Pneumonia Due to Unusual Organisms in Children

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Abstract. Generally antimicrobials for treatment of pneumonia are chosen to target the usual bacterial etiological agents. Such regimens are unable to cure patients of pneumonia caused by 'unusual organisms' mycoplasma, chlamydia, *Pneumocystis carinii* and *Legionella pneumophilus*). Thus, there is a need to anticipate their presence in appropriate cases and to plan the initial antimicrobial therapy accordingly. Studies in Europe as well as India have shown that such infections form a fairly substantial percentage of community acquired pneumonia in children. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are common in school age children while *Chlamydia trachomatis* occurs in early infancy. *Pneumocystis carinii* is an important pathogen in immunocompromised children. Routine laboratory tests and radiological features are not specific enough to give accurate diagnosis of these infections for which one has to depend on sophisticated culture techniques, immunological tests for the antigens or antibodies and polymerase chain reaction. Mycoplasma, chlamydia and legionella infections respond to macrolide antibiotics and for pneumocystis infections, trimethoprim-sulfamethaxozole or pentamidine is the drug of choice. Overall prognosis with appropriate treatment is good except for *P. carinii* infection in immunocompromised host which carries a high mortality and recurrence rate. **(Indian J Pediatr 1999; 66 : 929-936)**

Key words : *Mycoplasma; Chlamydia; Pneumocystis carinii; Legionella.*

Pneumonia is caused by a variety of microorganisms in children. The type of microorganism can be predicted with certainty only in a few cases because clinical features, radiological findings and laboratory tests have only a limited value in differentiating one microorganism from another. Choice of antimicrobials is often based on age group and epidemiological data.

Gram negative bacilli in the neonatal period and *Streptococcus pneumoniae, H. influenzae and Staphylococcus aureus* are the common organisms in older infants and children. A comparatively smaller number of cases of pneumonia are caused by organisms other than these 'usual' ones. Such unusual organisms can be divided into two groups :

(i)   Organisms whose main manifestation in human beings is pneumonia and

(ii) Organisms which mainly cause other illnesses but can result in pneumonia also.

This article will focus on the first group of microorganisms only.

Importance of Unusual Organisms

A third generation cephalosporin alongwith an aminoglycoside is the standard recommended treatment for pneumonia in neonatal period while penicillin alone

would suffice for older infants and children. Both these regimens will not be able to cure patients of pneumonia caused by the common unusual organisms. Thus, there is a need to anticipate their presence in appropriate cases and to plan the initial antibiotic therapy accordingly.

Pneumonia due to unusual organisms is, by no means, uncommon. In a recently reported study from Finaland[1] *Mycoplasma pneumoniae* and *Chlamydia* spp. accounted for 36% cases of community acquired pneumonia in a population of 3 months to 14 years age. Another study from Finland[2] found mycoplasma as the cause in 24 out of 278 (9%) pediatric patients with radiographically defined community acquired pneumonia.

Studies from India have also registered significantly, high incidence of these organisms. Thus, a study from Chennai[3] reported culture positivity for 18% and serological positivity for 31.5% cases in pediatric age group (n = 149) for *Mycoplasma pneumoniae*. Another study from Vellore[4] found 9.7% cases caused by mycoplasm and another 9.7% due to legionella. Ramamoorthi *et al*[3] quote two studies from Delhi showing even higher incidence of *Mycoplasma pneumoniae* in young children.

Mycoplasma Pneumonia

Just as pneumococcal pneumonia can be considered as a prototype of 'typical pneumonia' so can *Mycoplasma pneumoniae* be considered as prototype of 'atypical pneumonia'. The importance of *Mycoplasma pneumoniae* lies in its high incidence in school age children, second to pneumococcal pneumonia, in its special features as an etiological agent (mycoplasma do not have cell wall), difficulty in confirming the diag-

nosis and lack of response to treatment with penicillins and cephalosporins.

The disease occurs in both epidemic[5] and endemic form. Mycoplasma infection is transmitted from person to person and its incubation period is 2 to 3 weeks. Peak incidence is between 6 to 18 years age though all ages are affected. Upper respiratory tract infection, laryngitis, tracheobronchitis and pneumonia form the spectrum of clinical syndromes caused by this organism. Pathology, typical of bronchitis and bronchopneumonia with areas of atelectasis due to plugging of airways is seen. This organism has a special affinity for respiratory epithelium. The infection appears to be particularly severe in sickle cell disease[6] and Down's syndrome[7] patients and is not a common pathogen in AIDS children[8].

