What is the most appropriate empirical therapy for very severe pneumonia in children older than 2 months?

Primary Reviewer: **John Gavranich**[1] Secondary Reviewer: **Shamim Ahmad Qazi**[2]

First published online: 31st March 2006

1 Ipswich, Queensland, Australia
2 Medical Officer, Newborn and Child Health and Development, WHO/HQ Geneva, Switzerland

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the most appropriate empirical therapy for very severe pneumonia in children older than 2 months?*

The WHO Pocketbook of Hospital Care for Children recommends to give ampicillin and gentamicin for 5 days then complete at home or in hospital with oral amoxicillin t.d.s plus gentamicin daily IM for a further 5 days.

OR

Alternatively on admission give chloramphenicol 8 hourly IM or IV until the child has improved, then orally 4 times a day for total course of days.

OR

Use Ceftriaxone once daily

If in the event of non-improvement within 48 hours then switching to Cloxacillin 6 hourly plus gentamicin, followed by oral cloxacillin when the child improves for a total of 3 weeks treatment.

(Pocketbook chapter 4.2.1, page 55).

INTRODUCTION

Pneumonia is an important cause of morbidity and mortality in young children in developing countries, with an estimated 1.9 million deaths occurring in children under 5 years .[1] Compared to pneumonia in children in developed countries, in developing countries bacterial pathogens are more common, with Streptococcus pneumoniae (S.pneumoniae) and Haemophilus influenzae (H.infleunzae) being the main bacteria identified [2]. Initial antibiotic therapy is chosen empirically to treat the common bacterial organisms and choice of antibiotic will depend upon availability and cost. Failure to respond to initial treatment is an indication to change to second line therapy, and the antibiotic chosen should have antimicrobial activity against Staphlococcus aureus (S. aureus) and enteric Gram negative bacilli.

The current WHO definition of very severe pneumonia is a clinical diagnosis based on the presence of cough or difficulty breathing plus at least one of the following: central cyanosis; inability to breast feed or drink, or vomiting everything; convulsions, lethargy or unconsciousness; or severe respiratory distress. Severe respiratory distress is defined as the presence of head nodding in addition to other signs of respiratory distress such as chest indrawing and tachypnoea. This review intends to look at the evidence for the most appropriate empiric therapy for very severe pneumonia in children older than 2 months.

METHODOLOGY

The Cochrane Library 2005 (Issue 3) was initially searched using the terms “very severe pneumonia” AND “child”. There was only one randomized controlled trial (RCT) identified as potentially useful [3]. The search terms were broadened to “pneumonia” AND “child” and an additional eight RCTs [4-11] were identified as potentially useful. There were no systematic reviews identified.

PubMed (Clinical Queries) was searched using similar terms and only one additional RCT (Klein 1995) was identified. Abstracts or full text were obtained on the ten RCTs indentified as potentially useful. 4 articles met inclusion criteria of the current WHO definition of ‘very severe pneumonia’ and were relevant to developing countries [3,7,8,10]. 2 trials did not define severity of pneumonia but excluded children whose condition was severe enough to warrant parenteral antibiotics [9,12]. 3 trials excluded children with very severe pneumonia [5, 6, 11], and one trial excluded children with cyanosis [4]>.

RESULTS

Cetinkaya 2004 was a double-blind randomised trial of 97 infants (2-24 months) admitted to Sisli Etfal Education & Research Hospital, Istanbul, Turkey with severe pneumonia treated with either benzyl penicillin and chloramphenicol or ceftriaxone intravenously for 10 days. The patients were accepted as cured when all symptoms and signs had completely disappeared. Cure by 10 days was 84.7% versus 80.4% ($p>0.05$). All patients were clinically well after further oral

antibiotics for one week. The study had clear inclusion criteria , was double-blinded and there was good follow-up. However, randomization not described, allocation concealment was unclear, power analysis was not performed and there was no mention of intention-to-treat. [7]

