



ARI IN INFANTS UNDER 2 MONTHS OF AGE

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I. EPIDEMIOLOGY

Acute respiratory infections (ARIs) are the first or second cause of death in children under 5 years of age in developing countries, depending on the region. Infants in the extended neonatal period (the first 2 months of life) who develop any infection, especially pneumonia, sepsis, or meningitis, have a high risk of death. It is estimated that of the four million annual pneumonia deaths, two-thirds occur in infants (1, 2).

Infections in this age group, especially bacterial ones, may occur with nonspecific clinical signs, which makes it difficult to distinguish pneumonia from sepsis and meningitis. Therefore, the ARI Programme of the World Health Organization (WHO) has assigned high priority to various research efforts on the epidemiology, etiology, and management of ARI in this age group.

In a review of the cases of children under 5 years of age admitted to the Pediatrics Department of Roosevelt Hospital in Guatemala City, of 1,454 admissions, 359 (25%) were under 2 months of age; of 142 deaths (10%), 39 (27%) were of infants under 2 months of age (Table 1). Moreover, of the 359 infants under 2 months, 157 (44%) were diagnosed with pneumonia and 117 (33%), with sepsis (Table 2), while it is likely that a significant number of these patients were undergoing both infectious processes simultaneously.

It is interesting to observe that when dividing the 39 deaths in infants into two groups, i.e. under 1 month and between 1 and 2 months, the latter were primarily due to pneumonia/sepsis/meningitis (94%), while in the first group, 22% were due to congenital anomalies, perinatal asphyxiation, and premature birth (Table 3).

Table 1. ARIs in children 5 years of age and under,
Pediatrics Department, Roosevelt Hospital, Guatemala 1992

| Category/Age | N | % | % |
|----------------|-------|-----|-----|
| Total admitted | 1,454 | 100 | |
| < 2 months | 359 | | 25 |
| Total deaths | 142 | 10 | 100 |
| < 2 months | 39 | | 27 |

Table 2. Infants under 2 months admitted in 1992,
Pediatrics Department, Roosevelt Hospital, Guatemala 1992

| Diagnosis | N = 359 | % |
|--------------------------|---------|----|
| Pneumonia | 157 | 44 |
| Sepsis | 117 | 33 |
| Other ARI | 13 | 4 |
| Other infections | 20 | 6 |
| Acute diarrheal syndrome | 21 | 6 |
| Other pathologies | 31 | 9 |

Table 3. Mortality in infants under 2 months,
Pediatrics Department, Roosevelt Hospital, Guatemala 1992

| Age | N = 39 | Pneumonia/sepsis/meningitis | Other pathologies |
|---------------|-----------|-----------------------------|-------------------|
| < 1 month | 23 (100%) | 18 (78%) | 5 (22%) |
| 1 to 2 months | 16 (100%) | 15 (94%) | 1 (6%) |

In general, infants under 2 months are more susceptible to infection due to the following:

- Maternal factors: perinatal complications such as premature and prolonged rupture of the membranes, peripartum maternal infection, septic or traumatic delivery.
- High-risk environmental factors: including cross-contamination of infants by those caring for them (for example, from failure to wash hands) or by equipment used at the health institution.
- Premature birth.
- Delay of intrauterine growth
- Immunological immaturity: usually linked to two of the preceding factors, even though it is known that in general the newborn has an immature immune system, as seen in the insufficient function in the alternative complement pathway, insufficient chemotaxis, poor phagocytosis, slow transition in the production of IgM to IgG antibodies, insufficient fibronectin, diminished T-cell function, and possible deficient monocyte production of interleukin-6 (IL-6). These problems are accentuated in the immune system of premature newborns; it is also important to note that more than 20 million children are born annually with low birthweight, thus augmenting the magnitude of the ARI problem.
- Other factors: masculine sex, fetal hypoxia, and maternal colonization by group B β -hemolytic streptococcus are crucial factors in susceptibility to infections. In addition, neonatal predisposition to pneumonia arises from a certain degree of pulmonary immaturity: specifically, an immature ciliary apparatus and insufficient pulmonary macrophages (3-5).