Clinically, the child starts with signs and symptoms of upper respiratory infection which progresses to productive and at times paroxysmal cough of 'bronchitic' type. The disease may progress to chest pain and dyspnea. Otitis media, bullous myringitis and mild sinusitis may occur. Lower respiratory tract involvement is recognised by ronchi, rales and sometimes bronchial breathing. However, correlation between radiological and clinical findings may be poor. Localised bronchopneumonic infiltrates or consolidation may be seen. Pleural effusion are uncommon and small[9]. The patients recover over a period of 2 to 4 weeks without sequelae whether or not they receive appropriate treatment.

Laboratory tests have a limited role in diagnosis of mycoplasma pneumonia. Cold agglutinins, although appearing relatively early in the disease, are both nonspecific and insensitive indicators of *M. pneumoniae* infection. Complement fixation antibodies, although far more specific, do not rise early

enough in infection to be helpful in guiding diagnostic and therapeutic decisions. They are primarily useful in epidemiological studies[8]. Further, cultures for mycoplasma are not available in most of the clinical laboratories.

Recently, more sensitive and specific rapid diagnostic tests have been developed. They detect either the M. pneumoniae specific immunoglobulins in serum or detect specific antigen or nucleotide sequences in the clinical specimens. Enzyme-linked immunoassay (ELISA) test to detect IgG and IgM against M. pneumoniae have been found to be more specific. However, they become positive only after 7 to 10 days of illness[10-11]. An immunocard ELISA test has been developed as a screening test[12] which gives results in 10 minutes.

Sputum and nasopharyngeal aspirates when tested for M. pneumoniae specific antigens have been found to given encouraging results[13-14]. A commercially available gene probe rapid diagnostic system which gives results in 2 hours has been fairly satisfactory[15].

Polymerase chain reaction technology has been applied for diagnosis of mycoplasma infections in a number of centers. In a study from Germany mycoplasma specific probe without hybridization (MP-PCR) and a nested PCR (MPN-PCR) were found to be reliable methods for detection of M. pneumoniae in respiratory tract samples[16] while in Japan a somewhat different technique was used[17]. At present PCR doesn't appear to be a cost effective clinical tool for diagnosis of Mycoplasma pneumoniae.

A recent study used PCR on nasopharyngeal aspirate IgG and IgM serology tests and cultures and found the IgM serology test to be the best for diagnosis of M.

pneumoniae pneumonia in children of any age[2].

Standard treatment protocol is a macrolide antibiotic given orally for at least 7 to 10 days. Azithromycin may be given for a shorter period of 5 days. Eythromycin is cheaper than clarithromycin but has a higher incidence of gastrointestinal disturbances. Tetracycline, an inexpensive antibiotic can be used for children of more than 8 years age. Ofloxacin is also effective against mycoplasma.

Treatment with effective antibiotics remarkably shortens the illness and reduces the spread of infection in contacts. Response to antibiotics is slow and an incomplete course of treatment may result in the recurrence or resumption of the disease process.

Chlamydia Pulmonary Infection

Chlamydia are bacteria with special characteristics. Although they have a Gram-ve cell wall envelope, unlike most other bacteria they are obligatory intracellular parasites. The intracellular bodies are called reticulate bodies while the extracellular form (elementary bodies) is the other part of the life cycle and is infectious.

Three species are important for human pulmonary infection (Table 1).

Chlamydia trachomatis : This organism is transmitted from the pregnant women suffering from cervic infection to their infant during vaginal delivery who later develop conjunctivitis and pneumonia. Besides these perinatal infections C. trachomatis can cause classic ocular trachoma, lymphogranuloma venereum and other oculogenital diseases in adults.

Between 11 and 20% of infants born to

TABLE 1.