Deivanayagam 1996 ran a randomised controlled trial of 115 children (5 months- 4yrs) admitted to Institute of Child health and Hospital for Children, Madras, India, with pneumonia treated with either ampicillin or benzyl penicillin and chloramphenicol intravenously for at least 48 hours. Total duration of antibiotic therapy not stated. The primary outcome was cure rate (resolution of lung signs). Treatment failure was considered if there was no clinical improvement with regard to fever, tachypnoea & chest findings by 72 hours. The cure rate was 81% versus 90% (p>0.05). The duration of fever was in days was 4.48 versus 4.71, and time to cure in days was 5.64 versus 5.78. The study had clear inclusion criteria, adequate randomization, and good follow-up. Power analysis was performed; however allocation concealment was unclear and there was no mention of blinding or intention-to-treat. In addition, baseline characteristics differed with significantly more children in the ampicillin group having cyanosis (94% vs 82%, p=0.04) and nasal flare (96% vs 84%, p=0.03). [8]

Duke 2002 ranan open randomised trial of 1116 children (1 mo – 5 yrs) admitted to Goroka & Kundiawa Hospitals, PNG, with severe pneumonia treated with either chloramphenicol or benzylpenicillin and gentamicin intramuscularly for 5 days, followed by oral antibiotics to complete 14 days total. Primary outcome measure was either a good or adverse outcome. Adverse outcomes were death, treatment failure, readmission or absconding from hospital. Secondary outcomes included the time to resolution of hypoxaemia. The total primary adverse outcome was 26.3% versus 22.1% (p=0.11). The death rate was 6% versus 5% (p=0.35) and readmission rate was 9% versus 6% (p=0.03). The number of days oxygen saturation remained below 90% was 6.7 versus 8.0 (p=0.07). The study had clear inclusion criteria, adequate randomisation and allocation concealment, and follow-up was good. A power analysis was performed and primary analysis was by intention to treat. [3]

Shann 1985 was a single-blinded randomised trial of 748 children (age range not mentioned) admitted to Goroka, Kundiawa & Lae Hospitals, PNG, with severe pneumonia treated with either chloramphenicol or chloramphenicol and benzyl penicillin intramuscularly (total duration not mentioned). Treatment was defined as a failure if the child died or antibiotics were changed. Mortality was 13% versus 17 % (not significant; p value not given). The study had clear inclusion criteria, adequate randomization and allocation concealment; however 27% of children absconded and were lost to follow up (majority were improving). Power analysis was not performed and there was no mention of intention to treat. [10]

DISCUSSION

The studies eligible for inclusion in this review enrolled children who would fulfill the current WHO definition of very severe pneumonia. The clinical setting varied between studies and this may explain the difference in outcomes, especially mortality. 2 trials [7, 8] were conducted in major tertiary centres, whereas another 2 [3, 10] were conducted in regional and remote centres of PNG. The lower mortality in Duke's trial could reflect improved nutrition and general supportive care, particularly oxygen availability, during the intervening 17 years. [3]

Initial empiric therapy chosen for children with very severe pneumonia varied between studies with the exception of chloramphenicol, which was used alone or in combination with benzyl penicillin. There was no significant difference in outcomes for either combination in individual studies, apart from the slightly increased risk of readmission for the chloramphenicol group in one trial [3].

The use of second line antibiotics for very severe pneumonia has not been evaluated in a published controlled trial.

SUMMARY

The evidence supports the use of either chloramphenicol alone, or a combination of benzylpenicillin (or ampicillin) and gentamicin for the initial empiric therapy for very severe pneumonia in young children in developing countries. The final choice of antibiotic will depend upon availability and cost.

There is no evidence in the literature to assist with the choice of second line antibiotics and the decision should be made empirically and include drugs effective against S. aureus.

