

## Rational Use of Antibiotics for Pneumonia

INDIA CLINICAL EPIDEMIOLOGY NETWORK (INDIA CLEN) TASK FORCE ON PNEUMONIA

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**P**neumonia affects 156 million children under the age of five years every year across the globe, and is the leading cause of mortality in this age group(1). More than two million annual deaths are estimated to occur because of pneumonia in under-five children, and almost all of these occur in the developing world(2). Pneumonia kills more children in this age group than AIDS, malaria and measles combined. India carries the largest burden of disease and deaths because of pneumonia, accounting for 43 million cases and 0.4 million deaths(2). The median incidence of pneumonia in India is estimated to be 0.37 episodes per child per year(2). Fortunately, most of the deaths attributable to pneumonia can be prevented by relatively inexpensive and feasible strategies. An increasing focus on the scaling up of interventions for appropriate management of childhood pneumonia is crucial to achieve the Millennium Development Goal (MDG) 4 of “reducing by two-thirds, between 1990 and 2015, the under-five mortality rate.”

### ROLE OF ANTIBIOTICS AND CURRENT PRACTICES

Early diagnosis and appropriate case management by rational use of antibiotics remains one of the most effective intervention to reduce pneumonia-related mortality. As per the UNICEF/WHO report on pneumonia “estimates suggest that if antibiotic treatment were universally delivered to children with pneumonia, around 600,000 lives could be saved each year”(3). Management issues for pneumonia also include early diagnosis, availability of appropriate antibiotics, timely and appropriate referral, monitoring and follow-up. These components are addressed in the IMNCI/F- IMNCI/

ARI control programs as are being implemented in India. Access to universal availability of health services is also dealt within the broad framework of the National Rural Health Mission (NRHM). What requires strengthening is the rationalization of the use of antibiotics for the treatment of pneumonia, and ensuring that it is made synchronous with the actual field medical practices; so that the health care providers, in the public as well as the private sector, implement the same protocols.

### *Under-utilization and Misuse of Antibiotics*

There are critical inequities in the access to antibiotics and health services in most developing nations. There is a clear dichotomy between the need and use of antibiotics; a large proportion of children who need antibiotics for treatment of acute respiratory infection (ARI) never reach any health facility and among those who seek health care, irrational use of antibiotics is common. Almost two-thirds of children who die at home are never taken to any health facility before dying, and home treatments are given to majority of them. Cumulative data from 27 countries suggested that only 19 per cent of children with pneumonia received an antibiotic in the early 1990s(3). More recent (2005-2006) National Family Health Survey-3 (NFHS-3) data from India indicated that almost one-third (31%) of the children do not receive any advice or treatment from a health facility or health provider for their complaints of cough accompanied by short, rapid breathing that could be suggestive of pneumonia(4). Further, only 12.5% children received antibiotics for these complaints. The health seeking practices were poorer in socioeconomically disadvantaged population, rural areas, and

uneducated mothers. The situation is similar in Bangladesh and Nepal, where less than 25% of under-five children with suspected pneumonia receive antibiotics(5). The lack of any significant progress over the past 10 years across the developing world underscores the urgent need to act now to ensure that children with pneumonia receive appropriate medical care.

The reasons for the under-utilization of antibiotics are diverse. Caregivers often fail to recognize the importance of seeking care in presence of difficult breathing or chest indrawing. Inadequate resources, lack of political commitment, lack of coordination between various health and government agencies, and fragmented implementation are the other reasons for inadequate use of antibiotics in pneumonia. There is an urgent need to increase the utilization of facilities by spreading awareness about the importance of seeking care by children suffering from symptoms and signs of possible pneumonia. Education programs also need to emphasize that caregivers broadly understand the importance of the disease and its treatment regimen, and are convinced of treatment efficacy.

On the other hand, inappropriate antibiotic use, including prescribing antibiotics to children with simple colds or coughs, is extremely common amongst those who seek health care. Antibiotics are commonly prescribed for upper respiratory tract infections where they are not required. New and expensive antibiotics are preferred, even in rural areas, without knowledge about their safety and efficacy(6). The duration of the use of antibiotics is often not regulated and the caregivers frequently do not continue the drug for the prescribed period. These practices lead to the emergence of drug resistant strains not only of the causative bacteria but also for other bacteria present in the environment. Antibiotic resistance amongst the common pneumonia causing bacteria (*Streptococcus pneumoniae* and *Haemophilus influenzae b*) is being reported with increasing frequency worldwide, including India(7,8). Unnecessary antibiotic use also leads to wastage of healthcare resources, and unnecessarily exposes patients to risk of adverse effects.

