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Editorial

This issue of the Annals of the National Academy of Medical Sciences comprises of the proceedings of symposium on Community Acquired Pneumonia - the third in the series of symposia under the joint Tele-Medical Education Programme (North) of the National Academy of Medical Sciences and the Postgraduate Institute of Medical Education and Research, Chandigarh. The symposium on community acquired pneumonia held on December 23, 2007 at Chandigarh, constituted an important milestone in the Programme with remote site presentations and interactive participation of three different centres (Chandigarh, Shimla and Rohtak).

Pneumonia has continued to pose a challenge to the medical profession since the Pre-Biblical era as was described by Hippocrates in 4th - 5th century B.C. - "when pneumonia is at its height ... .it is bad if he had dyspnoea... ". Sir William Osler in the 19th century called pneumonia as the "friend of the aged.....so distressing to himself and to his friends ...". Although the clinical features and management of pneumonia have vastly changed over the centuries, the threat to the health and to the life remains the same. With time, both the morbidity and the mortality have multiplied manifold in view of the enormity of the burden and the ever expanding microbiological spectrum of pneumonias. The added issues of nosocomial and ventilator associated pneumonia have further complicated the problem.

Today, community acquired pneumonia accounts for an annual incidence of over 2 percent in this country. It is a problem confronted by not only the pulmonologists but by practitioners of several medical and surgical specialities such as of General Medicine, Paediatrics, General Surgery, Geriatrics, Neurosurgery, Obstetrics and Gynaecology and others. Every physician and surgeon is expected to manage this problem in his/her day to day clinical practice.

The Proceedings of the Symposium cover a comprehensive review of the subject, ranging from the epidemiology and microbiology to the clinical diagnosis and management. Specific issues with reference to pneumonias in children and in patients with immuno-suppressed states* such as the HIV

* These articles will appear in the January-March, 2009 issue

infection, malignancies and organ transplantation are also included. Attempts have been made to review the scanty data which is available from India on different issues.

There is a great need in this country to extend search into the microbiological spectrum and the diagnostic algorithms. Misuse of antibiotics in particular, is an important issue to deliberate. 'On the counter' availability of even the high-end and 'reserve' antibiotics add to the drug confusion with problems of costs, drug resistance and toxicity. It is of paramount important to develop national guidelines and local policies for use of antibiotics for treatment of pneumonias.

We hope that this issue of the Annals serves as one step forward in the overall care of pneumonias and in the development of the Academy's tele-medical education programme.

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Community Acquired Pneumonia : An overview

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Community acquired pneumonia (CAP) is an important cause of morbidity and mortality world-wide, affecting all age groups, particularly children under the age of 5 years and the elderly. Burden of disease is higher in developing countries, specially in children under the age of 5 years. Prevalence of various risk factors for pneumonia in developing countries is higher, namely, under-nutrition in children, inadequate coverage with childhood immunization program, indoor and outdoor air-pollution, tobacco-smoking, and over-crowding. Being in a state of epidemiologic and demographic transition, well recognized risk factors in the west such as old age, chronic cardiopulmonary disease, malignancy, diabetes mellitus, chronic renal failure, immuno-suppressed state are also quite prevalent in developing countries.

Early detection and prompt treatment of CAP with appropriate antibiotics saves lives, and is an extremely cost-effective intervention which has reduced mortality from 30-35% in the pre-antibiotic era to ~5% in adults in the western world (1). Decline in mortality from pneumonia has been less impressive in developing countries including India, more so in children under the age of 5 years, on account of lack of timely access to health-care providers and appropriate antibiotics. Facilities for management of severe pneumonia requiring hospital treatment or intensive care are limited even in urban areas adding to increased mortality. There is lack of consensus amongst physicians regarding the choice of antibiotics for patients in different clinical settings, largely because of limited information on the causative microbial pathogens and

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their antibiotic susceptibility patterns. Frequency of pneumonia caused by atypical pathogens, namely Legionella, Chlamydia and Mycoplasma, remains a matter of speculation. High prevalence of tuberculosis in the community adds to difficulty in diagnosis of pneumonia. Consensus guidelines for the management of community acquired pneumonia recommended by the professional societies of North America, Britain and Europe are sometimes used in the absence of reliable data from India, but their appropriateness in the local context has not been evaluated. Specifically, recommendation for the use of newer fluorquinolones to cover atypical pathogens and drug resistant *Streptococcus pneumoniae* remains questionable in countries with high prevalence of tuberculosis. Similarly the recommendation for routine immunization of patients with pneumococcal and influenza vaccines before discharge from the hospital is also debatable in view of different serotypes prevalent in India compared to other parts of the world.

CAP may develop in healthy individuals, or in persons with pre-existent lung diseases such as COPD, asthma, bronchiectasis or pulmonary fibrosis which impair local defense mechanism against microbial invasion. Lung defense mechanisms are also impaired in the very old, and are inadequately developed in the very young, making these subjects more vulnerable. Other common predisposing factors for pneumonia include immunosuppressed state, altered consciousness, impaired swallowing mechanism, gastro-oesophageal reflux disease, substance abuse and alcoholism.

Pneumonia is diagnosed by an acute febrile illness with cough and expectoration, and presence of inspiratory crackles over localized region(s) of the chest. Demonstration of consolidation by radiological examination is not mandatory, particularly in the ambulatory primary care setting. Tachypnoea (with hypoxemia), hypotension, mental confusion, elevated blood urea and age over 65 years are adverse prognostic factors and the presence of three or more of them signifies need for hospitalization, close monitoring and need for intravenous antibiotics (British Thoracic Society CURB-65 criteria) (2). Pneumonia Severity Index is more elaborate scoring system for scoring severity of pneumonia (3). The two methods for assessing severity are complimentary; CURB-65 being more

suited to identify patients requiring urgent hospitalization. Presence of one or more co-morbidities, such as diabetes, congestive heart failure or COPD increases the risk of death. Co-morbidities and certain epidemiologic factors need to be considered during initial evaluation as they increase the risk of infection with certain specific organisms, e.g., *Pseudomonas* spp (bronchiectasis, steroid or antibiotic therapy), *Staphylococcus aureus* including methicillin resistant strains (chronic renal failure, regional prevalence), *Hemophilus influenzae* (COPD), drug resistant *Streptococcus pneumoniae* (old age, steroid or antibiotic therapy, regional prevalence), *Klebsiella pneumoniae* (alcoholism), *Pneumocystis carinii* pneumonia (immunosuppressed subjects) and infection with anaerobic pathogens (aspiration). Atypical pathogens are more likely in patients requiring hospitalization, and *Legionella* spp in ICU patients. A detailed discussion of risk factors for specific pathogens causing CAP is included in guidelines recommendations of the ATS (4).

Initial diagnostic evaluation in patients with moderate to severe CAP should include an X-ray skiagram of the chest, total and differential white cell count and blood culture before instituting antibiotic therapy. Measurement of oxygen saturation by pulse oximetry is widely available and should be undertaken on all patients. Gram staining of the expectorated sputum and its culture for pyogenic organisms appear to be of limited value. Staining of sputum for acid-fast organisms should be undertaken in all patients with symptoms of longer duration, upper zone infiltrates or even a bronchopneumonic appearance, particularly in presence of diabetes, chronic renal failure or immunosuppression. Failure to do so may lead to transmission of tuberculosis amongst hospitalized patients and health-care providers. Sputum induction and special stains may be required in immunosuppressed patients suspected of *Pneumocystis jiroveci* pneumonia. Bronchoscopic procedures for possible identification of causative pathogen(s) are not recommended during initial evaluation even in patients requiring ICU admission. They may be considered at a later stage in patients with non-resolving pneumonia and suspected bronchial obstruction. Measurement of blood urea is required for assessment of severity of pneumonia and prognostic scoring in patients who are old and appear ill with increased respiratory rate or hemodynamic instability. Appropriate investigations would also

be required for evaluation of co-morbidities. A CT-scan of the chest may be required in patients with unusual radiological findings, poor response to treatment, suspected underlying bronchial obstruction, pulmonary cavitation or pleural complications, or interstitial pneumonia. Several investigators have evaluated the utility of serum markers C-reactive protein (CRP) and serum procalcitonin in diagnosis (bacterial, atypical pathogen or viral), gradation of severity, prognosis and decision regarding duration of antibiotic therapy in CAP (5) but routine use of these investigations does not appear cost-effective in the Indian context.

Treatment of CAP is based on empirical antibiotic therapy which is tailored to cover the most likely pathogens in a given patient taking into account age, underlying lung disease, co-morbidities, previous antibiotic or steroid therapy, immune status and the severity of illness. *Streptococcus pneumoniae* continues to be the most frequent pathogen responsible for pneumonia at all ages and in immuno-competent as well as immuno-suppressed individuals. A β-lactam antibiotic such as amoxicillin, usually in combination with clavulonic acid, cefuroxime axetil or cefpodoxime would be adequate for treatment of ambulatory patients. This may be combined with a macrolide (clarithromycin or azithromycin) or doxycycline to cover atypical pathogens. These agents may be used as stand alone therapy as they also are effective against *Streptococcus pneumoniae,* particularly if there is no underlying cardiopulmonary disease. Levofloxacin and newer fluoroquinolones are also effective against atypical pathogens as well as DRSP but it should be used cautiously in India where prevalence of tuberculosis is high. Concern regarding DRSP in India is perhaps unnecessary since organisms with intermediate sensitivity to respond to β-lactams. Parenteral antibiotics are recommended for patients with more severe CAP who require hospitalization. Intravenous ceftriaxone, cefotaxime and co-amoxyclav in combination with a macrolide are a reasonable choice but there are other options including levofloxacin. Anti-pseudomonas and anti-staphylococcal cover should be considered in patients with modifying risk factors in the ICU. Patients suspected to have aspiration pneumonia would need metronidazol or clindamycin to cover probable anaerobic pathogens. In general, the risk of resistance to a particular antibiotic increases if that agent has

been used by the patient in the past three months; this is particularly true for fluoroquinolones. One may therefore "rotate" antibiotics in a given patient in case of recurrence of infection within 3 months.

Management of a patient with CAP requires decisions regarding the need for hospitalization (in regular ward or in the ICU), use of intravenous antibiotics, monitoring of vital parameters, diagnostic investigations, and appropriate time to switch to oral therapy and discharge from the hospital. All decisions should be made in consultation with the patient and responsible family members who would provide social support after discharge. Advance directives regarding resuscitation in patients with multiple co-morbidities who appear terminally ill should also be obtained and documented.

Recognizing the burden of disease in the community and need for clarity on several issues related to diagnosis, prognosis and management of CAP in India, the National Academy of Medical Sciences sponsored a continuing medical education program which was organized as a National Symposium on 23rd December, 2007 under the aegis of NAMS-Regional Telemedicine Education Center (North) by the Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh. Speakers as well as the audience from three different centers interacted throughout the day-long presentations. The present issue of the Annals of the National Academy of Medical Sciences incorporates contributions at this symposium by the speakers from PGIMER Chandigarh, Postgraduate Institute of Medical Sciences, Rohtak, and Indira Gandhi Medical College, Shimla. I am sure the readers of Annals would find proceedings of the symposium useful and informative.

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Community Acquired Pneumonia - Definitions, Epidemiology And Risk Factors

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Abstract

Community-acquired pneumonia (CAP) refers to an infectious process resulting from the invasion and overgrowth of microorganisms in lung parenchyma in a non-hospitalized population. Occurrence of respiratory symptoms or signs in the presence of a chest infiltrate is essential for the diagnosis of CAP. CAP occurs in all age groups but children less than 5 years, the elderly and those with underlying risk factor(s) are particularly susceptible. CAP may be classified and managed by morphological patterns, etiological organism and empirical 'host-organism pattern' approach. Host factors play an important role in determining the severity of CAP and certain risk factors are associated with specific disease patterns and specific microorganisms.

Key Words: Community-acquired pneumonia, risk factor, epidemiology, etiology, micro-organism

Definitions

Pneumonia is a heterogeneous entity defined on the basis of the situation in which it is diagnosed, the etiological organism and co-morbidity in the host. Pneumonia is commonly classified as community- acquired or nosocomial (hospital acquired),

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depending on the environmental setting in which it is acquired. Ventilator associated pneumonia is a specific type of nosocomial pneumonia seen in the intensive care unit. Pneumonia may occur in healthy individuals or in those who are immunosuppressed or have a variety of comorbidities and risk factors. Community-acquired pneumonia (CAP) refers to an infectious process resulting from the invasion and overgrowth of microorganisms in lung parenchyma in a non-hospitalized population. Occurrence of respiratory symptoms or signs in the presence of a chest infiltrate is essential for the diagnosis of CAP (1). Lung infiltrates are sometimes not evident on frontal radiography but computed tomography which may reveal such occult infiltrates is seldom required for routine diagnosis (2). On the contrary, pneumonia occurring 48 hours or more after admission, and not incubating at the time of admission is referred to as hospital-acquired pneumonia (HAP). Pneumonia arising more than 48-72 hours after endotracheal intubation is called ventilator-associated pneumonia (VAP).

