

What are appropriate empiric antibiotics for empyema?

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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 are appropriate empiric antibiotics for empyema?*

The **WHO Pocketbook of Hospital Care for Children** recommends for antibiotic therapy in empyema; chloramphenicol every 6-8 hours until the child has improved then orally 4 times a day for a total of 4 weeks. If infection with staphylococcus is identified, then cloxacillin and gentamicin is recommended followed by cloxacillin orally at home for 3 weeks. Pleural effusions and empyema should be drained unless they are very small (Pocketbook chapter 4.2.4, page 81).

Introduction:

Thoracic empyema still contributes significantly to paediatric morbidity and mortality in the developing world, as well as the consumption of scarce hospital resources¹. Conservative treatment consists of drainage of pus and aggressive antibiotic treatment, though more invasive surgical procedures can be used^{2,3}. In the selection of empiric antibiotic regimen, it is imperative to consider the causative pathogens and their sensitivity pattern, pharmacokinetic properties, ease of availability and cost of drugs; however there is an absence of good evidence to inform the best regimen. Consequently current management of empyema is often based on institutional traditions, personal experience, availability of trained personnel and equipment and limited case reviews^{3,4,5,6}. Accordingly, the current review attempts to answer the question, "What are the appropriate antibiotics for

empyema in children?". However, to answer this, we need to attempt answer for; "What is the microbiology of empyema in developing countries?" and "How effective are antibiotics in the empyema fluid?"

Methodology

Articles were identified through PubMed by use of the 'Clinical Queries' framework. The search strategy employed was as follows: (empyema OR pleural empyema OR pleural effusion OR empyema thoracis OR complicated parapneumonic effusion OR pleural infection OR pyothorax) AND (exp Anti-bacterial agents OR antibiotic*). Clinical filters for both 'therapy' and 'narrow, specific' were used and only 2 randomised controlled trials (RCT) were identified. A similar strategy was adopted to search the Global Health (1973 to October 2005) and EMBASE (1980 to 2005 Week 44) databases, and the Cochrane Library (Issue 4, 2005) was also searched. Reference lists were handsearched, abstracts retrieved and read and articles checked for citations using the Cited Reference Tool on Web of Science. Where relevance was in doubt, the complete article was sourced. Articles were restricted to the English language. Trials on non-antibiotic treatment of empyema were excluded, as were subdural, tuberculous, malignant and gall bladder empyemas.

Methodological quality of selected articles was assessed using the Oxford CEBM LOE. Only 2 RCTs and 3 retrospective cohort studies were found. Four retrospective case series were also relevant.

In answering the ancillary question "What is the microbiology of empyema in developing countries?" recent studies (over past 25 years) were favoured to reflect the evolving microbiology of empyema; 8 retrospective audits were found. Articles were also searched for the

question “How effective are antibiotics in the empyema fluid?”

Results

Microbiology of Empyema in Developing Countries:

Studies giving microbiological details of childhood empyema in developing countries over the last 25 years are summarised in Table 1. *S. aureus* was grown in about three-quarters of culture-positive patients and are mostly methicillin-sensitive³. Pneumococci were seen in <10% of culture-positives and are increasingly being reported to be penicillin-resistant even in developing countries^{7,8}, however they are sensitive to chloramphenicol⁸. Gram-negative rods are also responsible in a significant number of cases. Of note, prior antibiotic use renders many cultures sterile where such facilities exist.

Antibiotic Penetration into Pleural Fluid:

Most antibiotics show good pleural fluid penetration with the antibiotic exceeding the MIC for the bacteria for which it would be normally used⁹, however gentamicin is a notable exception^{9,10,11}.

Antibiotic Therapy for Empyema:

In view of widespread use of semi-synthetic anti-staphylococcal penicillins for a long time – with perceived success – there is a paucity of quality evidence-based literature on antibiotic therapy in childhood empyema. Case series / retrospective audits have poor evidence and are methodologically unsound or suboptimal. Only 2 RCTs are available.

Ghosh *et al* suggest cloxacillin plus gentamicin¹², whilst Baranwal *et al* suggest cloxacillin plus gentamicin plus crystalline penicillin based on clinical recovery³. Similarly, Anyanwu *et al* found that flucloxacillin plus amoxicillin meant there was no requirement to resort to thoracotomy¹³. However, none offer any comparison.

Among retrospective comparative studies, Joshi *et al* found cloxacillin plus gentamicin to be more efficacious than penicillin plus chloramphenicol in terms of patients discharged within 3 weeks (80% vs. 60%), duration of tube drainage for > 7 days (20% vs. 50%) and mortality (0% vs.

33.3%)¹⁴. However sample sizes were small and no statistical analysis was performed. Fontanet found that 3 (11%) of the patients not treated with cloxacillin required thoracotomy compared to 1 (1%) treated with cloxacillin¹⁵. Almost all of their patients had received chloramphenicol. Though these studies support cloxacillin as an effective empiric therapy, they fail to show statistical significance. Only one, Padmini *et al*, found a significant difference in outcome of patients treated with cloxacillin plus gentamicin (n=31) versus those treated with crystalline penicillin plus gentamicin (n=15); 72.1% of the former regime could be discharged by 3-4 weeks as compared to 34.1% of the latter one (p<0.05)¹⁶.