REFERENCES

1. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2002;2(1):25-32.
2. WHO. Technical basis for the WHO recommendations on the management of pneumonia in children at the first level health facility. World Health Organisation. 1991.
3. Duke T, Poka H, Dale F, Michael A, Mgone J, Wal T. Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. Lancet 2002;359(9305):474-80.
4. Camargos PA, Guimaraes MD, Ferreira CS. Benzathine penicillin for unilateral lobar or segmental infiltrates presumptively caused by Streptococcus pneumoniae in children 2-12 years old. J Trop Pediatr 1997;43(6):353-60.
5. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet 2004;364(9440):1141-8.
6. Aurangzeb B, Hameed A. Comparative efficacy of amoxicillin, cefuroxime and clarithromycin in the treatment of community - acquired pneumonia in children. J Coll Physicians Surg Pak 2003;13(12):704-7.
7. Cetinkaya F, Gogremis A, Kutluk G. Comparison of two antibiotic regimens in the empirical treatment of severe childhood pneumonia. Indian J Pediatr 2004;71(11):969-72.
8. Deivanayagam N, Nedunchelian K, Ashok TP, Mala N, Sheela D, Rathnam SR. Effectiveness of ampicillin and combination of penicillin and chloramphenicol in the treatment of pneumonias: randomized controlled trial. Indian Pediatr 1996;33(10):813-6.
9. Mulholland EK, Falade AG, Corrah PT, Omosigho C, N'Jai P, Giadom B, et al. A randomized trial of chloramphenicol vs. trimethoprim-sulfamethoxazole for the treatment of malnourished children with community-acquired pneumonia. Pediatr Infect Dis J 1995;14(11):959-65.
10. Shann F, Barker J, Poore P. Chloramphenicol alone versus chloramphenicol plus penicillin for severe pneumonia in children. Lancet 1985;2(8457):684-6.
11. Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B. Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxycillin for pneumonia among children in Pakistan: randomised controlled trial. Pakistan Co-trimoxazole Study Group. Lancet 1998;352(9124):270-4.
12. Klein M. Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group. Pediatr Infect Dis J 1995;14(4 Suppl):S19-22

Table 1: Description of Included studies

Citation	Study group	Outcome	Key Results	Study Quality
Cetinkaya 2004	Double-blind randomised trial of 97 infants (2-24 months) admitted to Sisli Etfal Education & Research Hospital, Istanbul, Turkey with severe pneumonia treated with either benzyl penicillin & **chloramphenicol** or **ceftriaxone** intravenously for 10 days.	The patients were accepted as 'cured' when all symptoms and signs had completely disappeared.	**Cure by 10 days in 84.7% of pen+chloro vs 80.4% of ceftriaxone group (p>0.05).** **All patients clinically well after further oral antibiotics for 1 week.**	Clear inclusion criteria , study double-blind & good follow-up; however randomization not described, allocation concealment unclear, power analysis not performed & no mention of intention-to-treat.
Deivanayagam 1996	Randomised controlled trial of 115 children (5 months- 4yrs) admitted to Institute of Child health and Hospital for Children, Madras, India, with pneumonia treated with either **ampicillin** or benzyl penicillin and **chloramphenicol** intravenously for at least 48 hours. Total duration of antibiotic therapy not stated.	The primary outcome was cure rate (resolution of lung signs). Treatment failure was considered if there was no clinical improvement with regard to fever, tachypnoea & chest findings by 72 hours. Adverse reactions were monitored.	**Cure rate 81% vs 90% (p>0.05).** **Duration of fever (days) 4.48 vs 4.71.** **Days to cure 5.64 vs 5.78.**	Clear inclusion criteria, adequate randomization, and follow-up. Power analysis performed; however allocation concealment unclear, no mention of blinding or intention-to-treat. Baseline characteristics differed with more children having cyanosis (94% vs 82%) & nasal flare (96% vs 84%) in ampicillin group.
Duke 2002	Open randomised trial of 1116 children (1 mo – 5 yrs) admitted to Goroka & Kundiawa Hospitals, PNG, with severe pneumonia treated with either **chloramphenicol or benzylpenicillin** & **gentamicin** intramuscularly for 5 days, followed by oral antibiotics to complete 14 days total.	Primary outcome measure was a good or adverse outcome. Adverse outcomes were death, treatment failure, readmission or absconding from hospital. Secondary outcomes included time to resolution of hypoxaemia.	**Total primary adverse outcome 26.3% vs 22.1% (p=0.11)** **Death 6% vs 5% (p=0.35)** **Readmission 9% vs 6% (p=0.03)** **Days oxygen sat <90% 6.7 vs 8.0 (p=0.07)**	Clear inclusion criteria, adequate randomisation & concealment, good follow-up, power analysis performed & primary analysis by intention to treat.
Shann 1985	Single-blinded randomised trial of 748 children (age range not mentioned) admitted to Goroka, Kundiawa & Lae Hospitals, PNG, with severe pneumonia treated with either **chloramphenicol** or **chloramphenicol** & **benzyl penicillin** intramuscularly (total duration not mentioned).	Treatment defined as failure if child died or antibiotics changed	**Mortality 13% vs 17 % (not significant; p value not given)**	Clear inclusion criteria, adequate randomization & concealment; however 27% of children absconded & were lost to follow up (majority were improving), power analysis was not performed & no mention of intention to treat