Under-utilization and misuse of antibiotics are thus the two key features of the current scenario which need to be addressed.

### ANTIBIOTICS – WHEN, WHICH AND HOW?

One needs to address the following 3 questions to rationalize the use of antibiotics in pneumonia:

1. *Decision on antibiotic:* Whether antibiotic is needed at all in a particular child with acute respiratory infection (ARI)?
2. *Choice of antibiotic:* Which antibiotic to use in which situation?
3. *Appropriate regimen:* How to prescribe i.e. dose, frequency, route and duration of the antibiotic?

#### *Assessing the Severity of Pneumonia*

Children presenting with cough or difficult breathing are diagnosed as *pneumonia* if they exhibit ‘fast breathing’. The WHO algorithm for children presenting with cough or difficult breathing proposes that ‘fast breathing’ is the most sensitive sign to identify pneumonia in the community. The age related cut-offs of the respiratory rate to define ‘fast breathing’ are:  $\geq 60$ /min for age below two months;  $\geq 50$ /min for age two months up to one year; and  $\geq 40$ /min for children aged between one and five years. The respiratory rate should be counted with a seconds’ watch for one complete minute.

*Severe pneumonia* is diagnosed if there is presence of lower chest indrawing (definite inward motion of the lower chest wall during quiet breathing). Children having danger signs such as inability to feed, lethargy, central cyanosis, severe respiratory distress (head nodding) or grunt are classified to be having *very severe pneumonia*.

It is mandatory that the health care providers are trained in the recognition of fast breathing, lower chest indrawing, and danger signs. The skills to identify signs, especially lower chest indrawing, are awfully lacking in most health care providers who are not properly trained. Community health workers have shown to be capable of acquiring the skills needed to effectively manage ARI cases if training emphasizes how to count the respiratory rate of

children with tachypnea and how to identify chest indrawing(9). In hospital or clinic settings, additional clinical skills and investigations (wherever indicated), should be used to diagnose the exact cause of respiratory distress (e.g. pneumonia, bronchiolitis, asthma, croup, and non-respiratory causes); this should dictate the further need for appropriate antibiotics.

#### *Assessing the Need of Antibiotic*

Most children reporting with cough, fever, and running nose without presence of 'fast breathing' do not need antibiotics. Most cases of bronchiolitis, asthma and croup do not require antibiotic treatment.

A significant proportion of cases of pneumonia in under-five children are likely to be of viral origin where antibiotics will not be of any use. Studies from developing countries have documented Respiratory Syncytial Virus (RSV) to be responsible for 15-40% of cases of pneumonia in children admitted to hospital(2). Identifying cases who are likely to have a viral rather than bacterial cause of pneumonia may lead to decrease in antibiotic prescription. However, clinical differentiation of viral and bacterial pneumonias is difficult, and occasionally they may co-exist. Therefore, as of now, antibiotics need to be prescribed to all children from the developing countries *in the community setting* who are identified to be having pneumonia based on the clinical signs described above.

Wheezing is a very common sign present in cases of non severe and severe pneumonia in children. In most of the studies on pneumonia and severe pneumonia, wheezing is associated in a large proportion of children having lower chest indrawing or fast breathing. In a recent trial evaluating the efficacy of oral drugs in treatment of severe pneumonia, wheezing on auscultation was present in 62-82% of children with lower chest indrawing despite excluding known asthmatics from the study(10). Further, the signs of pneumonia and severe pneumonia disappear after an initial trial (2-3 times) of inhaled bronchodilator medications in almost half of these cases(11). History of two or more previous episodes of respiratory distress also serves as a reliable tool for diagnosing cases with

wheezing(12). Therefore, it is logical to give a trial of 2-3 doses of inhaled bronchodilators in children who have had two or more previous episodes of respiratory distress, or those who are identified to have wheezing in addition to 'fast breathing' or/and 'lower chest indrawing.' Antibiotics may be withheld from cases where wheezing is present, and signs of pneumonia or severe pneumonia disappear after an initial course of inhaled bronchodilator drugs. However, only about one-third of cases having wheezing and chest indrawing are known to have an audible wheeze(12). The feasibility of training health care providers in community to recognize and manage wheezing should be evaluated. At first referral units, the skills and equipments for recognizing and managing wheeze must be present.

