidemiology and aetiology of community-acquired pneumonia in children: South African Thoracic Society guidelines (part 1)'[46] and 'Diagnosis of community-acquired pneumonia in children: South African Thoracic Society guidelines (part 2)'.[47]

Radiological investigations

Radiological investigations should be individualised to evaluate for complications (e.g. pleural effusion, pneumothorax or segmental/lobar collapse), and associated cardiac disease. CXR or point-of-care chest ultrasound, where available, is recommended on admission to the PICU to define central line positioning, following endotracheal intubation, or with any significant deterioration.[48]

Oxygen therapy and monitoring

Clinical signs are inadequate for detecting hypoxia;[49] therefore, continuous pulse oximetry monitoring is required.

Respiratory support

High-flow oxygen

See above: General and supportive measues: Respiratory support.

Table 2. Criteria for discharge from hospital*

- Clinical improvement, indicated by improved activity, appetite, and resolution of fever for at least 12 hours. Do not discharge if increased work of breathing or tachycardia
- Pulse oximetry measurements consistently ≥90% at altitude (≥1 800 m) or ≥92% at sea level in room air for at least 12 hours
- Stable and/or return to baseline mental status
- If a chest tube was placed, no intrathoracic air leak for at least 12 - 24 hours after removal of the tube
- Ability to administer antibiotics at home, and child able to tolerate oral feeding and antibiotics
- Acceptable home circumstances and ability to return to hospital if clinical deterioration

*Adapted from the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America guidelines.[20]

Table 3. Indications for paediatric intensive care unit admission

- Rapidly deteriorating clinical condition despite appropriate management
- Need for respiratory support as evidenced by
  - apnoea (particularly in small infants)
  - increasing oxygen requirements, i.e. any child requiring FiO_2 >60% to maintain arterial saturations >88%[43-45]
  - increasing effort of breathing (as assessed by respiratory rate, chest-wall retractions, noisy breathing), with imminent respiratory collapse
  - hypercarbia resulting in respiratory acidosis
- Deterioration in level of consciousness or seizures, particularly if any concern about maintaining airway patency and avoiding aspiration
- Cardiovascular instability as reflected by severe tachycardia/hypotension/inotrope requirement

Nasal continuous positive airway pressure systems

nCPAP use for children with severe pneumonia (including bronchiolitis) is increasing as evidence emerges that supports its safety and efficacy.[50-54]

Invasive ventilation

Invasive ventilation is best provided in units experienced in such care, but often needs to be initiated prior to referral. High-frequency oscillatory ventilation may be considered for children requiring high mean airway pressure (MAP) using conventional ventilation.[55]

Children with significant airflow obstruction or hypercapnia require special consideration. Higher positive end-expiratory pressure (PEEP) and MAP may be required for children with refractory hypoxia (evidence level II).[56]

Nutrition

Critically ill children should be provided with enteral nutrition as soon as possible (evidence level Ib).[57,58]

Many ventilated children receive inadequate dietary intake, and provision of a higher proportion of prescribed dietary goals is associated with improved outcomes.[59] Parenteral nutrition administration is associated with higher mortality and increased complications (evidence level Ib).[59-61]

Children on HFHNO or non-invasive positive-pressure ventilation may receive enteral feeding without risk of aspiration.[62,63]

Antibiotic therapy

While PICU-specific issues should be considered, the principles of antibiotic therapy are similar as for other children with CAP. Consider broader antimicrobial therapy for children whose clinical status worsens despite initial empiric therapy. Therapy should be de-escalated based on microbiology investigations. Extrapolating from adult ICU evidence, procalcitonin levels may guide discontinuation of antibiotics,[64] although there are limited paediatric data.[65]

Corticosteroids, fluid and blood transfusion

These should be administered as per children with CAP managed outside of the ICU (see above: Adjunctive therapies: Corticosteroid therapy).

