



PROGRAMME FOR THE CONTROL OF ACUTE RESPIRATORY INFECTIONS

CLINICAL SIGNS AND ETIOLOGICAL
 AGENTS OF PNEUMONIA, SEPSIS, AND MENINGITIS IN YOUNG INFANTS

Report of a meeting

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1. INTRODUCTION

Among children in developing countries, pneumonia occurs with greatest frequency, severity, and fatality in young infants. Of the deaths attributed to acute respiratory infections (ARI) in children under 5 years of age, 20 to 30% occur in the first 2 months of life in most developing countries. Despite this fact, little is known about the etiology of pneumonia, meningitis, or sepsis¹ in this age group, the performance of clinical signs and symptoms in their diagnosis, and the clinical outcome of these infections. There is a need for carefully performed studies of acutely ill young infants in several developing countries, using standardized clinical and laboratory evaluations (chest X-rays, pulse oximetry, blood cultures, lumbar punctures, and other diagnostic evaluations), to further improve the current recommendations for case management and prevention. A meeting was therefore convened by the Programme for the Control of Acute Respiratory Infections (ARI) to prepare a protocol for a multicentre study of the clinical signs and etiological agents of pneumonia, sepsis, and meningitis in young infants. The meeting was attended by advisers and investigators from five study sites that are considered to have the interest and potential to carry out a technically demanding study in infants under 3 months of age.

Case management is the central strategy to reduce mortality from ARI. The WHO/ARI case management protocol for young (infants under 2 months of age) differs from that used for older children, for several reasons. The main one is that pneumonia can present with only non-specific clinical signs which overlap with those of meningitis and sepsis; thus case detection and rapid antibiotic treatment must be directed at this broader category of serious bacterial infections. Also, the efficacy of home antibiotic treatment has not been established for young infants with pneumonia or other serious bacterial infections; therefore, WHO recommends hospital referral of these cases and parenteral treatment with benzylpenicillin and gentamicin. The ARI Programme has relied on expert opinion and data from a small number of clinical studies to draw up a list of clinical signs and symptoms for the detection of cases of pneumonia, sepsis, or meningitis in young infants².

The study planned at this meeting will determine whether the current WHO protocol is sufficiently sensitive and specific for detecting cases of serious bacterial infection in young infants on first presentation at a health facility: the results may suggest that the list of danger signs can be shortened or that eliminating one sign (for example, "stopped feeding well") will lower the specificity of the protocol as a whole. The study will help to assess the ability of the clinical examination to distinguish pneumonia from sepsis, meningitis, and other respiratory illnesses and determine whether it is appropriate to use a cut-off at 2 months of age for the change in the diagnostic criteria and treatment recommendations. It is therefore necessary to include 2-month-old infants in the study³.

¹ Sepsis is defined here as a condition resulting from an invasion of the bloodstream by bacteria or their toxins. It includes septicaemia, septic shock, and bacteraemia with signs of illness but not necessarily with cardiovascular or pulmonary effects consistent with septic shock. It does not include pneumonia, cellulitis, or omphalitis without bacteraemia or systemic signs suggesting septic shock.

² ARI Case Management Chart: Management of the Child with Cough or Difficult Breathing.

³ Thus the study will recruit infants under 3 months of age, whereas the WHO/ARI case management strategy currently distinguishes the management of young infants under 2 months from that of children 2 months up to 5 years of age.

The etiological results obtained should help to determine whether it is appropriate to refer all neonates and 1-month-old infants for hospitalization and whether parenteral benzylpenicillin and gentamicin are the most appropriate antibiotics for treatment. This information will also be helpful for estimating the benefit that can be expected from maternal immunization against the pneumococcus or Haemophilus influenzae type b.

2. BACKGROUND INFORMATION

The meeting reviewed the results of 18 etiological studies of neonatal sepsis. These studies suggest that there may be important differences in the etiological spectrum of serious bacterial infection between developing and developed countries. For example, group B streptococcus was isolated in only a few developing countries, which is in striking contrast to the results from developed countries.