#### **SELECTION OF APPROPRIATE ANTIBIOTIC**

The two most common bacterial pathogens causing pneumonia in under-five children are: *Streptococcus pneumoniae* and *Haemophilus influenzae*(2). A recent study suggests that *Staphylococcus* is also an important cause contributing to 42% of bacterial causes of very severe pneumonia in children(13). It is imperative that antibiotic used for empirical treatment of pneumonia should cover these organisms adequately.

#### *Antibiotic of Choice for Pneumonia*

Co-trimoxazole and amoxicillin are the two most commonly recommended antibiotics for domiciliary treatment of pneumonia. In a large hospital-based multicentric study of pneumococcal diseases in children from India, co-trimoxazole resistance was found in 56% of the isolates(7). The resistance to penicillin was rare (1.3%), and none of the isolates was resistant to injectable third generation cephalosporins. Amongst *H. influenzae* isolated from these centers, resistance was common both to co-trimoxazole (45%) and ampicillin (38%)(8). Similarly, data from other centers in India show increasing resistance in *S. pneumoniae* isolates, with co-trimoxazole, the first choice of drug for pneumonia till recently(14,15). Amoxicillin is another suitable alternative which can be used in clinic setting as a first line drug for non-severe

pneumonia. Clear evidence regarding the superior efficacy of amoxicillin over co-trimoxazole in field settings (using the WHO definition of pneumonia) is lacking. A systematic review on the efficacy of various antibiotics for pneumonia has documented a superior efficacy of amoxicillin over co-trimoxazole(16). Co-trimoxazole was inferior in efficacy to both amoxicillin (failure rates odds ratio (OR) 1.33; 95% CI 1.05 to 1.67) and procaine penicillin (cure rates OR 2.64; 95% CI 1.57 to 4.45). However, a recent multicentric trial from India reported that there was no difference in effectiveness of oral co-trimoxazole or amoxicillin in treating non-severe pneumonia in a field setting(17). Also, none of the trials have documented any difference in mortality by using amoxicillin or cotrimoxazole.

Thus, at the community level in India, there is no compelling evidence to switch over from the current policy of using cotrimoxazole (dose 5-7 mg/kg of trimethoprim+25-35mg/kg/day of sulphamethoxazole for a duration of 5 days) as the first line antibiotic. However, amoxicillin (dose 30-40 mg/kg/day for 3-5 days) is a suitable alternative drug that can be used by the practicing physician in outpatient setting. Amoxicillin also has the advantage of shortening the duration of therapy to 3 days. A meta-analysis of three randomized controlled trials from developing countries, including India, has

demonstrated the equivalent efficacy of a shorter course of amoxicillin in comparison to the standard five-day regimen(18). The domiciliary management of pneumonia is outlined in **BOX**.

Oral cephalosporins (eg. cefixime) and quinolones should not be used for treatment of childhood pneumonia. The mother should be advised to return immediately if the child develops chest indrawing, is unable to feed or looks sick. Additionally, all children started on first line antibiotics need to be monitored for response (breathing slower, less fever, eating better) after 48 hours. If there is no improvement or chest indrawing or a general danger sign appears, the child should be referred for assessment and second line antibiotics.