	C. trachomatis	C. pneumoniae	C. psittaci
Major illness in children	Trachoma Pneumonia	Pneumonia Tracheobronchitis	Pneumonia PUO
Natural Host	Human	Human	Birds
Susceptible to sulfonamides	No	Yes	No
Age group involved	4-12 wks	> 5 yrs	Rare

infected mothers develop pneumonia due to C. trachomatis[18]. It is one of the most common pneumoniae seen in infancy[19]. Infected infants present between 4 and 12 weeks of age with nasal obstruction and/or discharge, cough and tachypnea. Most are only moderately ill and afebrile. A history of conjunctivitis is present in approximately half the cases[20]. On auscultation of chest bilateral scattered crackles are commonly heard but breath sounds are usually good and wheezing absent. They have prominent stacatto cough which may come in paroxysms and interfere with feeding and sleep. About half the patients have abnormal appearing eardrums.

Chest radiographs commonly reveal bilateral hyperinflation with diffuse interstitial infiltrates. Sometimes reticulonodular, bronchopneumonic or atelectatic shadows are seen. Lobar consolidation and pleural effusions are not a feature of chlamydia infantile pneumonia.

Laboratory findings include normal total leucocytic counts with eosinophilis, mild to moderate hypoxemia and elevated IgG and IgM levels.

Untreated, the disease takes a prolonged course of several weeks to months. In the very young, occasionally, the disease can be severe with prolonged spells of apnea or respiratory failure. Some long term follow up studies have shown higher than normal frequency of obstructive airway disease after 8 years in those children who had chlamydia infection in first few months of life[21-22].

Diagnosis of C. trachomatis infection is not easy in clinical settings. Culture of the organisms from nasopharynx remains the "gold-standard". The antigen detection enzymatic immunoassay test available do not give as good results with nasopharyngeal secretions as with conjunctival specimens, the sensitivity being poor.

The serologic diagnosis of chlamydial pneumonia has been successful in some series[19]. A single titer of higher than 1 : 64 for specific IgM antibody or a four fold rise in paired samples is taken as positive. Serologic test of choice is the microimmunofluorescent procedure of Wang and Grayston in which elementary bodies are used as antigen[23-24]. Presence of IgG antibody is not diagnostic.

There is convincing evidence that the administration of erythromycin at 50 mg/kg per day in divided doses for 10-14 days shortens the clinical course significantly. Newer macrolides may be used with advantage. Sulfonamides and tetracyclines (in children > 8 yrs age) are the alterna-

tives.

Chlamydia pneumoniae : *Chlamydia pneumoniae* (previously called TWAR) is an important etiological agent of pneumonia in older children and adults. It also causes bronchitis, tracheobronchitis and upper respiratory tract infections. More than half the adults in USA have serum IgG against *C. pneumoniae*, indicating past infection[25]. An age wise study shows that infection with this agent is infrequent in preschool-age children, is very frequent in school age children, and continues to be detectable throughout adult life. Although *C. pneumoniae* infections in young children in developed countries usually are mild, limited information suggests that it may play a role in mortality from acute infections of lower respiratory tract infection in tropical countries[26].

C. *pneumoniae* infections are both endemic and epidemic. Transmission probably occurs from person to person by respiratory tract secretions. In a study in children 3 to 12 years of age, Block *et al*[27] isolated *C. pneumoniae* in 31.1% cases by culture. A more recent study found 1, 4 and 15 cases of *C. pneumoniae* out of a total of 201 cases studied by serology in the age groups 0-4 yrs, 5-9 years and 10-14 years respectively[1].

Majority of cases of pneumonia caused by *C. pneumoniae* resemble the 'atypical' pattern followed by mycoplasma, legionella or respiratory viruses. Only seldom is the disease severe or life threatening. Typically, the onset is gradual, starting with signs and symptoms of pharyngitis and hoarseness. As the child appears to be recovering, with fever abating, the cough worsens and signs of lower respiratory tract infection may develop giving the appearance of a biphasic illness. Ronchi and rales are commonly heard on auscultation, even in patients with relatively mild symptoms. Rarely, pleural effusions, hypoxemia and respiratory failure occur.

A special association of *C. pneumoniae* infection with asthma has been proposed[28]. In a study[29] *C. pneumoniae* was isolated in 11% of children in 5 to 15 years age group who were evaluated for either new or acute exacerbations of asthma. It has been suggested that bronchial reactivity seen with *C. pneumoniae* infection may be IgE mediated. However, it is not yet proven that this organism plays a more important role in initiation of asthmatic symptoms than in other respiratory infections.

