

Multicenter Observational Study to Assess the Safety of Outpatient Treatment of Severe Pneumonia with Oral Amoxicillin in Children aged 3 – 59 months: A Pilot Safety Study

Acute respiratory illnesses (ARI) is the leading cause of childhood mortality in developing countries. In order to reduce ARI related mortality WHO developed standardized case management guidelines which were adopted by Ministry of Health Pakistan in 1989. A recent review published in the Lancet has shown that there has been a reduction of up to 36% in ARI related mortality in communities where these standardized case management guidelines have been implemented.

Despite the reduction in ARI related mortality, there is a continuous ongoing effort to further improve these case management guidelines. A trial carried out in 1991-92 showed that children with severe pneumonia responded better to oral amoxicillin as compared to oral cotrimoxazole. On the basis of this finding a large multi-country multicentre trial was conducted in which children with severe pneumonia were randomized to receive either oral amoxicillin or injectable penicillin.

The results of this trial (APPIS) have been published in Lancet recently (vol 364, 1141-1148). The results of this very impressive large multi country and multicentre trial show that oral amoxicillin is as good as injectable penicillin for the children who have lower chest indrawing and are being classified as severe pneumonia according to the current ARI case management guidelines. This is a major breakthrough finding which will have huge policy implications all over the world. Before this finding is translated to guidelines most experts in the field of ARI feel that this trial must be replicated in the community setting before changes in the Integrated Management of Childhood Illnesses (IMCI) guidelines are proposed.

The research protocol was developed to address this question by assessing the safety and efficacy of outpatient treatment of severe pneumonia with oral amoxicillin in children aged 3 to 59 months. This is a pilot study safety study where approximately 200 children diagnosed with severe pneumonia and eligible for outpatient management will be treated with oral amoxicillin for 5 days administered at home.

This multicenter study will be carried out in five centers. They include Bolivia and Ghana, amongst others. Each site is expected to enroll approximately 40-50 patients with WHO-defined severe pneumonia (cough with lower chest indrawing) and enrollment is expected to be completed within one ARI season. All children will be monitored very closely at home on a daily basis by trained health care workers. Daily monitoring will include a complete physical assessment and in the case of deterioration appropriate changes in the treatment regimen, including referral to the hospital will be made. Treatment will only be changed if any pre-defined signs of deterioration are present at the time of follow-up. The objectives are to assess the treatment failure rate at day 6 and day 14 and compare it to the treatment failure rates obtained in the APPIS trial. All children will be assessed 14 days after enrollment.

Background:

There are inherent disadvantages associated with hospitalization and injectable therapy. First, the routine use of injectable antibiotics, either intravenously or intramuscularly substantially increases the cost of health care. Second, it can increase the risk of transmission of HIV, hepatitis and other viral diseases transmitted through the use of contaminated needles. Third, a number of children who are referred may not be able to get to the hospital and do not receive treatment, placing them at risk of mortality. Fourth, hospitalization increases the risk of exposure to nosocomial pathogens that are increasingly difficult to treat due to antimicrobial resistance. Furthermore, the rationale for a parenteral antibiotic is not fully established. Injectable therapy is chosen because of the perception that it is more efficacious in the treatment of severe pneumonia rather than because of the children's inability to tolerate oral medication.

Frequency of amoxicillin administration

Traditionally amoxicillin has been used three times a day. The more frequent dosing may lead to non-adherence. A study that compared the pharmacokinetics and levels of oral amoxicillin 15 mg/kg/dose three times daily with the 25-mg/kg dose twice daily regimen in children ages 3 – 59 months with pneumonia reported that the serum levels with twice daily amoxicillin were higher than three times daily regimen. They however did recommend that a higher twice daily dose would be better for treatment. Other studies have also reported twice daily amoxicillin to be a feasible alternative for three-daily dosing. Thus for this study we will use antibiotic therapy for 5 days. Oral amoxicillin will be used in 80-90 mg/kg/ per day divided into two doses.

Duration of therapy

Clinically shorter course of 4-day antibiotic therapy has been shown to be equally effective versus 7-day antibiotic therapy in children aged 3 months to 15 years with pneumonia, sepsis-like infections, or other common acute infections warranting hospitalization and parenteral antimicrobials,. The clinical outcomes were similar between the two groups.