II. ETIOLOGY

In developing countries ARI etiology in infants under 2 months has not been completely defined as has been done in older children, in which *Streptococcus pneumoniae* and *Haemophilus influenzae* play a principal role. The majority of studies published do not reflect the real etiology of the general population, because they have been conducted at university hospitals and include many premature, high-risk neonatal infants and patients referred from other centers.

Furthermore, these studies do not report on the bacteriological methods or capacity for isolating harmful germs, such as *Ureaplasma urealyticum*, *Pneumocystis carinii*, *Chlamydia* spp., and *Mycoplasma hominis*. It is difficult to evaluate antimicrobial sensitivity; some methods do not differentiate between early and late sepsis; and the term "contaminant" is not appropriately defined. Thus many of these studies do not lend themselves to interpretation and comparison.

It is also important to bear in mind that the germs that cause septicemia in the first week of life are not necessarily the same agents of sepsis/pneumonia/meningitis between weeks 2 and 8, an area that has received only rare attention. Thus, in relation to the microbiology of neonatal or extended neonatal pneumonia, the different infection-causing germs may be classified according to the time at which the pneumonia occurs (Table 4) (4-13).

Respiratory viruses, especially respiratory syncytial virus (RSV), are known to be the principal agents causing respiratory infections of the lower airways during the first year of life in industrialized countries. In developing countries, certain bacteria also play an important role. They are listed with these viruses in Table 4.

| Table 4. Microbiology of neonatal pneumonia | |
|--------------------------------------------------------------------------------------------------|-----------------------------------|
| <ul style="list-style-type: none"> Congenital or intrauterine pneumonia: | |
| Herpes simplex virus | <i>Mycobacterium tuberculosis</i> |
| Cytomegalovirus | <i>Treponema pallidum</i> |
| Adenovirus | <i>Listeria monocytogenes</i> |
| <ul style="list-style-type: none"> Pneumonia contracted at birth: | |
| Group B and other streptococcus | |
| Gram-negative enterobacteria (<i>Escherichia coli</i> , <i>Klebsiella</i> spp.) | |
| <i>Haemophilus influenzae</i> | |
| <i>Ureaplasma urealyticum</i> | |
| <ul style="list-style-type: none"> Pneumonia contracted after birth: | |
| <i>Staphylococcus aureus</i> | Gram-negative enterobacteria |
| Respiratory virus (RSV and adenovirus) | Cytomegalovirus |
| <i>Chlamydia trachomatis</i> | Enterovirus |
| <i>Pneumocystis carinii</i> | |

Evidence exists that some less common organisms, alone or in combination with virus and bacteria, are etiologic agents that warrant serious consideration. They include *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Pneumocystis carinii*, *Mycoplasma hominis*, *Mycoplasma pneumoniae*, and cytomegalovirus (14).

Infants with early neonatal infection who have manifestations in the first 4 to 7 days of life are normally infected with germs from the birth canal such as *Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus aureus*, group B β -hemolytic streptococcus (relatively infrequent in Latin America), and *Salmonella* spp. Those with late sepsis have normally already been discharged from the hospital or have had neonatal problems such as premature birth, delay in intrauterine growth, respiratory difficulty syndrome, or perinatal asphyxiation, and thus require prolonged hospitalization. In general, the germs that infect them are nosocomial (Gram-negative enterobacteria, multi-antibiotic resistant) or are acquired in the community such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, type B or nonclassifiable *Haemophilus influenzae*, or enterobacteria.

Viral pneumonia, especially in previously healthy infants, produces many signs of generalized disease; the most important risk factor is contact with a sick family member at home. Although

RSV is the most frequently isolated virus, adenovirus is possibly the most aggressive viral agent and is responsible for many pneumonia deaths. The risk factors for severe viral pneumonia include prematurity and adenovirus infection (11).

III. DIAGNOSIS

For a correct diagnosis of a serious bacterial, viral, or other etiologic infection, a thorough clinical history and physical examination must be performed. Depending on the availability of resources, a subsequent series of office examinations may better define the diagnosis: chest X-rays, hematic biometry, hemoculture, lumbar puncture, swab culture of other body fluids or secretions, and more recently rapid immune tests.