CAP may be approached by morphological patterns, etiological organism and empirical 'host-organism pattern' approach. Etiologically, the most common bacterial causes of CAP include *Streptococcus pneumoniae,* and *H. influenza, Brahmanella Catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila.* The last 3 organisms are referred to as *atypical* pathogens. Enteric gram-negatives, *Staphylococcus aureus,* anaerobes, *Ps. Aeruginosa,* viruses, mycobacteria and fungi are unusual causes of CAP and constitute less than 5% of cases together.

The diagnosis is often clinical. A retrospective study found that ICD-10 codes had only moderate sensitivity for diagnosis (3). The accuracy of coding data to identify laboratory confirmed pneumococcal pneumonia depends upon case-definitions. Therefore to maximize the sensitivity of diagnosing by medical chart review, it is important to use a combination of many ICD-9-CM codes (4).

CAP is also defined on the basis of its response to therapy. Some of these terms which are commonly used but imprecisely defined include 'progressive pneumonia', 'slowly-resolving' or 'non-responding pneumonia' and 'non-resolving pneumonia'. With appropriate antibiotics, resolution of symptoms begins at 48-72 hours. The lack of complete radiological resolution at 12 weeks is described as 'non-resolving pneumonia' (5, 6).

Epidemiology

CAP is an important cause of morbidity and mortality world-wide. In the United States, pneumonia is the sixth leading cause of death. The disease affects all age groups but particularly the children under the age of 5 years, the elderly and those with an underlying risk factor. The annual incidence in those aged above 65 years is estimated between 25 and 55 cases per 1000 while the overall annual incidence of CAP is about 2%. In the U.S., the overall attack rate is about 12 cases per 1000 persons per year. The incidence is also high in people living in old-age homes or other similar institutions.

The prevalence is reported as high in the developing countries. Of 15 million deaths in children from acute respiratory infections worldwide, about a third result from pneumonia. This is attributable to both the environmental and the host risk factors. There are limited data on the epidemiology and population prevalence of CAP in India. Whatever data is reported is drawn from the hospitalized patients (7). A few other hospital based studies are also reported on clinical and/or microbiological features of atypical forms of CAPs, such as the Mycoplasma and Chlamydia pneumonia especially in children (8-10). Mycoplasma pneumonia was reported in 27.4% of 62 children admitted with CAP in a one year period in Delhi – only 4 (6.4%) were reported as seropositive for Chlamydia (11).

Streptococcus pneumoniae remains the most common cause of CAP in India as anywhere else in the world. In a multicentre hospital surveillance for *Strep pneumoniae*, in six hospitals in India over a period of 4 years, there were 3686 cases with suspected pneumonia and the clinical syndrome of pneumonia was identified in 93 out of 314 cases (29.6%) with invasive pneumococcal disease (12). A 19% case fatality of pneumonia was also described (12). In our own analysis of 167 patients of CAP admitted in the Respiratory Intensive Care Unit (RICU) over a 7-year period (Fig 1), 68 (40.7%) had died after an average hospital stay of 8 days (unpublished data).

Causes and Risk Factors

The pathogenesis of CAP involves an imbalance between the pathogen's invasiveness and the host immunity. What Louis Pasteur had said more than a hundred years ago about the host factors, is revealing: "The germ is nothing; the soil is everything". In general, there are numerous host factors which predispose to CAP. While the virulence of the microorganism

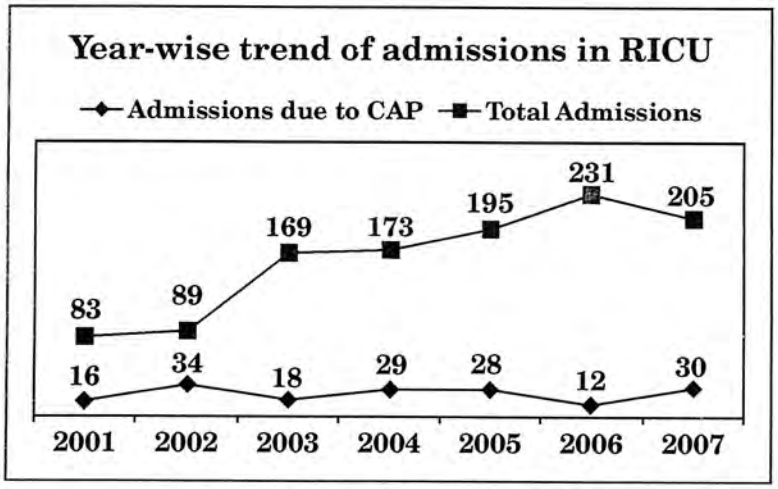

Figure 1: Year-wise number of patients with CAP against total admissions in the RICU at the PGIMER, Chandigarh

depending upon the group, the strain and the type is the root cause of infection, the host factors determine the occurrence and the severity (13). Infants, young children and the elderly are the most vulnerable. There are several predisposing and disease modifying factors which include the presence of a systemic illness, a behavioral problem or an extraneous environmental exposure (Table 1).

Table 1: Important host factors responsible for CAP

A.	Pre-disposing factors: Chronic Obstructive Pulmonary Disease, Diabetes mellitus, congestive heart failure, coronary artery disease, malignancies, neurological, renal or liver disease.
B.	Modifying factors: include those factors which increase the risk of infection with drug resistance and unusual pathogens:
	a. Age > 65 years
	b. β-Lactam therapy within past 3 months
	c. Immunosuppression
	d. Multiple medical co-morbidities
	e. Alcoholism
	f. Exposure to children in day care centres

Table 2: Risk factors linked to CAP with less common microorganisms

A.	Enteric gram negative infection
	a. Recent antibiotic therapy
	b. Underlying cardiopulmonary disease
	c. Residence in a nursing home
	d. Multiple medical co morbiditics
B.	*Ps.aeruginosa* infection
	a. Structural lung disease
	b. Antibiotic therapy for > 7 days in the past month
	c. Corticosteroids (at least 10 mg prednisolone/day)
	d. Malnutrition
C.	Drug-resistant *Streptococcus* pneumonia (DRSP)
	a. Sicker inpatient population
	b. Immuno-compromised patients
	c. New procedures & instrumentation
	d. Emerging pathogens
	e. Complacency regarding antibiotics
	f. Ineffective infection control and compliance
	g. Increased antibiotic use
D.	*Staph aureus* pneumonia
	a. Advanced age
	b. Prolonged hospitalization
	c. Underlying lung disease
	d. Prior antibiotic therapy
E.	Anaerobic bacterial pneumonia
	a. Aspiration
	b. Presence of gingivitis
	c. Bronchopleural fistula
	d. Pneumonia complicating bronchial obstruction

Some risk factors are also identifiable for specific types of CAPs caused by different microorganisms. For example specific risk factors for pneumococcal infections include dementia, seizures, HIV infection and systemic illnesses such as the chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and cerebrovascular disease (14, 15). *Haemophilus influenzae* is most common in patients with an underlying COPD and the use of antibiotics or oral corticosteroids within the past 3 months (16, 17). The risk factors for some of the relatively uncommon CAPs such as those caused by pseudomonas, *Staph aureus*, gram negative bacteria, drug resistant *Streptococcus pneumoniae* (DRSP) or anaerobic organisms are generally identifiable (Table 2) (18-22).

Immunosuppression with drugs or HIV infection is an important risk factor on the rise in the recent years. *Strep pneumoniae* and *H. influenzae* are the common organisms in the developed as well as the developing world (23, 24). Such patients are also likely to develop CAPs with different atypical organisms including the mycobacteria, the viruses (such as the cytomegalovirus, herpes simplex, influenza virus and respiratory syncytial virus) and the fungi (25, 26). In a recently published study from Chennai in South India on 200 HIV-positive adults with CAP and 75 HIV-negative adults with CAP, the prevalence of *M. pneumoniae* in HIV-positive patients was higher (17%) by induced sputum examination (27). The sero-prevalence of anti-*M. pneumoniae* Ig M was 11.7% and 14.3% respectively by ELISA and gelatin micro-particle agglutination test (27) in the two groups.

Tuberculosis is another important respiratory infection in HIV positive patients which may present with pulmonary infiltrates and clinical features of CAP (28-30). Tuberculosis therefore requires to be kept in the differential diagnosis of CAP in all immuno-suppressed patients especially those with HIV infection.

Conclusions

CAP remains an important cause of morbidity and mortality world-over. Diagnosis is often clinical, although radiologic confirmation is desirable, if readily available. Data on the epidemiology and population prevalence of CAP from India, despite being limited, suggest that pneumococcus remains the most common etiological agent. It is important to identify risk factors and other host factors in patients with CAP since these are known to influence the responsible etiological agents as well as presentation and course of the disease.

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Clinical Features of Community Acquired Pneumonia

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Abstract

The common symptoms of community acquired pneumonia (CAP) include fever with chills and/or rigors, productive cough, dyspnoea and pleuritic chest pain. These are typically of less than one week duration. Presence of bronchial breath sounds, whispering pectoriloquy, localized crackles and tachypnoea are important signs. However, host and microbial factors can alter the presentation of CAP such that typical symptoms and signs may not always be present. Even the onset of symptoms and their mean duration before presentation may vary in such cases. This is particularly true in extremes of ages and presence of comorbidities. Mental confusion and disorientation is a common feature in the elderly who may not manifest with the classical clinical features. Gastrointestinal symptoms are most often reported in atypical pneumonia. Assessment of severity is essential to determine the optimal site for management. Although several severity assessment tools have been proposed, presence of shock and/or acute hypoxemic respiratory failure invariably mandates admission to an intensive care unit. In less severe cases, the decision to hospitalize may be individualized with the help of any of the severity assessment tools available as well as other adverse prognostic factors.

Key Words: Community acquired pneumonia, severity assessment, symptoms, signs, prognostic factor.

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Introduction

While evaluating patients of community acquired pneumonia one should obtain detailed history with particular emphasis on the following features which would be helpful in making a probable etiologic diagnosis and initiating empirical antimicrobial therapy at the earliest.

1. The clinical settings in which pneumonia has occurred
2. Defects in host resistance that could predispose to the development of pneumonia (e.g. co-morbidities)
3. History of possible exposure to specific pathogens

While taking history, one should also look into the type of onset and the mean duration of symptoms before presentation. It has been seen that pneumococcal pneumonia generally has the shortest duration of symptoms before presentation. Helms *et al* (1) observed that the mean duration of symptoms was 2.9 days with pneumococcal pneumonia, 4.6 days with Legionella pneumonia and 12.6 days in case of pneumonia due to *Mycoplasma pneumoniae* infection. However, in elderly population, a clear history about the time of onset of illness is less often elicitable.

Symptoms and Signs of CAP

Symptoms of CAP include abrupt onset of fever with chills and rigors, cough with expectoration, shortness of breath and pleuritic pain. Mental confusion occurs more frequently in the elderly and is an adverse prognostic factor. Physical examination may reveal tachypnoea and a localized area of bronchial breath sounds, inspiratory crepitations and whispering pectoriloquy. Presence of cyanosis, respiratory rate > 30 breaths/ minute and hypotension are adverse prognostic factors.

Fever

Though fever has been reported in upto 87% patients of community acquired pneumonia, it is a non – specific feature. Febrile response may be observed less commonly in elderly patients which may make early diagnosis difficult. Absence of fever in bacteremic cases of pneumonia may be associated with poor prognosis. Chills are more frequently encountered in pneumonia than rigors. Rigors are more frequently observed in pneumococcal pneumonia (62%) with a higher rate in younger patients. It is less frequent in elderly and in atypical infection.

Cough

Cough is one of the most frequently reported symptoms (88%) in community

acquired pneumonia. It is less frequently noticed in the elderly. In a comparative study (1) it was found that the incidence of cough was maximum in subjects with Mycoplasma pneumonia (100%), whereas in pneumococcal pneumonia it was observed in 83% cases and in only 50% cases in case of Legionella pneumonia.

In patients admitted with CAP, cough is often associated with sputum production (50-60%) and about half of these reported purulent expectoration. Occasionally the colour of sputum may provide some clue in making possible etiologic diagnosis. Rusty (bloody) sputum is classically noted in pneumococcal pneumonia but it may sometimes be seen in other suppurative infections and in patients of community acquired pneumonia taking anti coagulation therapy. Similarly, Klebsiella pneumonia patients often show red currant- jelly sputum.

Dyspnoea

Presence of dyspnoea often varies widely in different studies with a reported range of 40-90%. There are different mechanisms in the causation of dyspnoea in community acquired pneumonia. First dyspnoea may be due to hypoxemia and tachypnoea. Secondly, it may be due to stimulation of stretch receptors in areas of lungs with decreased compliance due to consolidation. Third, about 40% of patients of community acquired pneumonia develop parapneumonic effusion and dyspnoea may be due to decreased thoracic excursions from pleuritic chest pain. Elderly subjects with CAP may have decreased perception of dyspnoea which may be responsible for delay in making diagnosis in this subset of patients.

Pleuritic Chest Pain

It has been reported in 31-72% cases of community acquired pneumonia. It is most frequently observed in cases of pneumococcal pneumonia, prevalence of chest pain decreases with age.

