Treatment of childhood pneumonia in developing countries

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Introduction

Definition of community acquired pneumonia (CAP)

CAP can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child due to an acute infection (of less than 14 days' duration) of the lower respiratory tract (usually occurs below terminal bronchioles) leading to cough or difficult breathing, tachypnoea, or lower chest-wall indrawing, which has been acquired in the community outside hospital (Zar et al., 2005; BTS, 2002). In developed countries this can be verified by the radiological finding of consolidation (BTS, 2002). In resource poor setting of the developing world, a more practical term - acute lower respiratory infection (ALRI) - is preferred, reflecting the difficulties in obtaining a chest radiograph, especially in rural areas (BTS, 2002).

Disease burden and epidemiology of CAP

In the developing world, pneumonia is not only more common than it is in Europe and North America (Riley et al.,1983; Berman & McIntosh, 1985; Selwyn, 1990), but also more severe and is the largest killer disease of children (Bulla & Hitze, 1978; Baqui et al., 1998). The fourth Millennium Development Goal has concentrated efforts on addressing the priority areas for improving child survival worldwide, with an aim of reducing the national child mortality rates by two-thirds by 2015 (UN, 2000). ALRI, particularly pneumonia, are currently the leading and biggest single cause of deaths among under-5 children 1 to 59 months of age in the developing countries (UNICEF & WHO, 2006; Graham et al., 2008), being responsible for at least 19% of the annual 8.8 million deaths in this age-group (Wardlaw et al., 2006). ALRI causes more than 2 million child deaths (one million in children aged 1 to 59 months and additional one million in neonates) worldwide each year, mostly from pneumonia, accounting for 20% of deaths in under-5 children (Bryce et al., 2005; Rudan et al., 2004), and 90-95% of all these deaths occur in the developing countries (Rudan et al., 2008; Murray & Lopez, 1997; Garenne et al., 1992; Mulholland, 1999; Williams et al., 2002; WHO, 1998). In terms of magnitude of the problem, there is an estimated incidence of 151 million new cases of pneumonia each year globally, and 11-20 million (7-13%) are severe enough to require hospitalization in the developing countries (Rudan et al., 2004; Rudan et

al., 2008). Recent estimates also suggest that 1.9 million (95% CI 1.6 to 2.2 million) children died from acute respiratory infection (ARI) throughout the world in 2000 and 70% of them occurred in Africa and Southeast Asia, one dying in every 7 seconds (Mulholland, 1999; Williams et al., 2002). Actually, CAP is a major cause of health care utilization, hospitalization, and death in children in the developing countries (Mulholland, 1999; Williams et al., 2002; WHO, 1998). Therefore, improvement in the case-management strategies of the major causes of child death, such as pneumonia and neonatal illnesses in developing countries, should be a priority in improving the child survival in the developing countries (Walley et al., 2008; Duke & Tamburlini, 2003). ARI is also a major cause of visits to the outpatient and emergency departments as well as admissions to the hospitals. Although bronchiolitis, tracheobronchitis and pneumonia, each accounts for one-third of ALRI cases, pneumonia is responsible for most of the ALRI deaths. In Bangladesh, ALRI account for 25% of deaths among under-5 children and constitute 40% of all infantile deaths (Baqui et al., 1998). In a study conducted at the Dhaka Hospital of ICDDR,B among 401 under-5 children with ALRI, it was observed that the most common manifestation was pneumonia and a respiratory pathogen (both bacterial and viral) was identified in 30% cases and the case fatality rates were 14% in bacterial pneumonia and 3% in viral pneumonia (Rahman et al., 1990). In another study also conducted at the Dhaka Hospital of ICDDR,B among 601 under-5 children with ALRI, it was observed that the most common manifestation was pneumonia (86.5%), and a viral pathogen was detected in 21% cases, and the overall case fatality rate was 6.8%, and that of viral pneumonia was 4.8% (Huq et al., 1990).