Laboratory diagnosis requires specialised studies. The organism can be cultured from the nasopharyngeal secretions on specific cell lines after the specimens have been transported to the reference laboratories in appropriate transport medium. Microimmunofluorescence test developed by Wang for *C. trachomatis* remains the only sensitive and specific serologic test for chlamydia and is the most sensitive method for diagnosis of *C. pneumoniae* infection. A four fold rise in IgG or IgM titer or a single IgM titer of more than 1 : 16 is taken as positive. A four fold rise or a titer of 1 : 64 or more with complement fixation test is also taken to be diagnostic.

Direct detection of *C. pneumoniae* in respiratory secretions by ETAs has not been found to be sensitive enough to be adopted into clinical use. The PCR has been used successfully to identify *C. pneumoniae* DNA[30-31]. It appears to hold promise in future.

At present, no effective diagnostic method for *C. pneumoniae* is available. The commercial methods used for diagnosis of

C. *trachomatis* have not been found to be reliable for diagnosis of C. *pneumoniae* infection.

For children erythromycin 50 mg/kg/day or clarithromycin 15 mg/kg/day orally for 10 to 14 days is the treatment of choice. Azithromycin can also be used.

Chlamydia Psittaci (Psitacosis or Ornithosis) : This is an uncommon infection in childhood caused by *Chlamydia psittaci.* The organism gains access to human body from infected pet birds and results in an acute respiratory illness which may be accompanied with multisystemic involvement. Thus, encephalitis, myocarditis, hepatitis or gastrointestinal symptoms may also be noted. Leucopenia, neutrophilia, normal ESR, hyponatremia and mild proteinuria are commonly seen. Chest X-ray may show patchy pneumonia in lower lobes or an interstitital pattern. Chlamydia can be cultured from blood or throat swab. Complement fixation test with fourfold rise of antibody or a single titer of more than 1 : 16 is considered diagnostic. Erythromycin or tetracycline may be used for treatment. With treatment the mortality rates have fallen from 20 to less than 1 percent.

Legionella Pneumonia

Legionella pneumoniae is a comparatively recently recognised illness (since 1976) and occurs predominantly in the middle aged and only rarely in infants and children. The importance of this disease lies in the difficulty in establishing the diagnosis, specific antimicrobial therapy required and high mortality if untreated.

This disease should be suspected in a child who develops high fever with recurring chills after a brief (24 hours) prodrome of "flulike" illness. The child usually has a nonproductive cough and patchy bronchopneumonia in initial chest X-ray which may progress to lobar consolidation - may be bilateral and sometimes with small pleural effusion. Child is toxic, may have encephalopathy, watery diarrhea without mucus, blood or abdominal pain (40-55% cases). Later, dyspnea (50%), signs of pneumonia and high fever predominate and chills continue to occur, unlike pneumococcal pneumonia where chills occur mainly in the early phase of the disease.

Leucocytosis with shift to left may be noted. Disturbed liver function tests (40%) and renal insufficiency (15%) are also seen. Chest X-ray shows prominent but nonspecific pneumonia. Absolute diagnosis is made by culture of the organisms from patient's sputum, tracheal aspirate, pleural fluid or lung biopsy on BCYE agar medium. The process takes 3 to 7 days. However, usual means to establish diagnosis is by indirect immunofluorescent antibody test showing a four fold or greater rise. Antigenemia can be detected by testing urine by ELISA.

Recently a single throat swab specimen has been used successfully as a simple, specific, sensitive and rapid test using polymerase chain reaction[32].

Erythromycin is the drug of choice and is preferable to tetracycline. Recently, clarithromycin has been shown to be more active than erythromycin. Therapy should be given for 3 weeks as with shorter duration therapy, relapse may occur. Rifampicin may be added (not recommended alone) in very sick patients. Flouroquinolones may also be useful.

Significant mortality still occurs with this disease (19 to 24%). Cancer, immunosuppression, nosocomial infection and end

stage renal disease are the principal factors associated with high mortality.

Nosocomial pediatric cases are now being reported in neonates, immunosuppressed children, and children with underlying pulmonary disease[33-34].

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