Gastrointestinal symptoms are most often reported in pneumonia caused by atypical pathogens. Most commonly reported symptoms are nausea, vomiting, anorexia, diarrhea etc. Some patients may present with myalgia (27%), arthralgia (16%) and headache (29%). Coryza and sore throat are more common in acute bronchitis than in pneumonia. In a study done at our institute amongst CAP patients (2), the most frequently reported symptoms were fever (90%), cough (97%) and pleuritic chest pain (34%). Altered sensorium was noted in 8.5% cases.

Crackles

Crackles are observed in upto 80% of patients with community acquired pneumonia on admission. This sound is due to reopening of distal atelectatic lung units during inspiration. In a study by Lehtomaki *et al* (3), crackles were more prevalent in mixed infection (70%) and pneumococcal pneumonia (63%) but less common in adenoviral infection (27%). Piirila *et al* (4) showed that characteristic of crackles undergo changes during the course of pneumonia. Initially they were mid inspiratory but after 3 days they were heard later in inspiration.

In the elderly, pneumonia often presents with different signs and symptoms than in younger patients. Classical pneumonic symptoms are often absent or minimal. They often present with extra pulmonary symptoms like weakness, confusion, incontinence of urine, etc. This atypical manifestation of pneumonia in the elderly may be due to impairment in host defense mechanism.

Mycoplasma Pneumonia

Mycoplasma pneumonia often presents with multiple extra pulmonary manifestations which may be due to development of humoral immune response. Japanese respiratory society proposed a guideline in 2006 for identifying pneumonia caused by atypical pathogens (Table 1). (5)

Table 1: Differential diagnosis of atypical pneumonia and bacterial pneumonia

1. Age < 60 years old		
2. No or mild co-morbidity		
3. Persistent cough		
4. Limited chest auscultatory findings		
5. No expectoration or pathogens on rapid diagnostic tests		
6. WBC count < 10,000/mm^3		
Differential diagnosis	**Atypical suspect**	**Bacterial suspect**
1 - 5 items	≥ 3 parameters	≤ 2 parameters
1 - 6 items	≥ 4 parameters	≤ 3 parameters

Severity Assessment

Assessment of the severity of community acquired pneumonia is essential to decide the site of care. There are several severity assessment criteria available including Pneumonia severity index (PSI), CURB – 65 (British Thoracic Society; BTS), modified American Thoracic Society (ATS) criteria and IDSA-ATS guidelines 2007.

Modified ATS Criteria (6)

Admission to the ICU is needed for patients with severe CAP defined as the presence of either one of two major criteria, or the presence of two of three minor criteria. The major criteria include need for mechanical ventilation and septic shock; the minor criteria include systolic blood pressure (BP) = 90 mm Hg, multilobar disease, and PaO_2/FiO_2 ratio < 250.

IDSA-ATS Guidelines (7)

In 2007 Infectious Disease Society of America (IDSA) published guidelines for the management of community acquired pneumonia and they proposed severity assessment criteria (Table 2) to identify the optimal site of care for pneumonia patients. Direct admission to ICU is recommended in patient with one major criterion or three of the minor criteria for severe CAP.

CURB-65 (8, 9)

This is a constellation of five "Core" clinical adverse prognostic factors, proposed by BTS.

- **C**onfusion (new onset)
- **U**rea (>7 mmol/L or 42 mg/dL)
- **R**espiratory rate (>30/min)
- **B**lood pressure (systolic BP <90 mm Hg *and/or* diastolic BP <60 mm Hg)
- **65** years or more (age)

Patients with a CURB-65 score of =3 are at high risk of death and should be considered to have severe CAP. Those with a score of 2 are at some increased of risk of death and should be considered for inpatient treatment while those with a score of 0 or 1 are at low risk of death and may be suitable for home treatment. In addition, there are two other clinical adverse prognostic factors, which if present, indicate severe CAP and the need for hospitalization:

- Hypoxaemia: SaO_2 <92% or PaO_2 <8 kPa (60 mm Hg) regardless of FiO_2
- Bilateral or multilobe involvement on chest radiograph

In routine practice, it is easier to measure CURB - 65 as less number of variables are needed to be measured.

Table 2: Severity assessment criteria of pneumonia proposed by IDSA and ATS

Major Criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors
Minor Criteria
Respiratory rate = 30 bpm
PaO2/FiO2 = 250
Multilobar infiltrates
Confusion/ disorientation
Uremia (BUN = 20 mg/dl)
Leukopenia < 4000 cells/ mm3
Thrombocytopenia (platelet count < 100,000 cells /mm3)
Hypothermia (core temperature < 36° C)
Hypotension requiring aggressive fluid resuscitation
Other Minor Criteria
Hypoglycemia in non diabetic
Acute alcoholism or alcohol withdrawal
Hyponatremia
Unexplained metabolic acidosis
Cirrhosis
Asplenia
ICU admission indicated for patients with:
≥ 1 major criterion
≥ 3 minor criteria

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Community Acquired Pneumonia - Radiological And Microbiological Diagnosis

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Abstract

This article addresses the role of radiological and microbiological tests in community acquired pneumonia (CAP). The main utilities include diagnosing the presence of CAP, assessing its severity and identifying the causative agent. Plain chest radiograph (CXR) remains the conventional imaging modality for establishing the diagnosis of CAP. However, it is not 100% sensitive and lacks specificity to identify the microbiological cause. Presence of specific patterns on CXR can suggest the likely etiological agent(s). Identifying the causative organism in blood and/or sputum cultures can help to narrow down the spectrum of antibiotic(s) to be used and thus reduce the risk of development of antibiotic resistance. However, problems with sample collection, storage, processing and isolation techniques limit their sensitivity and specificity. The etiology of CAP is often difficult to establish since the most effective methods are often invasive and serological methods yield results that are too late to be of any therapeutic use. Even after extensive evaluation, the causative agent remains unknown in about 50% of cases. Current recommendations therefore suggest that various microbiological and serological tests should be used only in patients with CAP who have severe disease, are hospitalized, have comorbidities and do not respond to empiric antibiotic therapy.

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Key Words: Community acquired pneumonia, chest radiograph, blood culture, sputum culture, serology, etiology, diagnosis

Introduction

Pneumonia is a microbial infection involving the terminal airways and alveoli of the lung (1). Community acquired pneumonia (CAP) remains a common and serious illness with significant morbidity and mortality (2). In U.S. it results in more than 5 millions hospital admissions annually and is the sixth leading cause of death (3). The problem is even greater in developing countries where it is the most common cause of hospital attendance in adults (4). Despite its high incidence and availability of large number of studies on this common entity, there are still controversies about certain issues of evaluation and management. The cause of CAP is often difficult to establish. The most effective methods are often invasive and serological diagnosis is too late to be of any therapeutic use (5). It takes few days to identify the causative organism in blood or sputum and even after extensive evaluation, causative agent remains unknown in about 50% of cases (3,6). Diagnostic tests have a role in three aspects of CAP namely (i) to diagnose presence of CAP, (ii) to assess the severity and (iii) to identify the causative agent of CAP. This article addresses the radiological and microbiological tests for CAP.

Radiological Diagnosis

The reference standard for diagnosis of CAP is Chest X-ray. However it is not 100% sensitive and lacks specificity to identify the microbiological cause. Usually alveolar densities indicate presence of typical pneumonia (i.e. bacterial) and patchy or interstitial densities suggest atypical infection. But this categorization is not always accurate (7). Nevertheless they can suggest a microbiological differential diagnosis (Table 1).

Non-segmental air space (focal or lobar) pneumonia is seen on radiographs as homogenous consolidation having sharp demarcation. Patent large bronchi are seen as classical *air bronchogram sign*. The fissure may bulge if exudate is extensive. This is classically seen in Pneumococcus and *Klebsiella* infections. Necrosis (pulmonary gangrene) is seen as small lucent areas within consolidation; if extensive they may coalesce resulting in large cavity (Fig.1).

Bronchopneumonia classically caused by *Staph. aureus* is seen as focal, peribronchial or peribronchiolar areas of consolidation which may be bilateral (Fig.2).

Table 1. Radiographic Presentations of Common Etiologic Agents

Chest Radiographic Pattern	Pathogen
Focal; large pleural effusion	Usually bacterial
Cavitary	Bacterial abscess, fungal, acid-fast bacilli (AFB), *Nocardia*
Miliary	AFB, fungal
Rapid progression/multifocal	*Legionella,* pneumococcal, staphylococcal
Interstitial	Viruses, *Pneumocystis, Mycoplasma, C psittaci*
Mediastinal widening without infiltrate	Inhalation anthrax

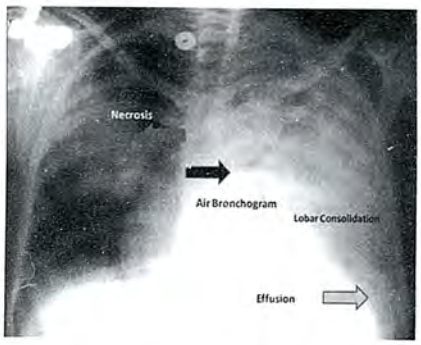

Figure 1

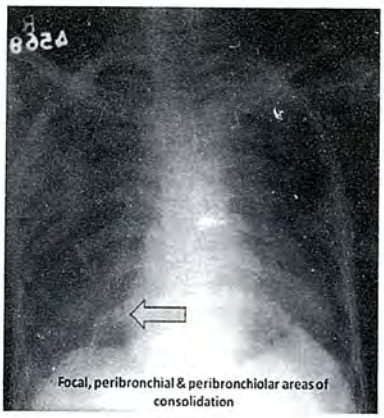

Figure 2

Interstitial pneumonia is seen as reticular or reticulonodular opacities. There may be prominent septal lines (Fig. 3).

Lung abscess is seen as single or multiple masses with cavitations which may have air fluid levels. The inner wall

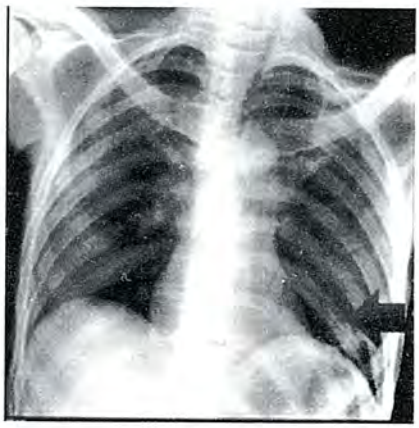

Figure 3. Interstitial pneumonia with ground glass haziness in *P. jirovecii* infection in a patient of AIDS

is relatively smooth with surrounding area of consolidation (Fig. 4).

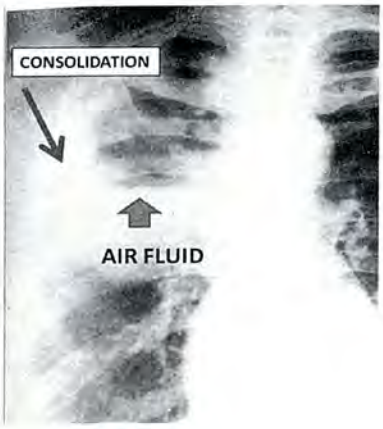

Figure 4

Fig. 5 depicts multiple small lung abscesses in both lung fields without air fluid levels usually seen with staphylococcal infection.

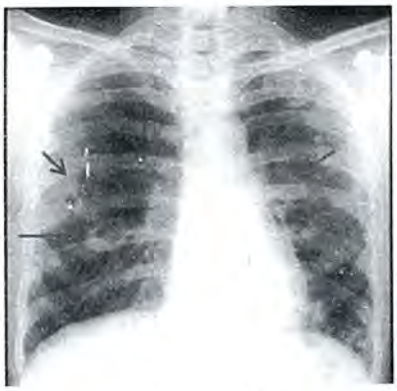

Figure 5

CT scan is not required in most cases. However it can be helpful in more complex situations such as strong suspicion of pneumonia clinically but no opacity on chest x-ray, complication of CAP like bronchial obstruction, lymphadenopathy or empyema, delayed resolution or in immunocompromised patients. Fig. 6 displays interstitial infiltrates with ground glass haziness more clearly seen than in Fig. 3. Further CT scan helps in excluding alternative diagnosis like pulmonary embolism.

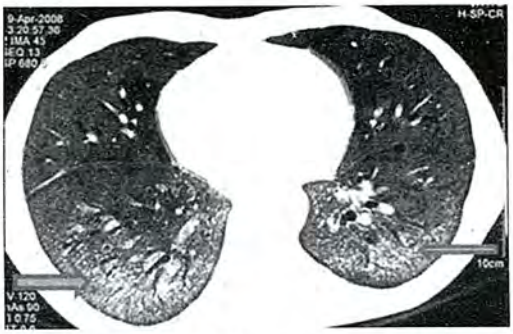

Figure 6. HRCT scan of the same patient as in Figure 3 showing clear-cut interstitial infiltrates (arrows)

Resolution of radiological opacities usually takes place in 10-14 days. In a series complete radiographic clearing of pneumonia occurred in 50% at 2 weeks and in 66.7% at 4 weeks (8). However a gamut of host and pathogen related factors affect resolution rates. Advanced age, smoking and various co-morbid conditions like diabetes, congestive heart failure, COPD, renal failure, malignancies, steroid use and immunosuppression all serve to delay resolution of pneumonic process (9). Likewise resolution was delayed in in-

hospital treated patients (Vs OPD patients), in patients with co-existent bacteremia and with multilobar involvement (9). Resolution time also varies depending uon the infectious agents causing pneumonia. Pneumococcal pneumonia usually gets resolved within 6 weeks whereas *Legionella* pneumonia may take 2-6 months to resolve. *Mycoplasma* infections usually resolve quicker than pneumococcal infections (10).