Objective
To develop guidelines for the physicians and nurses of the developing countries for the diagnosis and management of CAP in children

Options
- Clinical assessment
- Radiographic assessment
- Laboratory testing
- Empirical antimicrobial therapy

Outcomes
- Increased awareness of the age-related causes of CAP including those children with severe acute malnutrition (SAM), and those with dehydrating diarrhoea
- Improved accuracy of clinical diagnosis of CAP in children
- Better utilization of the available diagnostic testing
- Rational use of empirical antimicrobial therapy
- Decreased morbidity and mortality due to CAP

Benefits, harms, and costs
- Increased awareness of the causes of paediatric pneumonia
- Accurate diagnosis
- Prompt treatment
- Reduced cost associated with unnecessary investigations and complications due to inappropriate treatment

Rationale

As pneumonia is a major cause of morbidity and mortality in children in the developing countries (Williams et al., 2002), early and appropriate treatment of pneumonia can reduce the morbidity and mortality (Sazawal & Black, 2003), which has been the rationale for the development of guidelines for the management of CAP (Zar et al., 2005). The guidelines also aim to provide recommendations for effective therapy and to minimize the development of bacterial resistance through judicious use of antibiotics (Zar et al., 2005). This document aims to provide guidelines for the diagnosis and effective management of children with CAP so as to improve pneumonia-associated morbidity and mortality, thereby improving the case-management strategies of the major cause of child death, such as pneumonia in the developing countries which should be a priority in improving child survival globally (Walley et al., 2008; Duke & Tamburlini, 2003).

Clinical classification and management plan of CAP

Depending on the clinical presentation, pneumonia can be classified as very severe, severe, or non-severe according to the World Health Organization (WHO) (WHO, 1990; WHO, 1984; WHO, 2000; WHO, 1991). The specific treatment guidelines for each of them, and the diagnosis of pneumonia should primarily be based on the visible clinical parameters, including respiratory rate and lower chest-wall indrawing (WHO, 1990; WHO, 1991; Cashat et al., 2005). Pneumonia is usually caused by viruses or bacteria, but the most serious episodes are caused by bacteria. However, in the absence of clear cut demarcation for aetiological diagnosis of pneumonia on the basis of clinical and/or radiological features, empiric antibiotic therapy is needed for all cases of CAP. Hospitalization of children with severe pneumonia is recommended for giving supportive treatment including oropharyngeal or nasopharyngeal suction, oxygen therapy for hypoxaemia, fluid and nutritional management, and close monitoring (WHO, 1990; WHO, 1984; WHO, 2000; WHO, 1991). Therefore, management of severe childhood pneumonia relies on hospital-based treatment, but practical barriers often prevent children in areas with highest rates from receiving hospital care (Ashraf et al., 2008). In the developing countries, there are not enough paediatric beds in hospitals for admission of all severe cases of pneumonia (Ashraf et al. 2008). In addition, hospitalization may not be possible because of the inability of the parents to visit the hospital because of the long distances to travel or financial or other domestic reasons, such as the need to care for siblings at home and the need for the mother to work (Ashraf et al., 2008; Ashraf et al., 2007). It is, therefore, important to provide some form of institutional care for children who cannot be hospitalized, at least until stabilization of their acute condition (Ashraf et al., 2008). Radiological examination and determination of hypoxaemia by pulse oximetry, have been recently considered as the optimal methods for diagnosing pneumonia. But, they are clearly suitable only for use in the institutional settings like the day-care centres or out-patient clinics. Two prospective observational studies have shown that the day-care facility-based, modified primary care management of severe childhood pneumonia (Ashraf et al., 2008) and severe acute malnutrition (SAM) (Ashraf et al., 2007) is successful and cost-effective as an alternative to hospitalization. Provision of broad-spectrum antibiotics and appropriate supportive care during a stay at established day-care centre during their working hours, followed by the continuation of care at home at night, is an effective alternative to hospitalization of children with severe pneumonia without associated co-morbidities such as SAM (Ashraf et al., 2008). The results of this study