Physiotherapy

Current evidence is insufficient to provide strong recommendations for chest physiotherapy in the PICU.[66,67]

Summary: High care and intensive care of children with pneumonia

1. Where possible, blood cultures should be obtained from children requiring PICU admission, but should not delay initiation of antibiotic therapy (evidence level III).
2. CXR or chest ultrasound should be done to identify complications at PICU admission and after interventions, such as endotracheal intubation, chest drain or central line placement (evidence level III), and after clinical deterioration (evidence level III).
3. Oxygen saturation levels should be monitored continuously (evidence level IVa). Where possible, FiO_2 should be adjusted to achieve saturations of 92 - 96% (evidence level III).
4. nCPAP improves outcomes compared with nasal cannula oxygen (evidence level Ib), while nCPAP and HFHNO have similar efficacy in patients with severe bronchiolitis (evidence level Ib).
5. Antibiotic therapy should be de-escalated and discontinued as soon as possible (evidence level II).
6. Routine chest physiotherapy should not be provided for children (evidence level III), although some patients may benefit. Ongoing chest physiotherapy should be based on clinical improvement and lack of clinical deterioration (evidence level III).

Special circumstances: HIV infection or exposure

Treatment

Empiric CAP treatment of HIV-exposed uninfected (HEU) infants and HIV-infected children is the same as for HIV-unexposed children. There are currently no studies comparing regimens for and outcomes of HIV-infected and HEU infants.[68] HIV infection should be considered in all children with CAP, and appropriate testing must be provided (evidence level IVa).

Pneumocystis pneumonia

Few children currently acquire vertically transmitted HIV infection – most of these are diagnosed through early infant testing and receive antiretroviral therapy (ART) and co-trimoxazole prophylaxis.[69] Women who tested HIV-negative during pregnancy may acquire HIV infection late in gestation or while breastfeeding – their infants are at risk of PCP (evidence level Ib).[70-73] Some children with primary immunodeficiencies or severe malnutrition are also at risk of PCP (evidence level IIb).[74] Empiric therapy for PCP should not be withheld pending results of confirmatory laboratory testing.

Co-trimoxazole administered intravenously or orally, 5 mg trimethoprim/25 mg sulfamethoxazole/kg/dose, 6-hourly for 21 days, reduces mortality from PCP in infants.[75] Following treatment, daily co-trimoxazole prophylaxis needs to be continued until CD4+ counts recover as per South African (SA) ART guidelines.[76] There is conflicting evidence regarding the effect of adjunctive corticosteroids.[77] However, we recommend a short course of corticosteroids for children with PCP, initiated within 72 hours of diagnosis (prednisone 1 - 2 mg/kg orally daily for 7 days, tapered over the next 7 days) (evidence level IVa).[78]

Cytomegalovirus

Cytomegalovirus (CMV) pneumonia should be considered in HIV-infected or HEU infants <6 months of age with severe hypoxaemia or requiring mechanical ventilation.[79,80] The optimal treatment remains unclear. Some clinicians initiate treatment if the whole-blood CMV

viral load is >4.1 $\log_{10}$ copies/mL,[81] but this may delay therapy. Alternatively, initiate empiric ganciclovir and discontinue if CMV viral load results indicate low-level or absent viraemia (evidence level IVa).

In children with high-level CMV DNAemia, clinical improvement and/or a decline in viral load should prompt switching from intravenous ganciclovir to oral valganciclovir (evidence level IVa). Ganciclovir should be given at 5 mg/kg intravenously 12-hourly until oral therapy is tolerated, then switch to valganciclovir 16 mg/kg orally 12-hourly until completion of 21 days of treatment. Thereafter, administer valganciclovir 16 mg/kg orally daily to complete a total of 42 days of therapy.[10]

Atypical organisms

If 'atypical' organisms are considered in the differential diagnosis, a macrolide should be added (see above: Treatment of childhood pneumonia: Which empiric antibiotic?) (evidence level IVa).

Summary: HIV infection or exposure

Empiric antibiotic treatment is the same in HIV-infected, HEU and HIV-unexposed children, although treatment for PCP (evidence level Ib) and/or CMV pneumonia (evidence level IVa) should be considered in HIV-infected infants with severe hypoxaemia.

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