However, major methodological difficulties were found. In many studies, there was little differentiation between nosocomially-acquired and community-acquired infection; and there was inadequate information on whether patients had or had not been recently treated with antibiotics. Many of the culture techniques may have been inappropriate or inadequate for some of the more fastidious organisms. An absence of H. influenzae isolates, even in older children, was noted; this may be because human blood was sometimes used in the preparation of the culture media. There was no discrimination of staphylococcal species (Staphylococcus aureus and Staphylococcus epidermidis being reported together); and no attempt was made to determine whether positive cultures were colonizers or contaminants, or represented true infection.

Thus, despite the large number of studies, the general conclusion of the meeting was that the etiology of community-acquired pneumonia, sepsis, and meningitis in young infants in developing countries remains essentially unknown. There is a suspicion that H. influenzae and Streptococcus pneumoniae may play an important role, in contrast to the situation in developed countries. These two organisms are relatively difficult to isolate and require proper laboratory methodology to reduce the chances of their being missed. This emphasizes the need in a multicentre study to assure adequate, standardized bacteriology and stringent quality control measures.

3. METHODOLOGICAL CONSIDERATIONS IN DEVELOPING PREDICTION RULES

In many health facilities in developing countries clinical signs alone must be used to detect cases of pneumonia and other serious bacterial infections. Studies to determine which clinical signs best predict a particular disease present many methodological problems and potential biases which must be overcome to obtain valid results.

Approaches that could be used to ensure the validity of studies of diagnostic tests (including clinical signs predicting illness) were reviewed. These include a clear definition of the "gold standard" for diagnosis; a clear definition of predictive findings; a description of the clinical setting, prevalence of illness, and patient characteristics at the study site; application of the "gold standard" equally to patients who "test" positive and negative; and an evaluation of the role of chance.

No single, true, "gold standard" exists for pneumonia in young infants, since lung biopsy or bronchoscopy cannot usually be justified and radiological infiltrates are not always due to pneumonia. The diagnosis of sepsis is also difficult (especially in neonates), because relatively few will have proven bacterial disease and a large number of infants may clinically appear "septic" without there being any radiographic or laboratory evidence to establish the diagnosis. In the multicentre study, it will be necessary to consider several outcome measures: definite serious bacterial infection (positive cerebrospinal fluid or blood culture, or radiographic pneumonia with a positive blood culture or pleural fluid), probably serious bacterial infection, radiographic pneumonia, clinical pneumonia, and hypoxaemia⁴.

⁴ Detailed definitions of these outcomes are provided in the study protocol.

Clear definitions of the clinical signs and measurement of the inter- and intra-observer reliability in observing them should make it possible to assess their predictive value and later train health workers to use them in case detection. Standard definitions of clinical signs and symptoms were adopted by the meeting.

The sensitivity and specificity of a test in any population depends on the peculiarities of the patients under study. Although the sensitivity and specificity are often said to be independent of the prevalence of disease, patient characteristics such as stage and severity of the disease are associated both with sensitivity and specificity and with prevalence, because different kinds of patients are found in settings of high and low disease prevalence. In the proposed study, young infants brought for illness to a health facility will have a higher prevalence of disease than young infants visited at home in the community. Their disease may also be at a later and more severe stage. Thus caution must be exercised in extrapolating findings from this study to the community.

A potential for error lies in not applying the "gold standard" equally in patients with and without a positive test, in this case the presence of a clinical sign suggesting a serious bacterial infection. If patients who are test-negative are not examined for the presence of the "gold standard", the sensitivity will be falsely elevated but the specificity will be falsely reduced. The failure to verify the disease status of all patients also occurs when studies compare an equal number of "cases" (patients who test positive) and "controls" (patients who test negative). This verification bias has been present in most studies conducted to date of clinical signs predicting pneumonia. To avoid this bias, young infants who meet the study "entry" criteria both with and without positive clinical signs suggesting a serious bacterial infection will have a laboratory examination. To reduce the number of laboratory examinations among patients with no clinical signs of infection, a sample of these patients will be randomly selected for such evaluation.