The personnel in many health institutions in developing countries should simply use clinical signs alone to detect cases of pneumonia and other severe infections. There is no single, reliable golden rule to diagnose pneumonia in infants under 2 months of age. Normally, punctures and pulmonary or bronchial biopsies are not justifiable, given that radiological infiltration may occur as a result of causes not related to infections. Chest X-rays should be ordered only for feverish infants who display clinical signs of pulmonary disease (15); tracheal aspirates are especially used with neonatal infants placed in respirators. Positive hemocultures reveal only a fraction (one-fourth to one-third) of the true rates of pulmonary bacterial infection.

The clinical impression of sepsis in feverish infants under 2 months of age has been the only significant, important clinical variable found in several studies. A clear definition of clinical symptoms and a reliable observer are needed if their predictive value is to be assessed in order to train health personnel in detecting cases (16, 17). The physical examination may reveal a series of respiratory disorders, as follows:

| Respiratory disorders found in the physical examination of infants under 2 months of age | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Signs and symptoms observed upon inspection | Symptoms observed (without a stethoscope) | Signs detected by auscultation |
| <ul style="list-style-type: none"> • Skin color (cyanosis, paleness, plethora) • Configuration of the thorax • Tachypnea • Periodic breathing • Apnea • Retraction • Nasal flaring • Difficulty in eating | <ul style="list-style-type: none"> • Grunting • Stridor • Cough • Sneezing | <ul style="list-style-type: none"> • Entrance of air • Prolonged exhalation • Wheezing • Rales and hoarseness |
| <small>Source: Polgar G. <i>Practical pulmonary physiology: A functional analysis of symptoms and therapeutic measures in respiratory disorders of newborn infants</i>. <i>Pediatr Clin North Am</i> 1973;20:303-322.</small> | | |

There are also a series of signs and symptoms that are often mentioned in pediatric literature as indicators of severe bacterial infection:

- Loss of appetite;
- Fever or hypothermia;
- Drowsiness;
- Convulsions;
- Irritability and difficulty in being comforted;
- “Doesn't look well,” “Looks toxic.”

The last two symptoms are not included in the WHO classification of very severe diseases, although wheezing and stridor when at rest are noted (18). Observation, clinical history, and the physical examination are the most appropriate diagnostic elements; they are approximately 90% accurate in detecting very severe disease in infants under 2 months, and this accuracy may be even higher when laboratory tests are used. In 80% of the cases, the signs and symptoms of severe disease are those of the central nervous and respiratory systems.

Fever is one of the most alarming signs and a cause for concern in both mothers and health professionals. It is an uncommon sign in this group of patients, which usually has a temperature range between 38.1° and 38.9° C. There is a link between a severe bacterial infection and the elevated body temperature. As fever increases, so does the possibility of bacteremia, which occurs in about 7% of infants if the fever is under 40° C; in 13%, if the temperature is between 40.5° C and 41° C, increasing to 16% when the fever is 41.1° C or above. In addition, in 10% of the cases, meningitis may be present if the fever is above 41.1° C. A temperature of 40° C is the thermoregulating limit in the first 12 weeks of life; such a fever has the same implications of severe infection as a temperature of 41.1° C in an older child (17, 19). Many studies have shown that a fever above 40° C is uncommon: from 0% in those younger than 2 weeks of age to 8.3% in infants up to 12 weeks.

In addition to the danger signs used to qualify very severe disease, retraction and tachypnea (respiratory frequency above 60 per minute) are the most sensitive signs for diagnosing pneumonia, which at this stage of life is always considered severe.

It should be noted that in the neonatal period there are other pulmonary pathologies that may cause tachypnea or retraction, such as disease in the hyaline membrane, transitory tachypnea in the newborn (retained fetal pulmonary liquid), meconium-aspiration syndrome, blockage of pulmonary circulation (persistent pulmonary hypertension), some cardiopathy (in general without retraction), and a series of miscellaneous causes (including different congenital anomalies of the airways, the lungs, diaphragm, and rib cage), which usually are diagnosed at a higher level of care.