Rationale for treating severe pneumonia at home with oral amoxicillin

Community health workers can be trained to assess sick children for signs of pneumonia; select appropriate treatments; administer the proper dosages of antibiotics; counsel parents on how to follow the recommended treatment regimen and provide supportive home care; and follow up sick children. It is recognized that community acquired non-severe pneumonia is rarely associated with mortality if managed promptly with appropriate treatment. Deaths occur when the pneumonia progresses to severe or very severe categories. It is envisaged that providing training and support to community health workers in pneumonia case management will prevent deaths through early recognition and management of pneumonia, because some cases will progress to severe pneumonia and will die if not referred in time or where referral is not possible.

In summary, the potential benefits of oral therapy for severe pneumonia include 1) reduce mortality by reducing the progression to very severe pneumonia/disease, 2) reduce the risk of needle-associated complications such as needle-borne infections, 3) minimize the need for referral or hospitalization, 4) reduce the pressures on inpatient services, 5) decrease cost of delivering treatment, and 6) reduce transport, food and lost income costs for the family.

Objectives: the overall goal is to evaluate whether it is safe to treat children aged 3 to 59 months with pneumonia and lower chest indrawing with oral amoxicillin

Primary Objective: To determine in children with pneumonia and lower chest indrawing

The proportion of children 3-59 months old eligible for home therapy who fail treatment with oral amoxicillin by day 6 (In previous study comparing oral vs. injectable antibiotic, treatment failure was 19% in each group after 48 hours or therapy).

Hypothesis: The proportion who fail treatment will be 14% on day 6.

Study Design: This is a multicenter one arm intervention study which will take place in 5 different countries to assess the safety of treating severe pneumonia with oral amoxicillin for five days at home in children 3 – 59 months.

Selection criteria:

Inclusion Criteria:

1. Children aged 3 – 59 months with severe pneumonia
2. Severe pneumonia is defined by the following
 - a. Chest indrawing
 - b. fever
 - c. difficulty breathing
 - d. cough
2. Informed consent by a legal guardian

Exclusion Criteria:

1. Very severe pneumonia
2. Known prior episodes of asthma
3. Severe malnutrition
4. Hospitalization in the last two weeks

Source of Subjects:

Children who present to the outpatient department of a participating center with history of cough or difficult breathing and are found to have lower chest indrawing will be referred to a member of the investigation team.

Procedures for obtaining informed consent

Informed consent will be obtained from the parents or legal guardians of the children. If the parent or guardian is not literate, a thumbprint may be substituted for signature, duly witnessed by somebody in addition to the person requesting consent. A verbal witnessed informed consent may be obtained in settings where parents are willing to take part in the study, are illiterate, and unwilling to provide thumb prints due to socio-cultural reasons.

Procedures of the Study:

Baseline Assessment

- History of present illness
- Physical examination
- Blood sample for storage for future studies

High Dose Amoxicillin Administration: A total of 80-90 mg/kg per day for 5 days will be given to the children.

Follow-up

1. The mother/caregiver will be counseled to continue with the oral treatment prescribed for a period of 5 days. They will be advised to return to the healthcare facility at any time during the study period if the child develops danger signs. These symptoms will be clearly discussed with the mother. The child will be assessed at the health facility on day 14.

The caregiver will be reimbursed for transportation costs to the health facility.

Community health extenders (i.e. nurses and other non-doctor health care workers) will be clinically evaluating children at home on days 1,3, and 6 of the study. In any child in whom there is concern for treatment failure, extenders will be instructed to refer the child to the health facility for evaluation by the study physician.

Statistical Considerations

Criteria used to estimate sample size – 14% or fewer of children treated with oral amoxicillin at home will fail treatment as define previously. The proportion of treatment failures is estimated at 14% based on the results of APPIS I. Although APPIS I reported a 19% treatment failure with oral amoxicillin at 48 hours, the failure rate in this study is anticipated to be lower as 8% of children who had lower chest wall in-drawing alone on study day were declared treatment failure in APPIS I, but will not be declared treatment failure at this time point in the study.

Confidentiality

Data will remain confidential and accessible only to the senior project staff.