Radiography also provides a clue to the severity of the disease. Multilobar distribution and presence of complicating factors like pleural effusion and abscess formation indicate severe disease. It should be however noted that radiographic manifestations of chronic diseases such as congestive heart failure, COPD or malignancies may confound the infiltrate of pneumonia.

Microbiological Tests

Ideally speaking, identification of causative agent of pneumonia has many beneficial implications. It results in targeted narrow spectrum antibiotic treatment and hence less chances of antibiotic resistance, determines appropriate duration of treatment and provides accurate data for epidemiological studies. But because of delay in initiating treatment, various complications of invasive procedures in collecting samples and often unneeded antibiotic changes their cost effectiveness is debated. Currently available diagnostic tests for microbiological diagnosis include Sputum Gram Stain, Blood Culture, Sputum Culture, Serological studies, Antigen studies, Polymerase Chain Reaction (PCR).

These tests may be carried out on expectorated sputum or material obtained by invasive methods such as bronchoscopy on transthoracic needle aspiration of lung.

Sputum Gram Stain

The value of sputum gram stain is considerable but controversial. It is a cheap, readily available and rapid technique that may provide a tentative identification of pathogen and helps in guiding initial use of antibiotics. The main problem with gram staining of sputum is that due to contamination from upper respiratory tract sputum may not accurately represent lower respiratory tract infection. Murray and Washington (11) have suggested that presence of <10 squamous epithelial cells and >25 PMN's per low power (10X) field in sputum specimen is highly suggestive of secretions from lower respiratory tract. Interpretation of findings of gram stain is also difficult.

Sputum positivity has been defined on finding a predominant organism, an organism present in greater than 10 oil immersion fields, an organism that account for >50% of those seen or a combination of last two criteria (12). Some organisms like *Haemophilus* and *Neisseria* are difficult to identify on gram stain. Moreover gram stain fails to detect atypical organisms. Keeping in view these drawbacks, sputum gram stain should be used in a targeted fashion particularly in patients with severe CAP, immunosuppression, or in those who fails to respond to initial antibiotic treatment.

Blood Culture

Blood culture has low diagnostic yield (5-16%) (13) but high specificity. It must be done before the start of treatment. As many cases of CAP are due to mixed infections, it also misses the co-infection with atypical agents. Despite these limitations ATS & IDSA recommend that blood culture should be included in diagnostic work up if patient requires hospital admission.

Sputum Culture

This procedure encounters same problems as with gram stain such as inability of many patients to expectorate sputum and contamination of sputum with oropharyngeal secretions. This leads to low sensitivity and specificity of sputum culture results. Also isolation techniques for atypical pathogens and viruses are not easily available. To improve sensitivity and specificity of culture results comparison with gram staining is advisable. Although washing of sputum with saline before culture and quantitative culture techniques have been advocated by some, they are time consuming and are not widely available (12).

Serological Studies

These tests are more relevant for atypical pathogens like *Legionella, Mycoplasma* & *Chlamydia* which are not detectable by gram stain or routine cultures. They add little to management decisions because to be positive they require a four fold rise in acute and convalescent phase sera. Their main value is in collection of epidemiological data.

Antigen Studies

Various tests are available which can be performed on sputum, urine or serum. Prior antibiotic therapy does not affect results and they remain positive long after treatment. But these are rapid, simple and have high specificity. Urinary antigen test for *L. pneumophilia* type I has sensitivity of 70% & specificity of 100% (14). These tests are also available for *S. pneumoniae* and can be performed on sputum, urine or serum and its specificity is >90%.

Polymerase Chain Reaction

It can detect even minute quantities of organisms in various samples like sputum or serum. The results are not affected by prior antibiotic therapy. Also it can detect the antibiotic susceptibility of microbes by noting differences in DNA sequences of antibiotic susceptible and resistant strains. However it is a complex and time consuming technique which is not easily available. False positive results may be obtained if contamination occurs in laboratory or from upper respiratory tract. Until recently the only PCR assay for respiratory pathogens that was approved by US FDA was for diagnosis of *M. tuberculosis* on specimens which are positive for AFB (9). FDA has recently approved a new PCR assay for detection of all serotypes of *Legionella* in sputum (IDSA/ATS 2007) (15). Still in the developmental stage, PCR may become the ideal diagnostic test for CAP giving accurate identification of pathogen & finding its antibiotic susceptibilities.

Invasive Procedures

These include thoracocentesis, transtracheal aspiration, fibreoptic bronchoscopy, transthoracic needle aspiration, open lung biopsy and thoracoscopic biopsy. Generally they require consideration of risk-to-benefit and cost-to-benefit ratio and are reserved for patients with severe CAP particularly who are immuno-compromised. Thoracocentesis is required in patients with significant pleural effusion regardless of severity of CAP.

Recommendations

As already mentioned the diagnostic tests for CAP fall into three categories helping in diagnosis, assessment of severity and identification of causative agent. If a patient is suspected of having CAP, he/she should have a chest x-ray to confirm the diagnosis. Assessment of severity should be done using Chest x-ray, CBC, blood chemistries, oxygen saturation and blood gas analysis. As most patients do well on empirical treatment (16), there is absence of any statistically significant difference in mortality rates or duration of hospital stay between those receiving pathogen directed and those receiving empirical therapy (17). Because of lack of an ideal test till date, the identification of causative agent is the most difficult and controversial aspect. The intensity of diagnostic work up should take into account the following aspects: (1) severity, (2) response to treatment, (3) level of immune competence and (4) factors related to patients and environment. A general guideline is presented. (Table 2)

Table 2 : Diagnostic Tests for CAP (15)

Patient Category	Chest x-ray	Sputum Gram Stain & Culture	Blood Culture	Urinary Legionella/ Pneumo. Antigen	Serologic studies	Invasive Procedures
Ambulatory	√					
Hospitalized	√	√	√			
Severe CAP	√	√	√	√	?	?
Immuno-compromised	√	√	√	√	?	√
Treatment Failure	√	√	√	√	?	√

? = may be appropriate depending on clinical picture

Conclusion

Diagnostic tests play an important part in evaluation and management of CAP. There is still a lack of ideal diagnostic test for microbial diagnosis but when applied to properly selected group of patients, these tests may prove more cost-effective.

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Management of Community Acquired Pneumonia

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Abstract

Appropriate antibiotic therapy remains the cornerstone of management of community acquired pneumonia (CAP). Even though this is mostly empiric, host, microbiological and epidemiological factors should be taken into account while deciding the antimicrobial agent(s) to be used. Available data from India suggests that the prevalence of drug resistant *Streptococcus pneumoniae* (DRSP) in the community is at present negligible and therefore treatment failure is unlikely to result if penicillin derivatives are used for treatment of CAP in previously healthy individuals with no risk factors for drug resistance. It is important to choose antibiotics judiciously in order to prevent the development of drug resistant strains. Irrational and unnecessary prescriptions especially those involving newer/ costlier antibiotics or their combinations should be avoided since these are not superior in efficacy. Some patients with CAP present on rapidly progress to acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (MV). Mortality in these patients can exceed 50% and hence they should be managed in an intensive care unit (ICU) setting. The mainstays of management of CAP associated with AHRF are oxygen therapy,

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antibiotics and ventilatory support (when needed). Most patients with severe CAP and ARDS require invasive MV. The open lung approach should be used during MV.

Key Words: Community acquired pneumonia, antibiotic, acute respiratory distress syndrome, acute hypoxemic respiratory failure, mechanical ventilation

Introduction

The cornerstone of management of community acquired pneumonia (CAP) remains appropriate antibiotic therapy. However, treatment needs to be rational and evidence-based to prove beneficial to the patient, in particular, and the community, in general. Several clinicians tend to prescribe new and costlier antibiotics to these patients, with the hope that these will prove more efficacious. However, this generally is not always true. While it is proper to initiate treatment empirically once a patient presents with CAP, several epidemiological, patient, pathogen and drug related factors must be taken into account to tailor therapy to an individual patient's needs (Table 1).

Table 1 : Important considerations influencing antibiotic treatment in patients with community acquired pneumonia

■ Spectrum of pathogens in local community
■ Severity of disease
■ Comorbidities and other risk factors
■ Outpatient or inpatient or ICU management
■ Route of administration
■ Timing of initiation
■ Duration of treatment
■ Cost of drugs

Spectrum Of Pathogens

Data on microorganisms resulting in CAP is rather limited from India, and the reasons are not hard to fathom. Based on published reports and general clinical experience, it appears that *Streptococcus pneumoniae* is the commonest bacterial pathogen responsible for CAP in India, as elsewhere (1, 2). The data on atypical microorganisms causing CAP is even more sketchy from this country. Three reports from Delhi estimated the prevalence of Mycoplasma at about 30% in children and 35% in adults (3-5). Two reports from South India suggest estimates of 11% and 28% in adults (6, 7). Another study from Shimla reported Mycoplasma prevalence at 15% (2). The

prevalence of Chlamydia infection has been variably reported between 5.5% to 6.5% among children and adults with CAP (3, 8, 9). Since these studies are largely hospital-based, and have used different laboratory tests to identify presence of atypical microorganisms, it is not correct to extrapolate these data to the general population across the entire country. All one can infer from these results is that a significant proportion of CAP in India is likely to be caused by atypical pathogens, and therefore any treatment prescription should ideally ensure that these microorganisms are adequately covered.

Drug Resistance

Another important issue is that of CAP due to bacteria resistant of conventionally used antibiotics. There has been a recent global increase in the incidence of CAP related to beta-lactam resistant pneumococcal strains. It is generally believed that India shows a similar trend, and this has notably influenced prescription habits in the recent past. Unfortunately, this assumption is not fully backed by scientific evidence. In the recent Asian Network for Surveillance of Resistant Pathogens (ANSORP) study involving eleven Asian countries, 77 pneumococcal isolates from Vellore were evaluated (10). None of the isolates studied was beta-lactam resistant (defined as MIC exceeding 2.0 mg/mL), and only 7.8% isolates showed intermediate resistance (defined as MIC 0.12-2.0 mg/mL). In contrast, the Asian isolates together had an overall resistance of 25% and an intermediate resistance of 23% (10). This data suggests that beta-lactam resistance in pneumococcus is still not a significant problem in India. Similar results have earlier been published from Pondicherry, where only 7.3% intermediate resistance (and no resistance) was observed. Although the best treatment modality for resistant bacteria is still not clear, it can be concluded that the prevalent level and nature of drug resistance is unlikely to result in treatment failure if appropriate antibiotics in proper doses are chosen. In general, age more than 65 years, beta-lactam therapy in previous three months, medical comorbidities, alcoholism, and immunosuppressive states tend to increase risk of infection by beta-lactam resistant pneumococcus.

Inpatient Or Outpatient Treatment

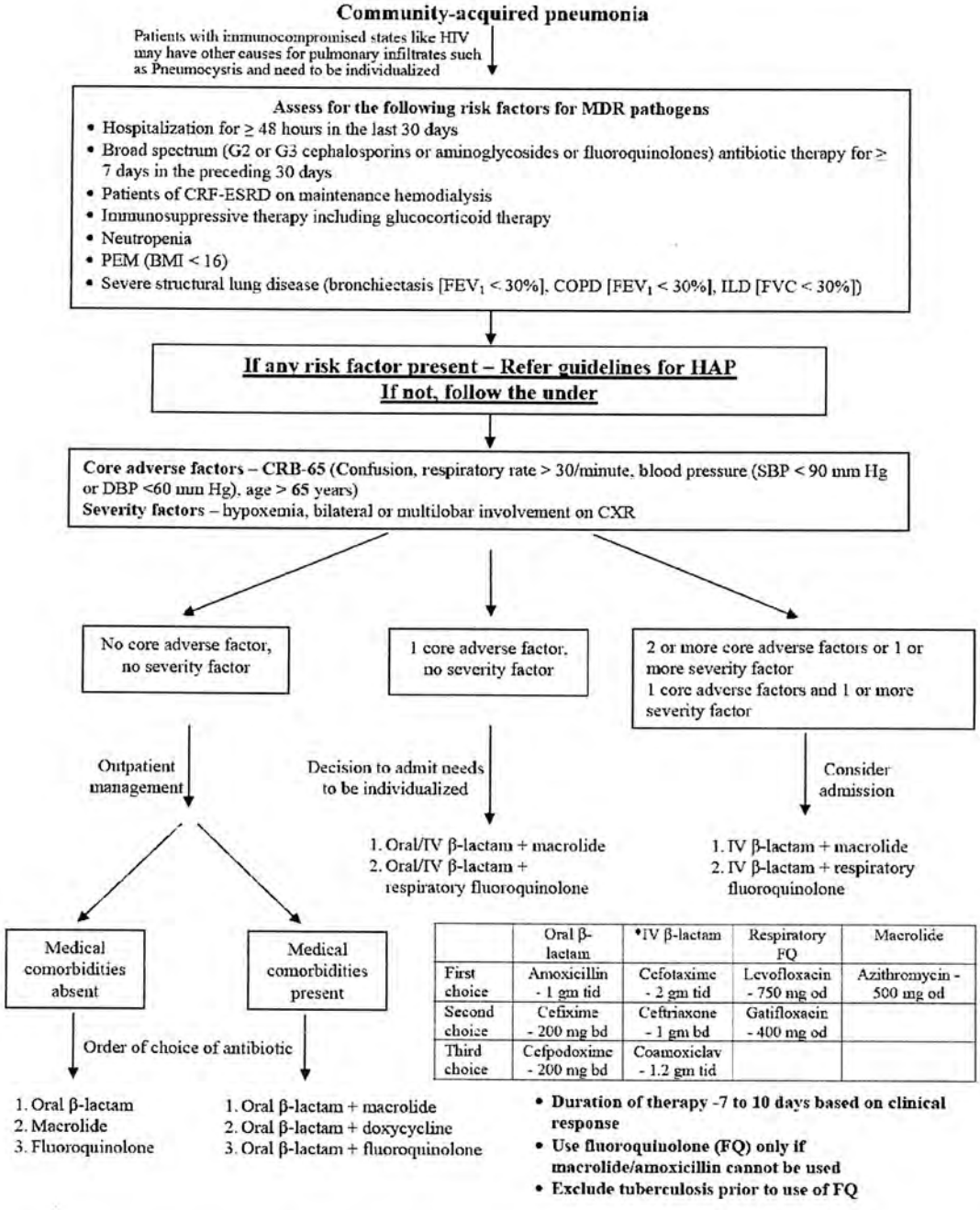
One of the most important decisions that ultimately guide antibiotic treatment is whether a patient with pneumonia needs therapy on outpatient or inpatient basis. Without doubt, the most important factor in this choice is the severity of pneumonia. However, other vital factors like presence of complications (such as lung abscess, empyema, meningitis, etc.), ability to take oral medications, and level of outpatient support