It is important to note that retractions are considered important only if they are severe, since at this age, especially in low weight neonatal infants, the rib cage is weak, and infants may demonstrate mild intercostal retractions, even under normal conditions. The respiratory fre-

quency should be evaluated in children when they are still for a period of 1 minute or if they are sleeping, since some newborns have periodic breathing and take short pauses between breaths, sometimes even apnea (stopping respiration for more than 20 seconds), which is abnormal and may be a serious warning sign. If the respiratory frequency is above 60 per minute, it should be counted again.

Evaluation of breathing is not as easy as it seems and requires practice. Few studies have been conducted on respiratory frequency in the first 2 months of life; even classic pediatrics texts offer different normal values. At present a respiratory frequency of less than 60 per minute is accepted as normal. Although it may vary according to the sleep of the newborn, as described by Ashton and Connolly in their study covering three continuous sleep cycles (24-28).

| | | | | |
|---------------|------|----|----|----|
| Non-REM sleep | Mean | 45 | 43 | 43 |
| | SD | 10 | 9 | 13 |
| REM sleep | Mean | 54 | 48 | 47 |
| | SD | 11 | 9 | 9 |


REM, rapid eye movement; SD, standard deviation.

The respiratory frequency and variability thereof are greater when the newborn is awake, much lower during peaceful sleep, and intermediate during active sleep (26):

| AGE OF INFANT | 1 week | | 2 months | |
|----------------|--------|----|----------|----|
| | Mean | SD | Mean | SD |
| Peaceful sleep | 38 | 9 | 30 | 5 |
| Active sleep | 50 | 8 | 36 | 6 |
| Awake | 50 | 10 | 48 | 7 |
| Indeterminate | 47 | 10 | 37 | 8 |

IV. MANAGEMENT

Due to the nonspecific and subtle clinical manifestations of sepsis in infants under 2 months, its rapid evolution, and high mortality rates, treatment should be initiated even when only minimum indications of infection are present. WHO, on the basis of numerous field studies and frequent and involved assessments by groups of technical advisors, has recommended that infants under 2 months be evaluated, classified, and treated in the following manner (29):

| THE YOUNG INFANT (AGE LESS THAN 2 MONTHS) | | |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SIGNS: | <ul style="list-style-type: none"> • Stopped feeding well, • Convulsions, • Abnormally sleepy or difficult to wake, • Stridor in calm child, • Wheezing, or • Fever or low body temperature. |  |
| CLASSIFY AS: | VERY SERIOUS DISEASE | |
| TREATMENT: | <ul style="list-style-type: none"> ▶ Refer URGENTLY to hospital. ▶ Keep young infant warm. ▶ Give first dose of an antibiotic. | |
| SIGNS: | <ul style="list-style-type: none"> • Severe chest indrawing, or • Fast breathing (60 per minute or MORE) | <ul style="list-style-type: none"> • No severe chest indrawing, or • No fast breathing (less than 60 per minute). |
| CLASSIFY AS: | SEVERE PNEUMONIA | NO PNEUMONIA: COUGH OR COLD |
| TREATMENT: | <ul style="list-style-type: none"> ▶ Refer URGENTLY to hospital. ▶ Keep young infant warm. ▶ Give first dose of an antibiotic. <p style="text-align: center;">(If referral is not feasible, treat with an antibiotic and follow closely)</p> | <ul style="list-style-type: none"> ▶ Advise mother to give the following home care: <ul style="list-style-type: none"> ▶ Keep young infant warm. ▶ Breastfeed frequently. ▶ Clear nose if it interferes with feeding. ▶ Return quickly if: <ul style="list-style-type: none"> ▶ Breathing becomes difficult ▶ Breathing becomes fast ▶ Feeding becomes a problem ▶ The younger infant becomes sicker. |

The recommendation to refer all infants with signs of very severe disease or severe pneumonia to a hospital is clear and categorical. However, a series of variations in the management of these cases may occur:

- Treatment should be given at home or should be outpatient when:
 - access to the hospital is very difficult;
 - the family, for any reason, refuses hospitalization;
 - the attending hospital physician determines that outpatient treatment with antibiotics can be provided;
 - the attending hospital physician determines that ambulatory treatment without antibiotics can be given.
- The patient is admitted to the hospital for evaluation, observation, and antibiotics.
- The patient is admitted to the hospital for evaluation and observation without antibiotics.