4. OBJECTIVES OF THE STUDY

The meeting agreed to form an international study group to develop and implement a multicentre study to answer the Programme's priority research questions (see section 1). The following objectives were adopted:

In young infants (under 3 months of age) brought for illness to a health facility, the study will:

Primary objectives:

- (a) Assess the sensitivity and specificity of initial signs, symptoms, and historical factors (alone and in combination) in the diagnosis of serious bacterial infection (pneumonia, sepsis, and meningitis), in an attempt to define specific clinical features (or combinations of features) that would facilitate early recognition of these infections by health workers;
- (b) determine the relative prevalence of pneumonia, sepsis, and meningitis cases among sick infants in this age group;
- (c) assess the prevalence of positive bacterial cultures H. influenzae, S. pneumoniae, gram negative organisms, group B streptococcus, and S. aureus using standard blood and cerebrospinal fluid culture techniques; characterize the isolated bacteria, including their antimicrobial sensitivity; and
- (d) assess the prevalence of significant hypoxaemia.

Secondary objectives:

- (e) identify the etiology and characterize the clinical features of other potentially important causes of pneumonia in young infants (such as respiratory viruses, Chlamydia trachomatis, Pneumocystis carinii, and Bordetella pertussis);
- (f) determine the relationship between selected risk factors (which can be ascertained during the clinic visit) and outcome in infants with pneumonia, other respiratory diseases, sepsis, and meningitis;
- (g) evaluate antigen detection and other laboratory methods for identifying bacterial infections; and
- (h) compare antibiotic treatment regimens for pneumonia, sepsis, and meningitis.

5. PROPOSED STUDY DESIGN

5.1 Study population

Each study site will serve a population with a high neonatal mortality rate (>40 deaths/1000 live births) in which ill neonates present to a clinic where they can be thoroughly evaluated (i.e., a hospital or a well equipped and staffed clinic). The study will be performed over a long enough period (at least one year) to minimize the effect of any seasonal variation in etiological agents. Because the etiological agents may affect the sensitivity and specificity of the clinical signs for radiographic pneumonia, information on epidemic disease such as outbreaks of measles, pertussis, or bronchiolitis will be recorded. If many deaths in young infants occur at home, consideration will be given to training traditional birth attendants and other appropriate community-based practitioners and educating families to promote the referral of sick young infants to hospital.

5.2 Subject selection and sample size

Infants will be considered for the study if they are less than 3 months old and have been brought to the hospital or clinic for illness. Amongst these young infants, those meeting certain "entry" criteria will be enrolled (cough; difficult, fast, or noisy breathing; fever or hypothermia; poor feeding; abnormally sleepy or difficult to wake; convulsions; very sick, including infants who cannot be consoled or are very irritable; apnoeic episodes; and obvious bone or joint infection).

Infants will be excluded if: the illness began in hospital (unless the infant was born in hospital); they are attending the clinic for trauma, a burn, or routine care such as immunization; their weight was less than 1500 grams during the first 48 hours of life; they have had a documented episode of pneumonia within the last three weeks; or they have a known major congenital malformation.

Sampling will be stratified by age to ensure that there is an adequate number of infants in the 0-6 days, 7-30 days, and 1-month and 2-month age groups. For final sample size estimates it will be necessary to obtain further information on the current yield of bacterial pathogens from blood and CSF cultures and the prevalence of radiographic pneumonia among young infants presenting to the study site's clinical facility. Initial estimates, based on preliminary data from the potential sites and a desired sensitivity of 80% (with a 95% confidence interval of $\pm 10\%$) for a set of clinical signs for the detection of serious bacterial infection, indicate that within each age group approximately 640 infants would need to be enrolled to identify 60 subjects with evidence of bacterial infection. This large sample size requires several study sites if results are to be obtained within one to two years; hence the need for a multicentre study.