#### *Antibiotics for Severe and Very Severe Pneumonia*

The issues in the treatment of severe pneumonia are:

1. Whether these children require hospitalization?
2. What should be the first line antibiotic for in-patient treatment?

There is a general consensus that all children aged less than 2 months of age presenting with cough and fast breathing should be diagnosed as having severe pneumonia and hospitalized in view of the high mortality, treatment failure rates, and

#### **BOX** DOMICILIARY TREATMENT OF PNEUMONIA

- Give Cotrimoxazole (trimethoprim[T] + Sulfamethoxazole[S]) (5-7 mg/kg/day of T + 25-35 mg/kg/day of S) in two divided doses for 5 days
- OR
- Amoxicillin (30-40 mg/Kg/day) in 2-3 divided doses for 3-5 days
- Advise mother to return immediately if the child develops chest indrawing, is unable to feed or looks sick
  - Follow-up after 2 days
    - \* Check the child for general danger signs
    - \* Assess the child for cough or difficult breathing
    - \* Ask: Is the child breathing slower? Is there less fever? Is the child eating better?
  - Treatment
    - \* If the answer to above questions is Yes, complete 5 days of cotrimoxazole or 3-5 days of amoxicillin
    - \* If condition is same, refer for second line antibiotic to FRU
    - \* If chest indrawing or a general danger sign, refer urgently for treatment of severe / very severe pneumonia

co-existence of other serious morbidities such as sepsis and meningitis in this age group.

According to current guidelines, all children diagnosed as severe pneumonia need to be hospitalized for detailed assessment, injectable antibiotics, other supportive therapy and monitoring. Regarding choice of injectable antibiotics for inpatient treatment of severe community-acquired pneumonia; there is evidence that penicillins are superior to chloramphenicol. In the systematic review evaluating all antibiotics in pneumonia, penicillin in conjunction with gentamicin was found to be better than chloramphenicol alone (re-hospitalization rates OR 1.61; 95% CI 1.02 to 2.55)(16). A recent multicentric trial (published after the last significant update of the systematic review) also concluded that injectable ampicillin plus gentamicin was superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings(13). As chloramphenicol is currently the recommended first choice drug for inpatient treatment of very severe pneumonia, there is a need to update the current WHO guidelines for management of ARI. All children with severe pneumonia should be initially treated with ampicillin (50 mg/kg IM/IV every 6 hours). Gentamicin (7.5 mg/kg IM/IV once a day) should be added for children aged less than two months, children having very severe disease at the outset, or those who fail to respond at 48 hours. The antibiotic should be changed to parenteral third generation cephalosporins such as cefotaxime and ceftriaxone, if still there is no improvement after another 48 hours. Those with associated septicemia and meningitis should receive intravenous cefotaxime or ceftriaxone as first line drugs. Staphylococcal infection needs to be recognized based on clinical and radiological features (skin boils, abscesses, rapid progression/deterioration, pneumatoceles, empyema) and cloxacillin (50mg/kg/dose, every 6 hourly) should be added. Antibiotics should be continued for 5-7 days for severe pneumonia and 7-10 days for very severe disease (*Fig. 1* and *Fig. 2*). The temptation of using new and fancy antibiotics promoted and pushed by pharmaceutical companies should be resisted. In addition, all children hospitalized with severe or very

severe pneumonia should be monitored to detect any complications or deterioration. If possible, a chest X-ray should be obtained. The health provider should consider transferring the patient to a higher facility in case of poor response or deterioration despite second line therapy.

Regarding the use of oral amoxicillin for severe pneumonia, a couple of studies have demonstrated that injectable penicillin and oral amoxicillin are equivalent for severe pneumonia in controlled settings(10,19). However, these results are not applicable to all settings, especially where the risk of mortality is high such as those with very severe disease (cyanosis, lethargy, recurrent vomiting, unable to feed) or child having severe malnutrition. These subjects and those who received prior antibiotic therapy, were invariably excluded by these studies. Unless the evidence is more compelling, and is replicated to all settings, it is not justified to change the current practice of hospitalizing all children with severe pneumonia for detailed assessment, injectable antibiotics, oxygen and other supportive therapy and monitoring. Oral treatment with amoxicillin can be given to selected patients (who are aged more than three months old, look stable otherwise, are not severely malnourished) where hospitalization is not possible despite adequate counseling.