Many experiences and several criteria can be applied to any of the above procedures. Bartlett et al. (30) succeeded in reducing the neonatal mortality rate by 85% in a hamlet in Guatemala through early intervention in potential sepsis cases, consistent administration of ampicillin and gentamicin, and in some cases erythromycin or cephalosporin. Bang et al. (31) in the District of Gadchiroli, India, succeeded in reducing the neonatal mortality rate by 40% and 78% in month 2 with cotrimoxazole administered by community health workers and midwives.

The nursing 2- or 3-month-old infant with fever who is at high risk of severe disease has been an object of controversy and numerous studies at the hospital level. Attempts have been made to determine the predictive value of a combination of variables in order to develop strict criteria for the initial evaluation that would distinguish infants who do not have severe bacterial infection. The most widely accepted criterion at this time includes the following parameters (21-23):

- Previously healthy nursing infant;
- Absence of infection in the ears, soft tissues, or bones;
- Normal hematic biometry (leukocyte count between 5,000 and 15,000 per mm³ and fewer than 15,000 neutrophil bands per mm³)
- Normal urine sample;
- Absence of polymorphonuclear leukocytes in stool samples.

If one uses this strict screening criterion, a significant number of feverish infants can quite safely receive outpatient care without antibiotics. Unfortunately, this criterion cannot be applied in regions, such as rural areas, where no laboratory facilities are available. Thus, WHO continues to recommend that infants with fever be referred to hospitals and treated with antibiotics. If access to a hospital is not possible or is delayed, however, the ARI Programme guidelines recommend immediate use of antibiotics.

The choice of antibiotics for treatment is based upon the prevalent microorganisms in the antibiotic sensitivity charts, taking into account that infants may contract the infection perinatally or become infected with hospital organisms that are rare in the community. Empirical treatment with antibiotics is justified when results from cultures taken dictate their use. The choice of antibiotics will depend on each national program for ARI control or the procedures of each hospital.

Ampicillin (50 mg/kg dose every 8 hours, IV or IM) and gentamicin (2.5 mg/kg dose every 12 hours in the first week of life and every 8 hours between week 1 and 2 months of age, IV or IM) after many years continue to be the combination of choice for early sepsis and even for those infants admitted to the hospital up to 8 weeks after birth. WHO has recommended the combination of penicillin G, at 50,000 U/kg dose every 12 hours in the first week of life and every 6 hours from 1 to 8 weeks in addition to the recommended dose of gentamicin. In special cases, such as when meningitis is suspected or an infection of the soft tissues, an intestinal focus, or when the child had already received a course of ampicillin and gentamicin, other

antibiotics may be used (e.g., chloramphenicol, cefotaxime, ceftriaxone, or cotrimoxazole, using the doses and special precautions recommended by each institution).

Infants classified as not having pneumonia, with simple cough or cold, should be sent home and professional and appropriate communication with the mother should make clear which support measures are needed (e.g., such as frequent nursing, cleaning the nose if mucus interferes with breathing, keeping the infant well-covered to avoid hypothermia—the “kangaroo mother” method is an excellent option with premature or low-weight babies). The mother should know how to recognize danger signs in order to return the baby immediately to the closest health center. Treatment with antipyretics is generally not recommended for infants under 2 months since they can give a false sense of security in reducing the fever, thus delaying the diagnosis and treatment of severe infection (32).

V. PREVENTIVE MEASURES

A series of preventive measures against ARI will contribute to achieving the principal program goal: reduction of the number of pneumonia deaths. They include:

- Immunization
- Promotion of breast feeding
- Avoiding exposure to cold, smoke, and disease at home.

VI. A GLANCE AT THE FUTURE

Among the series of activities and strategies that would improve and strengthen the ARI Programme throughout the world:

- Extend coverage: ensure that standard case management be conducted at all levels of care;
- New vaccines, especially against pneumococcus;
- Improve and teach techniques for communication with mothers;
- Change in attitudes among health sector personnel;
- Promote and facilitate research related to epidemiology, diagnostic etiology, and treatment of ARI;
- Make every effort to ensure that care be based on quality and excellence.

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