Among RCTs, Palacios *et al* (n=40) compared dicloxacillin plus chloramphenicol and cefuroxime for treatment of parapneumonic effusion or empyema in children¹⁷. There was no difference in terms of duration of tube drainage, antibiotic treatment, hospital stay, or whether the illness followed a complicated / uncomplicated course. They suggested that cefuroxime might be a simpler alternative to the standard regimen of dicloxacillin plus chloramphenicol. However, the latter is economical and easily available in a developing country scenario. In the only other available RCT (n=56) with *S. aureus* (73%) and *Streptococcus* (27%) being the predominant causative organisms, a regimen of ampicillin plus sulbactam was shown to significantly reduce duration of antibiotic therapy (16±0.5 vs. 20.6±0.6 days), tube drainage (7.8±0.5 vs. 9±0.4 days), hospital stay (16.4±1.2 vs. 21.8±1.5 days) and the numbers requiring pleural decortication (10 vs. 19) compared to the group treated with cephalothin plus netilmicin (P<0.05)⁵. In both, method of randomisation was not stated, nor whether there was adequate blinding.

Duration of Antibiotics

Information on optimal duration of parenteral antibiotic therapy is lacking. Initial parenteral therapy is generally accepted^{3,4,15,18}, however the need for current practice of ≥3-4 weeks of parenteral therapy is poorly documented¹⁵. In a retrospective comparative audit, a shift to oral therapy once patients become afebrile, respiratory distress subsided, and significant loculations were ruled out - usually after 7-14 days - has reduced the hospital stay compared to prolonged parenteral therapy (17.2±7.2 vs. 23.2±7.4 days, p<0.01) without compromising final clinical

outcome³. Oral antibiotics were continued to complete a therapy of 4-6 weeks. Fontanet *et al* had also used short course parenteral antibiotics followed by oral therapy for 3 weeks successfully¹⁵.

Discussion

This review highlights a lack of good quality evidence for appropriate empiric antibiotic therapy. However, despite wide variations in the selection of drugs, their combinations, doses, durations and various limitations, the following inferences can be drawn:

1. *S. aureus* is the commonest causative organism for childhood empyema in developing countries, and currently most of these community-acquired strains are methicillin-sensitive.
2. Semi-synthetic anti-staphylococcal penicillins (e.g. cloxacillin, flucloxacillin, dicloxacillin) are the standard therapy with demonstrable success, at an acceptable cost.
3. Available evidence is against the use of gentamicin in pleural empyema due to its low penetrability.
4. Other empyema-causing organisms are mostly sensitive to chloramphenicol, a broad-spectrum, affordable and easily available antibiotic.

Empiric antibiotic treatment needs to be effective against the common causative pathogens, especially *S. aureus*. The WHO recommendation for first line therapy is chloramphenicol alone, a broad-spectrum cheaply available antibiotic to which most *S. aureus*, pneumococcus and Haemophilus are still susceptible. However, evidence is not sufficient to use chloramphenicol monotherapy in childhood empyema.

Cloxacillin is an appropriate anti-staphylococcal antibiotic displaying good activity against *S. aureus* in most of the studies identified at an acceptable cost. The addition of gentamicin as an anti-staphylococcal drug is recommended by the WHO and is used in many studies^{3,12,14,16} for possible synergism^{3,14}, though quality evidence supporting this is lacking and needs further investigation. Chloramphenicol may provide an effective alternative for gentamicin, and indeed, one RCT found dicloxacillin plus chloramphenicol to be similar to cefuroxime¹⁷. Cloxacillin plus chloramphenicol may be more

acceptable and applicable in developing countries due to its lower cost and easy availability.

Duration of any antibiotic therapy also remains to be clearly established. At present, initial parenteral therapy until signs of active infection have subsided – usually over 7-14 days – followed by switching over to oral antibiotics is satisfactory and cost-effective.

Summary

This review has identified a lack of research into the best antibiotic therapy for empyema, and highlights a new research priority for the WHO. Evidence is lacking for chloramphenicol monotherapy, as is evidence for addition to gentamicin to cloxacillin. With available evidence, a cost-effective combination of cloxacillin and chloramphenicol is suggested as first line therapy. Various combinations of easily available and orally effective antibiotics *viz.* fluoroquinolones, rifampicin, co-trimoxazole and chloramphenicol may be suggested for further research.

ABBREVIATIONS

CEBM LOE	Centre for Evidence-Based Medicine Levels of Evidence
MIC	Minimum Inhibitory Concentration
RCT	Randomised Controlled Trial
SR	Systematic Review
WHO	World Health Organisation

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Table 1: Organisms causing childhood empyema in developing countries									
Authors	Baranwal <i>et al</i> ³	Belet <i>et al</i> ⁵	Mishra <i>et al</i> ²⁰	Mangete <i>et al</i> ¹	Maziah <i>et al</i> ²¹	Asindi <i>et al</i> ¹⁹	Ghosh <i>et al</i> ¹²	Padmini <i>et al</i> ¹⁶	Total
Country	India	Turkey	India	Nigeria	Malaysia	Nigeria	India	India	
Study period	1989-98	1992-97	1993	1989-91	1985-89	1982-89	1985-87	1985-86	
Culture-positive cases	121	33	40	46	18	27	30	38	353
<i>S. aureus</i>	90	24	19	36	15	15	28	19	246 (70%)
<i>Pneumococcus</i>	10	4	-	-	2	?	-	4	20 (6%)
<i>H. influenzae</i>	2	-	-	-	-	?	-	2	4 (1%)
<i>S. pyogenes</i>	1	-	-	-	1	?	-	3	5 (1.5%)
<i>S. viridans</i>	-	5	-	-	-	?	-	-	5 (1.5%)
Gram -ve rods	14	-	21	10	-	?	2	9	56 (16%)
Others	4	-	-	-	-	?	-	-	4 (1%)