#### EPILOGUE

Pneumonia is a significant public health problem with India carrying the largest burden of morbidity and mortality attributable to pneumonia. A large proportion of these deaths can be prevented by following the rational guidelines for management of acute respiratory infections. Selection of the appropriate antibiotic in adequate dose and correct duration is the need of the hour. There is a clear need of strengthening health care practices related to pneumonia, including care seeking and referral systems. Health care providers need to be trained in recognizing the important signs that guide antibiotic therapy or referral. Doctors working in all capacities need to be made aware of the standard treatment protocols for pneumonia. Unnecessary and inappropriate use of antibiotics should be restricted to prevent antibiotic resistance. Capacity building

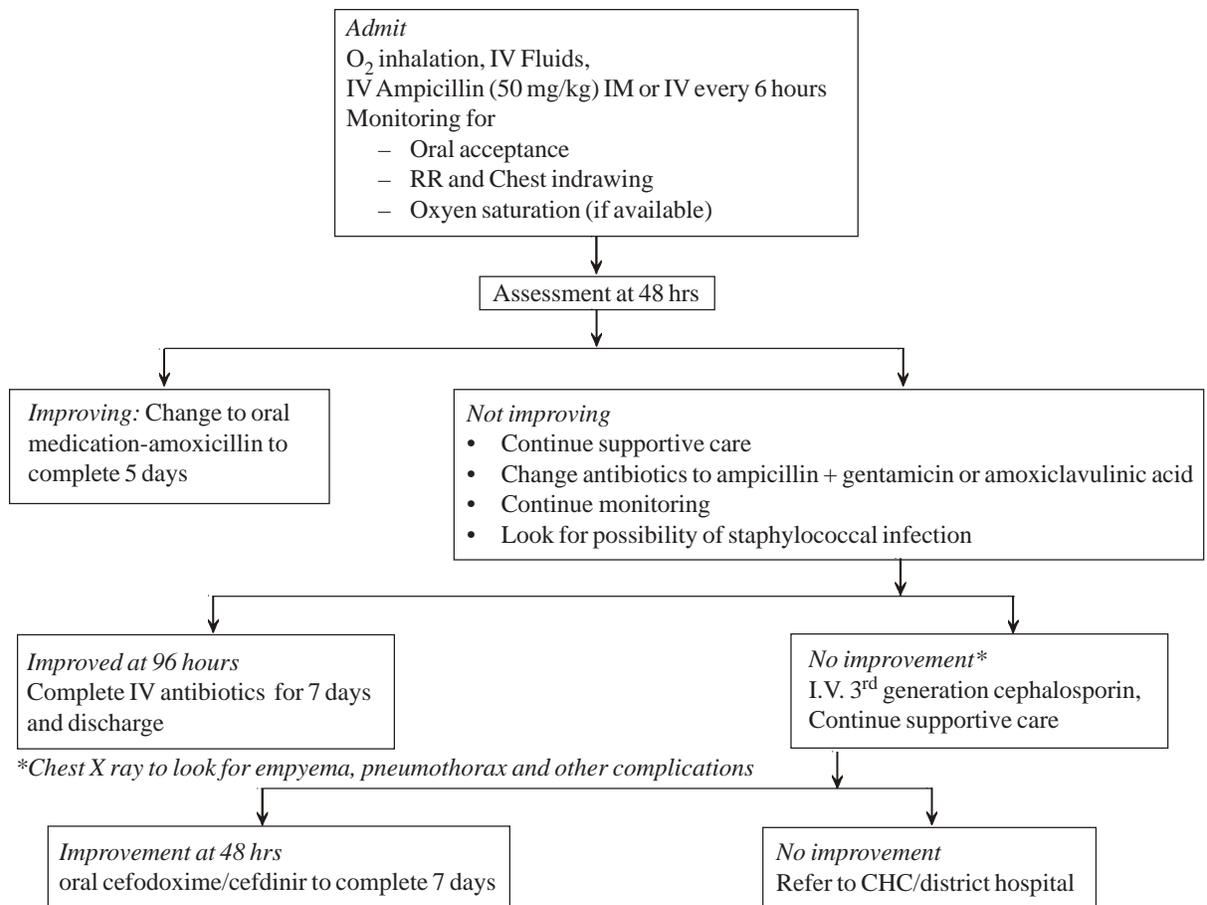


FIG. 1a Management of severe pneumonia in children aged > 2 months

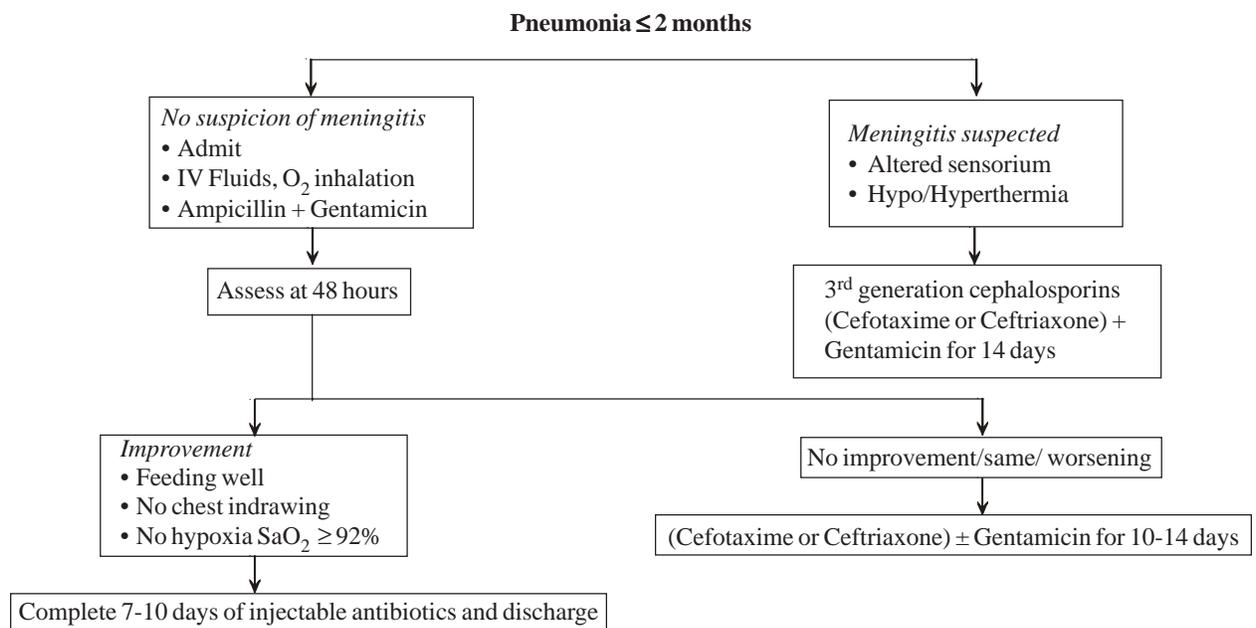
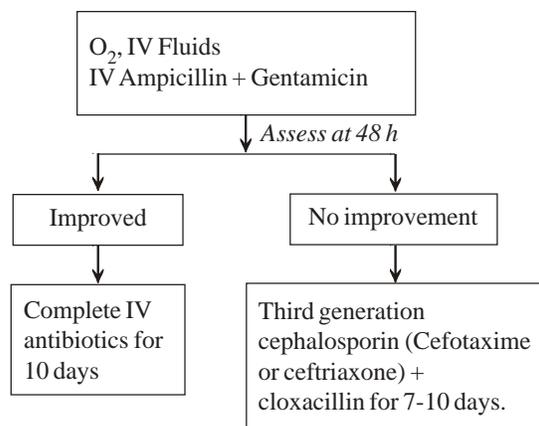


FIG. 1b Management of Severe Pneumonia in children aged ≤ 2 months



\*Chest X-ray is to be done for all cases of very severe pneumonia to look for empyema, pneumothorax and other complications.

**Suspecting Staphylococcus:** Add cloxacillin to the regimen.

**FIG. 2** Management of Very-severe Pneumonia.

should also be done at referral units for other supportive treatments such as bronchodilator and oxygen therapy.

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**KEY MESSAGES**

- Fast breathing and lower chest indrawing are sensitive signs to diagnose pneumonia and severe pneumonia, respectively in the community.
- Most children with cough, runny nose and fever without the presence of 'fast breathing' do not need antibiotics.
- Many children with lower chest indrawing caused by bronchiolitis, asthma and croup also do not need antibiotics.
- Oral co-trimoxazole (5 days) or amoxicillin (3-5 days) should be used for domiciliary treatment of non-severe pneumonia.
- All children with severe or very severe pneumonia need hospitalization for injectable antibiotics, and supportive therapy that may include oxygenation, intravenous fluids, and monitoring.

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