resources (such as family and social support, and distance of residence from health care service providers) are also central to this decision process.

There are several ways to assess disease severity. The judgment of treating physician is of course the most important. However, it remains largely subjective, and based on one's experience and clinical acumen. Physicians often tend to overestimate severity and hospitalize otherwise low-risk patients. It is therefore desirable that severity assessment in this fashion be supplemented by more objective and easily measurable parameters. Lately, several objective site-of-care scales have been developed for this purpose. Pneumonia Severity Index is a prognostic model developed from data on more than 14,000 patients, that classifies patients into five categories of increasing mortality risk (11). It has been suggested that Class I and II patients can be treated on outpatient basis, Class III patients should be placed in an observation unit, and Class IV and V patients should receive treatment as inpatient. However, calculation of this index is based on a large number of demographic features, patient history and examination, and laboratory variables. A much simpler score - CURB65 - takes into account only five variables (confusion, uremia, respiratory rate, low blood pressure, and age above 65 years) (12). Patient with none or one of these factors can be treated on outpatient basis, those with two factors need hospitalization, and patient with more factors often require ICU care. To make these criteria more suitable for primary level, it has also been suggested that of blood urea assessment can be altogether dropped (CRB65 score) (13) without compromising the value of the scoring system.

Empiric Choice Of Antibiotics

Antibiotic treatment for CAP is generally started empirically, as important time may be lost in submitting sputum samples for culture and awaiting microbiological results. The treatment generally aims at coverage of important pathogens (both typical and atypical) causing pneumonia in a particular group of patients. Elaborate guidelines exist to assist the clinician in selecting antibiotics suitable for a given patient. The most recent and widely followed among these were recently jointly issued by the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) (14). However, these guidelines may not be truly applicable to Indian conditions due to differences in prevalence of pathogens, drug resistance patterns, and cost and availability of antibiotics. We had recently formulated guidelines on this issue for use in India (15). This algorithmic approach (Fig. 1) serves to emphasize important differences in



	Oral β-lactam	*IV β-lactam	Respiratory FQ	Macrolide
First choice	Amoxicillin - 1 gm tid	Cefotaxime - 2 gm tid	Levofloxacin - 750 mg od	Azithromycin - 500 mg od
Second choice	Cefixime - 200 mg bd	Ceftriaxone - 1 gm bd	Gatifloxacin - 400 mg od	
Third choice	Cefpodoxime - 200 mg bd	Coamoxiclav - 1.2 gm tid		

Figure 1: Algorithmic approach recommended for use in India for patient stratification and initial empiric antibiotic choice for patients with CAP

ideal treatment practices as appropriate to the Indian clinical setting.

The initial empiric choice of antibiotics is guided by several host and pathogen factors, since different antibiotics (and their combinations) may be more suitable for specific groups of patients. A brief summary of these guidelines is provided in Table 2. Certain notable differences between the IDSA/ATS recommendations and our institutional guidelines deserve special attention. For previously healthy

Table 2: Summary of options available for initial antibiotic therapy

Patient category and site of treatment	IDSA/ATS Guidelines[14]	PGIMER Guidelines[15]
Outpatient treatment for previously healthy patients with no risk factors for drug resistant *Streptococcus pneumoniae*	Macrolide (Azithromycin or Clarithromycin) *OR* Doxycycline	Beta-lactam (Amoxicillin or Cefpodoxime or Cefixime) *OR* Macrolide (Azithromycin)
Outpatient treatment for patients with comorbidities	Respiratory fluoroquinolone *OR* Beta-lactam plus Macrolide *OR* Beta-lactam plus Doxycycline	Beta-lactam plus Macrolide *OR* Beta-lactam plus Doxycycline *OR* Beta-lactam plus Respiratory fluoroquinolone
Inpatient (non-ICU) treatment	Respiratory fluoroquinolone *OR* Beta-lactam plus Macrolide	Beta-lactam plus Macrolide *OR* Beta-lactam plus Respiratory fluoroquinolone
ICU treatment [a,b]	Beta-lactam plus Macrolide *OR* Beta-lactam plus Respiratory fluoroquinolone	Beta-lactam plus Macrolide *OR* Beta-lactam plus Respiratory fluoroquinolone

[a] In patients where Pseudomonas infection may be a consideration, antipneumococcal antipseudomonal beta-lactam (piperacillin-tazobactam, cefepime, or imipenem), plus either a fluoroquinolone (ciprofloxacin or levofloxacin) or a combination of aminoglycoside plus azithromycin, may be preferred

[b] If methicillin-resistant *Staphylococcus aureus* (MRSA) is a consideration, add vancomycin or linezolid

individuals with no risk factors for drug resistance, it may be acceptable to use penicillin derivatives as the prevalence of penicillin-resistant pneumococcus appears negligible in the community at present. On the other hand, a high proportion of strains at our institute are innately resistant to tetracycline, and hence this group of drugs should be avoided. Tetracycline derivatives may, however, be used in combination with beta-lactam antibiotics in patients with comorbidities or other risk factors for drug resistance. The use of respiratory fluoroquinolones should also be discouraged in any setting with high tuberculosis prevalence. Since similar clinical and radiological findings may be present in pulmonary tuberculosis, inappropriate administration of fluoroquinolones that possess good antimycobacterial activity as well may lead to delay in diagnosis of tuberculosis in case it is the true diagnosis. Some other drugs recommended in the IDSA/ATS guidelines are either not currently freely available in Indian market or quite expensive for routine use.

While the initial treatment is empiric, it must be suitably modified if and when a microbiological diagnosis is achieved. Therapeutic options may be simplified, and the antibiotic spectrum must be appropriately narrowed based on drug sensitivity profile.

Time To First Antibiotic Dose

Two retrospective studies in USA have shown better survival among patients of CAP who received antibiotics early (16, 17). However, prospective studies have failed to show a similar improvement in either outcome or clinical stability (18-20). It is therefore difficult to recommend a specific window period within which antibiotics should preferably be started, although the general dictum, that treatment should be initiated as early as feasible after the diagnosis of CAP is considered likely, remains valid. For patients needing inpatient care, the initial dose may be instituted prior to hospitalization (for instance, the emergency services) (18).

Route Of Administration Of Antibiotics

Critically ill patients, those with severe disease, and those unable to swallow or tolerate oral medications are preferably treated with intravenous antibiotics. An attempt must be made to switch to oral therapy as early as possible. Generally this is feasible once the patient has shown clinical improvement, is hemodynamically

stable, can ingest oral drugs, and has a well functioning gastrointestinal tract (21). Nearly two-third patients meet these criteria within three days of initiating treatment. In general, the antibiotic being administered parenterally is preferred in its oral formulation. If this is not available, then an oral antibiotic from the same drug class should be given. Once an oral switch has been made, it may not be necessary to keep the patient in hospital for further management or observation.

Duration Of Treatment

In past, most patients of CAP received treatment for 7-10 days. However, shorter courses of antibiotics as associated with a similarly good outcome. Much of this data has been generated from studies on newer antibiotics having more favorable pharmacokinetic profiles (such as azithromycin and levofloxacin) (22,23). A five-day course of standard antibiotics should prove sufficient for most patients having CAP. A longer duration of therapy may be necessary if the initial antibiotic was not active against the identified microorganism, or if CAP gets complicated by extrapulmonary dissemination. Patient should be otherwise clinically stable and afebrile for atleast 48-72 hours before discontinuation of antibiotics.

Management of Respiratory Failure in CAP

About 20% of patients with CAP require hospital admission for respiratory failure. The incidence of the disease severity varies with age, being higher in very young children and elderly people (24). Of the 167 patients with CAP admitted in the Adult Respiratory Intensive Care Unit of this Institute, the mean age was 44 years (Table 3). About 58-87% of patients with CAP seen at PGIMER, Chandigarh presented with respiratory failure requiring mechanical ventilation. Mortality in these patients can exceed 50% (25). In a retrospective study at the Respiratory ICU of this institute, the overall mortality was 49% (95% CI, 36-63) in 49 of 201 patients admitted with severe CAP over 15 months (26). In another recent report from this institute, infective pneumonia accounted for about 61% of all patients with acute respiratory distress syndrome, 22% cases were due aspiration and rest were due to other etiologies like vasculitis, tuberculosis, fat embolism, drowning, paraquat poisoning, etc. (27).

The mainstays of management of CAP are oxygen therapy, antibiotics and ventilator support when needed.

Table 3 : Distribution characteristics of patients with CAP admitted in the Adult RICU at the PGIMER, Chandigarh.

Age (years)	44 (28-58)
Gender distribution	
• Males	94 (56.3%)
• Females	73 (43.7%)
Transfer to RICU from	
• Emergency	119 (71.2%)
• Ward	48 (28.8%)
Days in hospital before transfer to RICU	1 (0-2)
Duration of RICU stay (days)	5 (2-9)
Duration of hospital stay (days)	8 (3-14)
Mortality rate	68 (40.7%)

Values are expressed as Median (IQR) or Number (%)

Oxygen Therapy

High-flow oxygen therapy with Venturi-mask is of prime importance and the inspired oxygen concentration (FiO_2) should be adjusted depending on the severity of acute respiratory failure. The basic objective is to achieve a desirable arterial oxygen tension (PaO_2) of about 60 mmHg with the lowest possible FiO_2.

Ventilatory Support

Non Invasive Ventilation

Non invasive ventilation (NIV) is institution of mechanical ventilation without the use of an endotracheal airway. There are several studies for and against its use in management of acute respiratory failure (ARF) in CAP.

The proponents of use of NIV in pneumonia and acute respiratory distress syndrome (ARDS) hypothesize that inspiratory positive airway pressure increases the tidal volume, decreases the inspiratory workload, decreases dead space ventilation, and decreases rate-related intrinsic PEEP by decreasing RR. On the other hand expiratory positive airway pressure prevents microatelectasis by increasing FRC prevents recurrent alveolar derecruitment (atelecto-trauma) acting akin to PEEP (28).

In a meta-analysis by Keenan *et al* on the role of NIV in pneumonia which included 8 trials (366 patients), there was 23% reduction in rate of endotracheal intubation (95% CI, 10-

35) and 17%; reduction in ICU mortality (95% CI, 8-26) (29). Among the studies (5 trials, 218 patients) which reported the data on hospital mortality, the analysis revealed that there was10% reduction in hospital mortality; 95% CI, -7 to 27. Among the 7 trials included in the analysis for evaluation of reduction in length of ICU stay it was shown that the use of NIV decreased ICU length of stay by 1.9 days; 95% CI, 1.0-2.9 (29).

Although the data is encouraging but in a recent meta-analysis by Agarwal *et al* it was demonstrated that NIV does not decrease the rate of endotracheal intubation or hospital mortality in patients with ARDS (28).

Currently it can only be said that the role of NIV in pneumonia with ARDS/ARF is at best controversial. It should be judiciously and vigilantly used in management of pneumonia and/or ARDS with facilities for endotracheal intubation and mechanical ventilation being readily available.

Invasive Ventilation

Most patients with severe CAP/ARF receive invasive ventilation (88% in BTS study). There are no controlled trials on MV in patients with pneumonia without ARDS (30). Most centres manage these patients with ARDSnet strategy (Table 4) (31).