5.3 Clinical signs, symptoms, and historical factors

A detailed questionnaire was developed. The history will include questions on prior treatment for the presenting illness, the mother's perceptions of the signs and symptoms and her assessment of the severity of the infant's illness, and limited information on labour and delivery. If the infant was born in hospital, more detailed information on labour, delivery, and birth weight will be obtained.

The physical examination will include an assessment of chest indrawing, nasal flaring, grunting, stridor, auscultatory findings (crepitations and wheeze), and central cyanosis; and observation of the infant's function and interaction with his caretaker (state of alertness, ease of arousal, quality of cry, consolability, attentiveness, level of activity, ability to feed). Careful, repeated measurements of the respiratory rate will be performed.

5.4 Laboratory evaluation

All infants enrolled in the study will be examined for historical and physical factors by the study physician and will have their oxygen saturation measured by pulse oximetry. If a positive clinical sign suggesting pneumonia, sepsis, or meningitis is found, the infant will be hospitalized (if possible) and undergo a laboratory evaluation consisting of a chest X-ray, blood culture, culture of nasopharyngeal aspirate, white blood cell count with differential (for calculation of the immature to total polymorphonuclear cell ratio), and quantitative assay for C-reactive protein. A sample of infants without a positive clinical sign will also undergo the laboratory evaluation. A lumbar puncture will be performed if the infant is febrile or has certain clinical signs.

In the etiological studies, assessment of the prevalence of bacterial pathogens is of highest priority. Standard bacteriology for H. influenzae, S. pneumoniae, gram negative organisms, group B streptococcus, and S. aureus will be employed using techniques that are consistent among the sites. All isolates of S. pneumoniae and H. influenzae will be sent to reference centres designated by the Programme for serotyping and antimicrobial sensitivity testing. Frozen urine and serum samples from all cases will be stored for later testing when techniques with adequate sensitivity and specificity are available.

Although the etiological studies will give priority to assessing the prevalence of these bacterial pathogens, immunofluorescence tests for respiratory syncytial virus and C. trachomatis will be performed at all sites and more complete virological studies and cultures for Mycoplasma pneumoniae, Mycoplasma hominis, and Ureaplasma urealyticum will be done at one or two selected sites. When possible, post-mortem, true-cut lung biopsies will be obtained for histology and staining for P. carinii.

All chest X-rays will be performed according to the technical standards set by the WHO/ARI radiology working group and will be read by members of this group⁵. The same model of pulse oximeter will be used at all study sites to assess oxygen saturation.

5.5 Analysis

The combined data from all the study sites will be analysed with the objective of identifying a simple set of clinical signs with high sensitivity, specificity, and predictive value for pneumonia or other serious bacterial infections.

⁵ Report of a meeting of the Radiology Working Group. Document WHO/ARI/90.13

6. ANCILLARY STUDIES

At several locations, hospitalized infants will also be enrolled in a treatment study that will compare intramuscular chloramphenicol or oral cotrimoxazole with the current standard regimen - benzylpenicillin and gentamicin. An initial evaluation of the pharmacokinetics of these alternative regimens in young infants will be carried out prior to the treatment studies.

7. PREPARATORY ACTIVITIES

The study protocol, data collection instruments, and definitions of clinical signs will be revised in the light of discussions at the meeting. A uniform system for data entry and management, and methods to ensure the comparability of the clinical and laboratory results from the different sites are being developed. It is planned to conduct pilot studies in one or two sites by April 1990. The results will be closely monitored by the investigators and the ARI Programme and used to determine the adequacy of the sample size estimations and to guide plans for further studies in young infants.

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