Table 4: Components of ARDSnet strategy

Ventilation strategy	
Mode	Volume Assist-control
Initial tidal volume	5-8 mL/kg PBW
Respiratory frequency	10-35/minute
PEEP as per FiO_2 requirements	0.3-6; 0.4-8; 0.5-10; 0.6-12; 0.7-14; 0.8-16; 0.9-18; 1.0-20
I:E	1:1-1:3
Flow waveform	Descending ramp
Goals	
Plateau pressure	= 32 cm H_2O
PaO_2	55-80 mm Hg
pH	7.2-7.4
Weaning	
Mode (once PEEP < 8 & FiO_2 0.4)	Pressure-support

The ARDSnet strategy was proven to be most useful strategy for the management of ARDS. In the famous ARMA study, the in-hospital mortality rate was 39.8 percent in the group treated with traditional tidal volumes and 31.0 percent in the group treated with lower tidal volumes (P=0.007) (31). Thus, mortality was reduced by 22 percent in the group treated with lower tidal volumes, a finding of major importance. Also, there was significant reduction in ventilator free days, breathing without assistance and days without non pulmonary organ failure.

Conclusions

It is important to chose antibiotics judiciously for treatment of CAP, and avoid irrational or unnecessary prescriptions. Empiric antibiotic administration remains the mainstay of therapy, but should take into account host, microbiological and epidemiological factors. Newer or costlier antibiotics, or their combinations, may not be necessarily superior in efficacy. There is high incidence of mortality in patients with CAP who develop respiratory failure. These patients should be managed in an ICU setting. Use of NIPPV in a controlled setting may be beneficial in a select group but most patients will eventually require mechanical ventilation. Ventilation with "Open lung approach" (ARDSnet protocol) should be the standard of care as per the available evidence.

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Community Acquired Pneumonia In The Elderly

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Abstract

Pneumonia is the leading cause of death from infectious diseases in the geriatric age group and also the second most frequent illness requiring hospitalization in this age group.. The interaction between host-related risk factors and setting in which pneumonia develops leads to substantially higher morbidity and mortality in the elderly. Major differences occur in the presentation and management of pneumonia in the elderly as compared with young adults. Therefore an organized approach to assessing elderly patients and an awareness of common pitfalls in the diagnosis and management of pneumonia in this population are essential to improve outcomes in this setting.

Key Words: Pneumonia, elderly, diagnosis, management

Introduction

Osler and his colleagues had rightly observed about pneumonia in the geriatric population as "Captain of the men of death"(1). It is the leading cause of death from infectious diseases in the geriatric age group and also the second most frequent illness requiring hospitalization in this age group. From 18.2 cases per 1000 person years in patients aged 65 to 69 years to 52.3 cases per 1000 patient years in those aged greater than 85 years Jackson *et al* demonstrated that incidence of

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community-acquired pneumonia increased dramatically with increasing age (2). The disease assumes even greater significance considering that 20% of the world's population (over 2.9 million people) will be over the age of 65 years by 2050 (3).

Major differences occur in the presentation and management of pneumonia in the elderly as compared with young adults. The interaction between host-related risk factors and setting in which pneumonia develops leads to substantially higher morbidity and mortality in the elderly. Marston and colleagues (4) evaluated 2776 patients who were hospitalized with CAP in a single year in two Ohio counties. The overall mortality of CAP was 8.8%, 4.5% in individuals aged 18 to 44 compared with 12.5% in persons over age 65.Considerable controversy exists whether this significant difference in morbidity and mortality is a consequence of aging itself or the result of co morbid illnesses that are increasingly common in the aging population. Therefore an organized approach to assessing elderly patients and an awareness of common pitfalls in the diagnosis and management of pneumonia in this population are essential to improve outcomes in this setting.

Biological aging is characterized by a progressive, and, to a large extent, predictable loss of coordinated cell and tissue function, such that the organism becomes gradually less fit to reproduce and survive. The basic mechanisms underlying aging are unknown. The extent to which differentiated cells are affected by aging determines physiological function, while the extent to which stem cells are affected determines the capacity to replace damaged cells and repair tissues. A number of changes occurring in an aging lung i.e. impaired elasticity and mucociliary clearance, a waning cell-mediated/ humoral immunity and phagocytic function, contribute to increased incidence of infections in elderly.

Pneumonia develops when an infecting pathogen overwhelms the patient's host defense system, whether because of a virulent pathogen, a large inoculum of bacteria, and impairment in the patient's ability to fight infection, or a combination of these factors. In addition to impaired host defenses secondary to aging, underlying disease states (malnutrition, diabetes, cancer, chronic pulmonary disease, heart failure, renal failure and asthma and the therapy given for them influence host defenses)(5,6), play an important

role in the development of pneumonia in elderly populations.

Clinical presentation

More than 100 years ago Osler and his colleagues had observed that "Pneumonia in the geriatric age group may be latent, coming on without a chill; the cough and expectoration may be slight, the physical signs ill-defined and changeable, and the constitutional symptoms out of all proportion"(7).

Instead of the classical pneumonic symptoms, an older patient can present a large variety of atypical or subtle findings which often lead to a delay in initiation of treatment thus adversely affecting the final outcome. Coexisting chronic diseases not only mask the presence of symptoms of infection but may also decompensate and may be the first sign of the presence of pneumonia, further adding to the confusion in the mind of the treating clinician. Longer duration of symptoms at onset (cough, dyspnea, sputum production), non respiratory symptoms such as failure to thrive, frequent falls and confusion are some of the atypical presentations of pneumonia commonly seen in elderly. Respiratory signs and symptoms such as cough and dyspnea are less frequent, so are pleuritic chest pain and hemoptysis. Fever a prominent symptom of clinically significant pneumonia in younger population is not seen frequently in older patients. Among the 1812 patients with CAP which Metlay et al (8) reported fever and tachypnea in 85% and 36% of the younger patients as compared with 53% and 65%, respectively, in older age group. Physical examination in elderly is often misleading as findings consistent with the diagnosis of pneumonia may be totally absent in up to 20% to 47% of patients (9). In contrast tachypnea and the presence of rales have noted more commonly in the elderly as compared to the younger population. Riquelme et al (10) in their study of 101 elderly patients with CAP have reported dyspnea in 71%, cough in 67%, and fever in 64% of them. 19% of these patients did not present with the classic pneumonic symptoms i.e. (cough, pleuritic chest pain, or purulent sputum), whereas 44.5% presented with predominantly non respiratory symptoms in form of delirium and acute confusion, thus leading to a delay in diagnosis of pneumonia.

The Infectious Diseases Society of America/American Thoracic Society (IDS/ATS) guidelines for CAP, state that all patients suspected of having infection should have a chest radiograph to define the presence of pneumonia and the severity of illness

(11). This gains upmost importance given the variation and subtlety of presentation of pneumonia in the elderly, but frequently even radiology in elderly may be difficult to interpret and may even be normal at presentation (12) in some of the patients. Therefore although the chest radiograph is a vital component of making a diagnosis of pneumonia, and, in fact, should be obtained in everyone in whom the diagnosis of pneumonia is being entertained, it is not definitive and wherever there is strong suspicion, a CT scan of the chest should be undertaken.

The nonspecific presentation of disease often leads to delays in obtaining and examining appropriate diagnostic material such as sputum and blood. Even obtaining diagnostic material for gram stain and culture can be difficult in this thin and debilitated subset of population. Recommended diagnostic tests are a sputum Gram stain and culture before antibiotic therapy, provided a good quality specimen is available and more importantly whether it can be transported to the laboratory immediately. Unfortunately, 30% to 40% of patients fail to produce sputum and in many cases prior antibiotic use leads to a marked decrease in the yield for Gram's stain and culture (13). Blood cultures are only recommended for patients with more severe illness, these too preferably in patients who have not received antibiotics in the recent past. Routine serologic testing is not recommended and has been valuable only in population studies and in epidemiologic investigations. Invasive procedures such as fiberoptic bronchoscopy and bronchoalveolar lavage are usually used in patients who have severe pneumonia, or in patients who have non-resolving pneumonia.

Despite the use of the best diagnostic techniques only 5% to 50% of patients have a microbiologically proven diagnosis. Therefore it has been rightly said that the rule of thumb followed in managing pneumonia in elderly is "A positive finding may help guide therapy, but a negative one does not alter approach"

Causative organisms and bacteriology

Identification of a specific etiologic organism is often difficult in the older population, as a good sputum examination is often lacking. Complicating the problem further, prior antibiotic therapy, alcoholism or chronic imunosupression and presence of multiple co morbidities commonly leads to an increased incidence of drug-resistant *S pneumoniae* (DRSP) in

patients over age 65(14). Data from the Western literature suggests that *S pneumoniae* is the most common etiologic agent of CAP in the elderly population accounting for 20% to 60% of cases (15). Other organisms commonly isolated are Legionella, *Haemophilus influenza* (particularly in cigarette smokers), *Staphylococcus aureus* (more common diabetics and patients with chronic kidney disease), anaerobes (aspiration secondary impaired swallowing or neurologic illness) and viruses. Gram-negative enteric bacilli and *Pseudomonas aeruginosa* are generally not common causes of CAP in elderly but may be present in individuals who reside in nursing homes and persons with exposures to the health care environment (eg, recent hospitalization or care in a hemodialysis center) (15). Atypical pathogens have a variable role in causing pneumonia in the elderly, *Mycoplasma pneumoniae* is a rare cause of pneumonia, whereas Chlamydia species infections occur in 16% to 28% of cases (16)

Riquelme *et al* in their study of 101 elderly patients with CAP could establish an etiological diagnosis in only 42%, *S pneumonia* was the most common organism (36%) followed by *C pneumoniae* (17%), *C burnetti* (11%), *L pneumophila* (6%) and *M pneumonia* (4%)(10). Similar results were reported by Metlay et al (8) and Fernandez et al (9), but in the latter study aspiration was more common as was gram-negative infection, and atypical pathogens were less frequently seen.

Prognostic Factors

The important issue of deciding when, whom and where to treat a patient of pneumonia remains foremost in the mind of any treating physician. A variety of models have been developed to address this issue. Two prognostic scoring systems: the Pneumonia Severity Index (PSI) and a modification of a rule developed by the British Thoracic Society, termed the CURB-65 are widely used to assess severity. CURB-65 is an acronym that refers to an assessment of five factors: (1) confusion, (2) elevated blood urea nitrogen (BUN) (>19.6 mg/dL), (3) elevated respiratory rate (=30/min), (4) low systolic (<90 mm Hg) or diastolic (=60 mm Hg) blood pressure, and (5) age (=65). The PSI divides patients into five risk groups (I–V) on basis of a scoring system based on age, co morbidity, certain laboratory data, and physical findings. All these scoring systems are well validated in younger individuals but whether they can be extrapolated to the geriatric population is a matter

of question and it may be best to view them as complementary, identifying patients at extreme ends of the disease spectrum (17, 18, 19)

Once pneumonia has been documented and its severity assessed, a decision has to be made as to where the patient will be treated. Hospitalization has its own advantages and also its attending complications in elderly patients. The basic principal in this subset of population should be that hospitalization should be long enough to allow close observation and help determining further continuation in the outpatient setting. Home care for CAP is increasingly being encouraged in the elderly only after ensuring a caregiver to provide support at home, availability of home nursing and home intravenous therapy, and the availability of an intermediate care which can provide sub acute care at the earliest. Prognostic scoring systems though serve as guides to admission, must be viewed as supportive and not as replacement of the clinical judgment. ICU admission according to the IDSA/ ATS guidelines is recommend if a patient has at least one major criterion of severity (need for mechanical ventilation or septic shock) or three minor criteria (respiratory rate =30/ min, PaO2/FiO2= 250, multilobar infiltrates, confusion /disorientation, BUN = 20 mg/dL, white blood cell count<4000/mm3), temperature less than 36°C, and hypotension requiring aggressive fluid resuscitation) (11).

Treatment

Before an appropriate antimicrobial therapy is selected, certain important points are to be considered. Eliciting a past history of penicillin allergy or a documented anaphylactic reaction to any antimicrobial in the past is of upmost importance as the offending class of the drug is generally avoided. Coexisting renal and hepatic dysfunction also influence the choice of the antibiotic. Creatinine in elderly patients may not reflect the true renal function, the dosage adjustments of renally eliminated antibiotics should be based on measurements or indirect estimates of the creatinine clearance.

Maintaining a good intravenous access is the hallmark of a good resuscitation, this can be difficult in the geriatric age group. Intramuscular route may be used but with caution because of the presence of a decreased muscle mass. Recently there has been an increasing reliance on treating elderly patients with pneumonias totally or partially with oral antibiotics

and early switch over to oral route is usually recommended even in the patients who are receiving intravenous antibiotics.

The guidelines for antibacterial selection for elderly patients with community-acquired pneumonia do not differ from those for immunocompetent young adults. Several guidelines have been proposed but the most recent ones published by the Infectious Diseases Society of America and the American Thoracic Society are the most widely accepted(11)

Empiric therapy for ambulatory patients with community-acquired pneumonia should cover against *S pneumoniae* and atypical pathogens. For a previously healthy patient who has not received antibiotic therapy in the previous 3 months, macrolides (erythromycin, clarithromycin, or azithromycin) monotherapy is recommended. Recent antibiotics use or presence of co morbidities (chronic heart, lung, liver, or renal disease, alcoholism, malignancy) increase the risk of infection with drug-resistant *S pneumoniae*. In these cases, a respiratory fluoroquinolone (gemifloxacin, levofloxacin, moxifloxacin) or combination therapy with a macrolide plus a beta-lactam is recommended. Preferred oral beta-lactams include high-dose amoxicillin or a combination of amoxicillin-clavulanate. Alternatives include ceftriaxone, cefpodoxime, and cefuroxime. In patients with history of allergy to macrolides doxycycline can be tried, but its efficacy as monotherapy has always been under a scanner (20).

Patients who require hospital admission but not ICU care are treated with a anti pneumococcal fluoroquinolone or combination therapy which includes a beta lactam and a macrolide or doxycycline. The available intravenous quinolones are levofloxacin and moxifloxacin. The recommended intravenous beta-lactams are cefotaxime, ceftriaxone, ampicillin/sulbactam or ertapenem (especially for individuals who are at risk for non-pseudomonal gram-negative organisms). The recommended intravenous macrolide is azithromycin. Gleason et al in their study observed a lower 30-day mortality in elderly patients admitted in hospital with pneumonia when they were treated empirically with a second generation cephalosporin plus a macrolides or a non-pseudomonal third generation cephalosporin plus a macrolide, or fluoroquinolone monotherapy as compared with monotherapy with a non-pseudomonal cephalosporin alone(21).The most appropriate

explanation for the above observation is a better atypical pathogen coverage with the combination therapy in the setting of coinfection, synergistic effects of the two drugs, or a possible anti-inflammatory effect of the macrolide therapy.

Elderly patients with severe pneumonia should be preferably admitted in the ICU. All of these individuals must receive intravenous combination therapy (pneumococcal beta-lactam plus either a macrolide or respiratory fluoroquinolone) thus adequately covering drug resistant pneumococci and atypical organisms including legionella. No patient should receive monotherapy because the safety, efficacy, and proper dosing of these agents when used alone in patients with severe pneumonia has not been established.(11). Anti-pseudomonal combination chemotherapy (piperacillin-tazobactam, cefepime, imipenem, or meropenem plus either ciprofloxacin/ levofloxacin or the above β-lactam plus an aminoglycoside and azithromycin or the above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone) must be considered in any patent with known risk factor predisposing to increased pseudomonas infection (structural lung disease, chronic corticosteroid use and recent intake broad-spectrum antibacterial therapy). In the presence of history of penicillin-allergy, the above b-lactam can be substituted with aztreonam(11). Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) although primarily an etiology of necrotizing pneumonia in young, should be considered in any non resolving pneumonia, vancomycin and linezolid are the available therapeutic options.

Hospitalized patients with CAP typically respond to appropriate therapy with clinical stabilization and improvement over the first several days, with up to half of patients reaching clinical stability by day 3 of therapy (20, 22). In the ATS guidelines, the recommended total duration of therapy is a minimum of 5 days, discontinuation is recommended once the patient remains afebrile for at least 48 to 72 hours.(11) Elderly patients may show a delayed response to therapy secondary to an altered immune response and presence of co-morbid conditions. Radiographic resolution takes a longer time than clinical resolution, and most patients require 4 to 6 weeks for radiographic resolution.

It is usually not helpful to follow a chest film early in the course of illness unless a patient is not clinically improving. A non resolving pneumonia may be due to number of causes e.g., pathogen not covered by the agent chosen, an unusual and unsuspected pathogen (tuberculosis, virus, fungus), a pneumonic complication (empyema, endocarditis, meningitis, pulmonary embolus), or the presence of a noninfectious illness that presents like a pneumonia (bronchiolitis obliterans, bronchogenic carcinoma, pulmonary vasculitis).(22)

Prevention

Vaccination remains the primary preventative strategy for CAP in the elderly. Persons older than 50 years should receive inactivated influenza vaccine annually; pneumococcal vaccination should be given once to persons aged more than 65 years. A second pneumococcal vaccination is recommended after 5 years for those persons in whom the first dose was administered before age 65 years(11). Both these vaccines can be given at the same time but each one has to be administered at a different site.

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Community Acquired Pneumonia In Children- Contemporary Issues And Current Concerns

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Abstract

Community acquired pneumonia (CAP) remains the leading cause of mortality in children less than five years of age. This article reviews the main issues related to CAP in children namely recognition of seriousness, need for standardized case management, use of appropriate antibiotic therapy, predictors of treatment failure, role of chest radiography and prevention of CAP. Early recognition and use of appropriate effective antibiotic therapy can significantly reduce mortality of childhood pneumonia. Education of primary care-givers in the community especially parents and community health workers is an important and much needed measure to help achieve the above. Effectiveness of standardized case management can be further improved by addressing the various risk factors associated with poor response to antibiotic therapy namely malnutrition, incomplete immunizations and hypoxemia at presentation since these are amenable to interventions. Primary prevention of pneumonia through appropriate vaccination policies is likely to reduce the burden significantly.

Key Words: Community acquired pneumonia, children, prevention, recognition, standardized case management, immunization

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Introduction

Pneumonia is the single most important cause of death in children (1). It is estimated that each year, over 2 million children die of pneumonia; which translates to 20% of the mortality among under five children. Pneumonia accounts for more childhood deaths than diarrhoea and is responsible for greater mortality than malaria, measles and AIDS put together (2). This relatively high mortality is not restricted to developing countries; even in industrialised nations, pneumonia is responsible for a disproportionately large share of childhood mortality. UNICEF data show that a handful of 15 countries account for over three-quarters of childhood pneumonia across the world; India has the dubious distinction of topping this list, contributing 44 million (39%) of the estimated 113 million global episodes. What is more alarming is that these 44 million episodes of pneumonia also translate to the highest number of episodes per child per year. Therefore, the importance of appropriate health care interventions at the individual, community national and regional levels cannot be over-emphasized. It has recently been calculated that standard case management of pneumonia is likely to have an impact even greater than that of oral rehydration therapy for diarrhoea; this is an important observation considering that the latter is often universally hailed as the most effective heath intervention over the past century (3). Therefore, it is pertinent to examine contemporary issues and current concerns related to community acquired pneumonia in children.

Issue 1: Recognition Of Seriousness

The first step to accessing effective health care is the recognition of seriousness of the problem. Unfortunately, for pneumonia there is considerable deficiency on the part of primary care-givers in this aspect, which results in poor health-seeking behaviour. There could be many reasons for this, including confusing symptoms and signs of pneumonia with trivial childhood illnesses, failure to recognise danger signals and putting off a visit to health care centre until advanced stages. It is indeed unfortunate that appropriate health care is sought in only about 50% cases of childhood pneumonia. Table 1 reflects the burden of childhood pneumonia and the health seeking behaviour of populations in developing countries within UNICEF regions. These data imply that about half the children with pneumonia do not present to a health provider. These dismal trends prevail for both genders, and also in rural as well as urban areas of

Table 1: Burden of childhood pneumonia and health-seeking behaviour

UNICEF region	Episodes per child per year	Percentage taken to appropriate health care provider
Developing countries in general	0.29	54%
South Asia	0.36	59%
Sub-Saharan Africa	0.30	41%
CEE/ CIS	0.29	50%
Middle East and Sub-saharan Africa	0.26	66%
Latin America	0.22	52%
East Asia and Pacific	0.24	62%
Middle East	0.26	66%

Data from reference 2

residence, although it is worse in the rural areas.

Recognition of seriousness is hampered by the fact that less than 20% primary care-givers are aware that common physical signs such as fast breathing and difficult breathing, independently herald serious disease. There is some evidence that children of less educated mothers are less likely to be taken to a health care provider (Table 2A). There is also emerging evidence that the likelihood of visiting a health centre is directly proportional to the level of economic capacity, although it must be emphasized that even 'rich' parents display 'poor' health seeking behaviour (Table 2B). These findings argue for educating primary care-givers in the community about the importance of childhood pneumonia as well as imparting knowledge and skill to identify simple symptoms and signs of severe disease. This is particularly important because recent management protocols are emphasizing the importance of home-based treatment, which again necessitates that caregivers should understand and be convinced of treatment efficacy.

Issue 2: Standard Case Management

Standard case management depends on correct diagnosis and classification of severity of children with pneumonia. The Integrated

Table 2: Factors affecting health-seeking behaviour

2A. Relationship of health-seeking behaviour and maternal education	
Level of maternal education	Percentage of under-five children taken to appropriate health-care provider
Secondary education	59%
Primary education	47%
No formal education	43%
2B. Relationship of health-seeking behaviour to economic status	
Relative economic status	Percentage of under-five children taken to appropriate health-care provider
Richest	53%
Middle	45%
Poorest	40%

Data from reference 2

Management of Childhood Illness (IMCI) guidelines (4, 5) define pneumonia among children upto 5 years of age, as the presence of cough with fast or difficult breathing. Fast breathing is defined as respiratory rate greater than 50 per minute for children aged 2 to 12 months old and more than 40 per minute for those 12 months to 5 years old. Pneumonia is categorised as severe when there is lower chest wall indrawing (retractions) and as very severe pneumonia in presence of cyanosis and/or inability to drink. It is immediately evident that this diagnosis and classification system is practical, simple to apply and does not require sophisticated instruments or advanced training. Further, there is evidence which suggests that tachypnea may be a characteristic sign of pneumonia across all ages (6). However, it should be noted that the case definition does not give importance to fever and estimates of oxygenation. This may be because the former is very non-specific and the latter difficult to measure in community settings. Similarly, auscultatory signs have not been included in the standard case definition because it requires considerable training and skill, and yet has low specificity and poor inter-observer concordance (7).

As per the standard case management guidelines, only children

aged 2 months to 5 years with 'non-severe' pneumonia may be treated at home. These children should receive a complete course of antibiotic therapy. Children with severe pneumonia and infants less than 2 months old with any pneumonia should be referred to the nearest health facility immediately. It may be prudent to administer the first dose of antibiotic before referral to a facility where oxygen and injectable antibiotics can be administered. The effect of community based management of pneumonia has been recently established through a meta-analysis of trials on this intervention. This showed that there was significant decline in all-cause mortality as well as pneumonia-specific mortality across all age groups in those who received community based management (Table 3).

Table 3: Impact of community-based management of pneumonia

Age group	Reduction in all cause mortality	Reduction in pneumonia related mortality
Neonates	27%	42%
Infants	20%	36%
Children	24%	36%

Data from reference 2

Issue 3: Appropriate Antibiotic Therapy

Although it may appear strange to discuss something as obvious as antibiotic therapy for pneumonia, this is a very important issue because data from various developing countries shows that only a small fraction of children with pneumonia receive antibiotic therapy. Figure 1 shows the dismal scenario in these countries across all continents. India fares slightly better than some of these countries, but the level of coverage is far below that expected. Although some countries have shown progress, what is alarming is that some other countries actually report a further decline in the number of children receiving antibiotics for pneumonia (Table 4).

Clinical experience in many developing countries suggests that cotrimoxazole and amoxicillin are effective antibiotics to treat childhood community acquired pneumonia in developing countries. The key factor is the completion of a full-course of therapy.

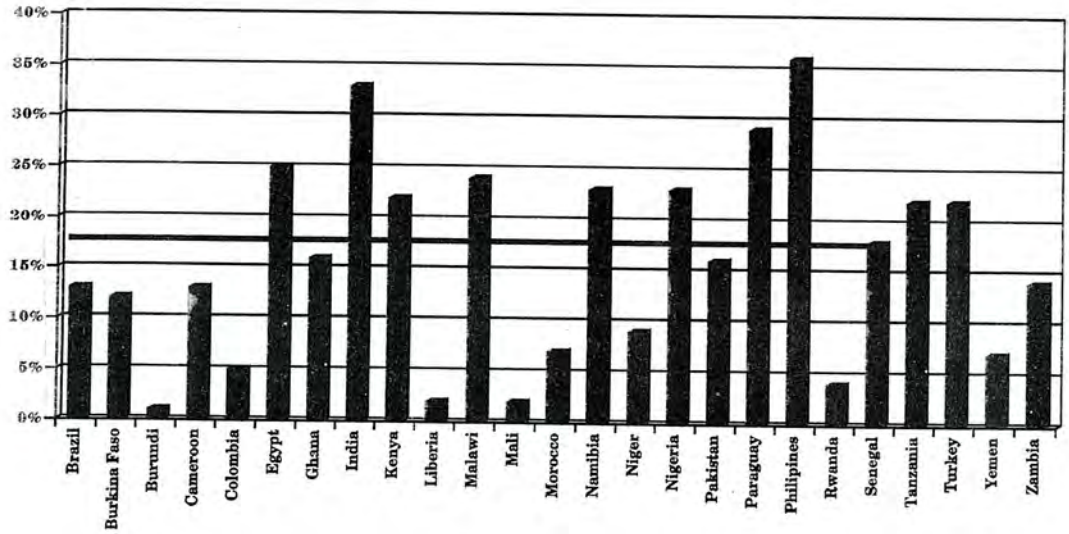

Figure 1: Proportion of children receiving antibiotic therapy for pneumonia.

The solid line indicates the average data of 27 developing countries
Data from reference 2

Table 4: Change in trends of antibiotic therapy for children with pneumonia

Country	Year	Percentage of under five children treated with antibiotics
Brazil	1991	13%
	1996	15%
Colombia	1986	5%
	1990	30%
Dominican Republic	1991	29%
	1996	10%
Egypt	1992	25%
	2000	75%
Ghana	1993	24%
	1998	16%
Philippines	1993	44%
	1998	36%

Recent years have witnessed a spate of studies that confirm the clinical success of therapy with amoxicillin or cotrimoxazole in children with pneumonia. A summary of these is presented in Table 5 (8-13). A more recent randomized trial has confirmed that oral therapy may be as efficacious as intravenous therapy; this trial with almost 250 participants demonstrated the equivalence of efficacy with oral amoxicillin as compared to intravenous benzyl-penicillin, with respect to treatment success, duration of fever and time to complete resolution of symptoms (14). Further, it is now evident that treatment duration as short as three days may be adequate, in terms of comparable efficacy of the longer five-day course (12).

The trend towards progressively shorter antibiotic courses for non-severe pneumonia had led to a pertinent question whether such children require antibiotics at all. This is a natural extension of the question on the likely etiology of pneumonia in

Table 5: Efficacy studies on antibiotic therapy in developing countries

Study	Country	Sites	Year	Population	Intervention and outcome			
					Antibiotic	Treatment failure	Antibiotic	Treatment failure
Strauss et al	Pakistan	2	1991-1992	595 children, age 2-59 month	Amoxicillin 45mg/kg/day for 5 days.	13%	Cotrimoxazole 20/4 mg/kg/day for 5 days	23%
COMET study	Pakistan	9	1995-1996	1143 children, age 2-59 month	Cotrimoxazole 20/4 mg/kg/day for 5 days	19%	Cotrimoxazole 40/8mg/kg/day for 5 days	21%
CATCHUP study	Pakistan	8	1998-1999	1471 children, age 2-59 months.	Amoxicillin 45mg/kg/day for 5 days.	16%	Cotrimoxazole 20/4 mg/kg/day for 5 days	19%
MASCOT Pneumonia Study group	Pakistan	7	1999-2001	2000 children, age 2-59 months.	Amoxicillin 45 mg/kg/day for 3 days.	21%	Amoxicillin 45 mg/kg/day for 5 days.	20%
ISCAP Study	India	7	2000-2002	2188 children, age 2-59 months.	Amoxicillin 31-54mg/kg/day for 3 days.	11%	Amoxicillin 31-54mg/kg/day for 5 days.	10%
Hazir T et al	Pakistan	4	2003-04	896 children, age 2-59 months.	Amoxicillin 45 mg/kg/day for 3 days.	5.9%	Amoxicillin 90 mg/kg/day for 3 days.	7.9%

children. It has been known for long that majority of childhood pneumonia in developed countries is related to viral infection, whereas it is predominantly bacterial in developing countries. Further, the frequent isolation of atypical organisms in children with pneumonia could argue against prescribing antibiotic treatment. If children in developing countries also have predominantly 'viral' pneumonia, it could account for the 'success' of a short course of oral antibiotic therapy. Short of determining the etiology of pneumonia through sophisticated investigations, the only way to determine this indirectly would be to with-hold antibiotic treatment in a cohort of childhood pneumonia and assess the outcome. This important issue has recently been addressed in an elaborately designed double-blind multi-centric trial in India. This trial was designed to evaluate whether 'placebo administration in children with non-severe pneumonia and wheezing, had equivalent effects compared to therapy with amoxicillin (15). Wheezing is a common presentation in childhood pneumonia, especially viral and atypical pneumonia. Table 6 shows the primary outcome (treatment failure) for each of the centres that participated in the trial. It is interesting that although the effect was comparable between the two

Table 6 : Is antibiotic therapy required in children with non-severe pneumonia: results of a double-blind multicentric trial in India.

Place	Treatment failure in Placebo arm	Treatment failure in Amoxicillin arm	OR (95% CI)	RR (95% CI)
New Delhi	23/92	14/93	1.88 (0.90-3.94)	1.66 (0.91-3.02)
Chandigarh	4/81	3/79	1.32 (0.28-6.08)	1.30 (0.30-5.62)
Nagpur	5/108	10/110	0.49 (0.16-1.47)	0.51 (0.18-1.44)
Trivandrum	32/128	20/127	1.78 (0.96-3.32)	1.59 (0.96-2.62)
Mumbai	19/108	17/109	1.16 (0.56-2.36)	1.13 (0.62-2.05)
Chennai	54/120	49/118	1.15 (0.69-1.92)	1.08 (0.81-1.45)
Vellore	34/111	30/111	1.19 (0.67-2.13)	1.13 (0.75-1.72)
Lucknow	31/91	23/88	1.46 (0.77-2.78)	1.30 (0.83-2.05)
Overall	202/839	166/835	1.28 (1.01-1.52)	1.21 (1.01-1.45)

arms within each centre, the pooled effect was in favour of therapy with amoxicillin as compared with placebo. The importance of this landmark trial is that it not only demonstrates that the beneficial effect of short course antibiotic therapy in childhood pneumonia has a scientific basis, but also indirectly points towards bacterial etiology of this condition, which is also amenable to other interventions such as vaccination.

Issue 4: Predictors Of Treatment Failure In Childhood Pneumonia

From the foregoing sections, it is clear that although short course of oral antibiotic therapy is successful in childhood pneumonia, there are a significant number of children encountering treatment failure. A number of reasons could be responsible for this; such as greater severity of disease within a category, presence of co-morbid conditions, organisms that respond poorly to the antibiotics used, and of course inadequate antimicrobial therapy. An emerging factor is the trend of antimicrobial resistance among many bacterial species. Therefore, it would be of immense clinical value, if one could predict the likelihood of treatment failure in a given patient. The multi-centric WHO-SPEAR study (16) assessed treatment failure between treatment arms based on chloramphenicol versus ampicillin with gentamicin, in children with very severe pneumonia, at serial intervals (5 days, 10 days and 21 days). Although the latter combination therapy proved to be superior, the trial provided a number of risk factors that were associated with treatment failure. These included female gender (OR 1.95, 95% CI 1.11-3.43), incomplete immunization (OR 1.77, 95% CI 1.00-3.15), severe malnutrition defined as weight for age Z-score less than -3.0 (OR 1.48, 95% CI 0.69-3.19) and the presence of hypoxemia (OR 4.7, 95% CI 2.29-9.67). The latter is clinically important as this is easily correctable at short notice. Univariate analysis of data from Chandigarh showed that children with treatment failure had significantly higher temperature at admission, hypoglycemia and a positive blood culture at admission. An important difference among those in whom treatment was successful compared to treatment failure, was the degree and duration of hypoxemia. The latter group had hypoxemia that was more severe and lasted longer than the former (Fig. 2). The recent multi-centric Indian trial in children with non-severe pneumonia demonstrated that the presence of vomiting was a significant independent risk factor associated with

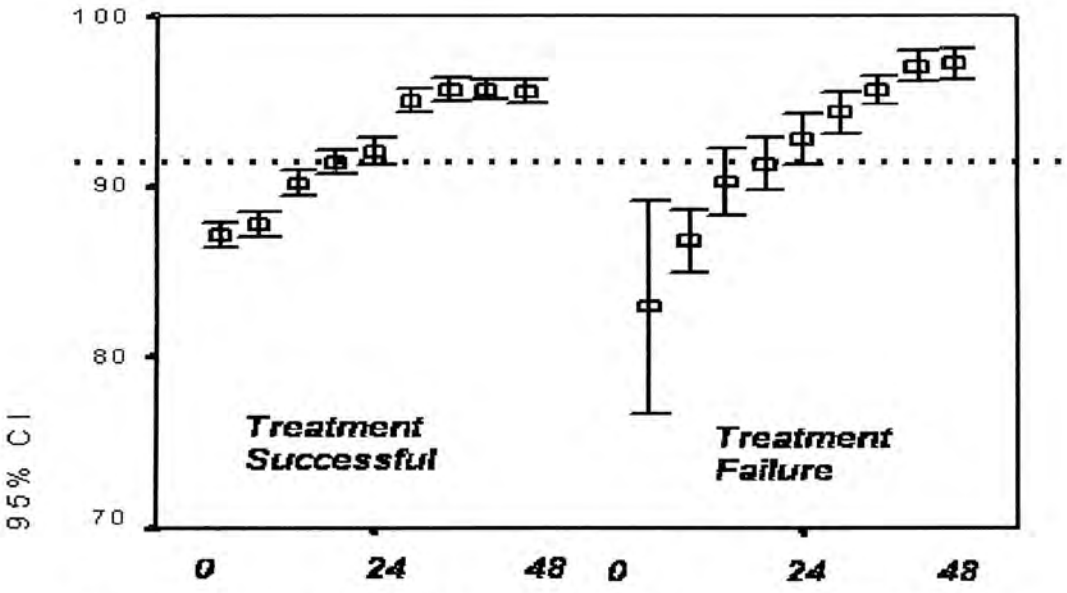

Figure 2: Oxygenation and relationship to outcome in children with pneumonia

worse outcome. Another very significant clinical finding predictive of treatment failure was a respiratory rate more than 10 breaths per minute beyond the cut-off.

Issue 5: Role Of Chest Radiography

It is interesting that there is scant mention of the role of chest radiography in most of the recent guidelines for the management of community acquired pneumonia in children. This is because of three major reasons, first it has little impact on treatment policy in the setting of community acquired pneumonia, especially where home-based care is concerned, second it has poor specificity to identify bacterial infection (where antibiotics are necessary) as against viral infection (wherein antibiotics may not be necessary) and third, the radiological definitions of pneumonia are very variable and have poor specificity (17, 18). Therefore current treatment protocols of non-severe community acquired pneumonia do not lay much stress on chest radiography.

Issue 6: Co-Infection With HIV

Pneumocystis jiroveci (formerly *P. carinii*) pneumonia is the most common opportunistic infection in HIV positive children. It is responsible for about 25% deaths in HIV positive infants. These

data argue strongly in favour of antibiotic prophylaxis in all HIV positive children and babies born to IIIV infected mothers. There is empiric data that attests to improved outcome with such intervention. The WHO therefore recommends cotrimoxazole prophylaxis in all such children

Issue 7: Prevention Of Community Acquired Pneumonia

The high morbidity and mortality associated with childhood pneumonia makes it necessary that every possible effort be made to prevent its occurrence. Potentially beneficial measures are community education, improvement of nutrition and vaccination against preventable causes of pneumonia (19-22).

Vaccination for the prevention of pneumonia has been in practice for several decades in developed countries and for about 30 years in most developing countries. Measles immunization and universal immunization with DPT have resulted in significant decline in morbidity and mortality across the world. This is true in developing countries as well. It is expected that vaccination against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, for

Table 7 : Efficacy of Hib and Pneumococcal vaccines in developing countries

Country	Vaccine used	Study design	Vaccine efficacy (95% CI)
Colombia	Hib conjugate vaccine	Case-control	55% (7-78)
Chile	Hib conjugate vaccine	RCT	22% (7-43)
Brazil	Hib conjugate vaccine	Case-control	31% (9-57)
Gambia	Hib conjugate vaccine	Double blind RCT	22% (2-39)
Indonesia	Hib conjugate vaccine	Double blind RCT	12%
Bangladesh	Hib conjugate vaccine	Case-control	44% (20-61)
South Africa	9 valent Pneumococcal conjugate vaccine	Double blind RCT	25% (4-40)
Philippines	11 valent Pneumococcal conjugate vaccine	Double blind RCT	22.9% (1-41)
Gambia	9 valent Pneumococcal conjugate vaccine	Double blind RCT	35% (26-43)

which safe vaccines are currently available, can further improve child survival. This is based on the calculation that *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* are the leading causes of childhood pneumonia; together accounting for more than half the mortality related to childhood pneumonia (23,24).

The early randomized controlled trials in developing countries proved that Hib vaccination resulted in significant protection against pneumonia and meningitis; although it is estimated that the burden of pneumonia prevented is nearly ten-fold higher. Similar observations have emerged from case–control studies also. Similarly, a limited number of trials of Pneumococcal conjugate vaccine in the developing world have reported encouraging results. The World Health Organization has been pressing all countries; especially developing countries to include both Hib and Pneumococcal conjugate vaccine into individual routine immunization programmes (25, 26). It is expected that the financial assistance extended through international organizations such as GAVI Alliance will help make this a reality in resource poor settings.

Conclusion

Globally, childhood pneumonia is a problem of enormous public health importance; it remains the leading cause of mortality in under five-children, with an undesirably high disease burden in resource poor countries. Early recognition and use of appropriate effective antibiotic therapy that can be delivered at patients' door-step can have significant impact on pneumonia mortality. Educating and empowering primary care-givers in the community, particularly parents and community health workers, to enhance the proportion of children who receive antibiotic therapy, has the potential to reduce mortality. The current IMCI guidelines for recognition and categorisation of childhood pneumonia facilitate this process. The yield of standard case management can be further improved by addressing various risk factors associated with poor response to antibiotic therapy; malnutrition, incomplete immunizations, hypoxemia at presentation; that are eminently amenable to interventions. Primary prevention of pneumonia through appropriate vaccination policies is likely to reduce the burden significantly.

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