indicate that severe childhood pneumonia without SAM can be successfully managed on a day-care basis at established day-care clinics, if adequately trained and motivated staff and the necessary logistic support can be made available (Ashraf et al., 2008). The results of a randomized controlled clinical trial (RCT) have shown that in a select group of under-5 children with severe pneumonia, without associated co-morbidities such as SAM, can be safely and effectively managed on a day-care basis as effectively as the hospital set-up management, except those children with hypoxaemia requiring prolonged oxygen therapy for more than six hours, and that day-care based treatment option is less expensive than hospital-care (Ashraf et al., 2010). The results also indicate that severe pneumonia without hypoxaemia can be successfully managed on a day-care basis at a day-care clinic, however, identification of those severely pneumonic children having hypoxaemia requiring prolonged oxygen therapy for more than six hours are necessary, as they are at increased risk of death and therefore need to be hospitalized for support and care for a longer period of time (Ashraf et al., 2010). These results would have great impact in the treatment and care of childhood pneumonia, particularly in resource-poor countries where hospital beds are scarce. It can be easily replicated in most urban and rural out-patient clinics and day-care centres, provided that proper training and motivation of the staff as well as provision of logistic support are guaranteed. The additionally needed funds are well invested facing the lower costs of the day-care treatment model compared to those of hospital-care (US$ 114 vs. 178) (Ashraf et al., 2010). However, policy and programme changes would be necessary to add such components to the out-patient clinics and day-care centres, and this would require additional human and financial resources, which is not an easy task. Therefore, this would be important in selecting the intervention for wider implementation in national programmes. The results of our RCT identified a way to more efficiently use scarce hospital beds in developing countries by selecting out children with severe pneumonia for the day-care management, who following existing guidelines, would have been identified as the ones requiring hospitalization. This would be a practical approach in developing countries - a smaller investment in upgrading the day-care facilities through development of trained resources and procurement of some supporting equipment, which could pay back in a much greater way.

Rapid/fast breathing (WHO)
Rapid/fast breathing is defined as when the age-specific respiratory rates become ≥60/minute in neonates and infants aged <2 months, ≥50/minute in infants aged 2 to <12 months, and ≥40/minute in children aged 12-59 months, as shown below:

- Age < 2 months: ≥ 60/minute
- Age 2 to <12 months: ≥ 50/minute
- Age 12 months-5 years: ≥ 40/minute

(N. B. A child who is exactly 12 months old would have fast breathing if s/he breaths ≥ 40/minute. Tachypnoea is the best single predictor of pneumonia in children of all ages).

Lower chest-wall indrawing
Indrawing of the chest wall is a manifestation of reduced lung compliance resulting from the tendency of declining intra-alveolar pressure due to pneumonic consolidation or

airways obstruction. WHO recommends the use of lower chest wall indrawing as a sign of pneumonia requiring admission to hospital, defined as the inward movement of the bony structures of the lower chest wall with inspiration. Lower chest-wall indrawing is also called "subcostal indrawing"/"subcostal retractions"

Clinical types of pneumonia (WHO)
● Very severe pneumonia (up to 5 years)
● Severe pneumonia (up to 5 years)
● Pneumonia (not severe) (only for children aged 2 months to 5 years)
● No pneumonia: cough or cold (up to 5 years)

Very severe pneumonia
If a child with cough or difficult breathing has any one or more of the following danger signs, s/he is classified as having very severe pneumonia (WHO, 2005)

● Not able to drink
● Cyanosis
● Head nodding

"No danger signs" are defined as the absence of all of the following danger signs: not able to drink/feed, central cyanosis, head nodding, stridor in calm child, abnormally sleepy, convulsion, and severe clinical malnutrition.

If a child presents with severe malnutrition with any sign of pneumonia (any of the WHO defined signs of pneumonia or severe pneumonia or very severe pneumonia or crackles or bronchial breath sound in lungs or radiological pneumonia) should be considered as very severe pneumonia.

Severe pneumonia
Severe pneumonia is defined as an young infant (< 2 months) with cough or difficult breathing having fast breathing and/or lower chest-wall indrawing, or a child (2 months to 5 years) with cough or difficult breathing having only lower chest-wall indrawing.

Pneumonia (not severe)
Pneumonia (not severe) is defined as a child (2 months to 5 years) with cough or difficult breathing having only fast breathing, but no lower chest-wall indrawing, or no signs of very severe pneumonia.

Aetiology of CAP
Rational treatment for pneumonia depends on knowing the most likely pathogens in each community, as the relative frequency of different agents may vary from one geographical region to another and depends on the age of the patient, vaccination status, immunological status, relevant exposure and clinical setting at which pneumonia was acquired. Mixed bacterial and viral infections may occur in 30-40% of cases of CAP (Zar et al., 2005). *Streptococcus pneumoniae* is the most common bacterial cause of childhood pneumonia (BTS, 2002)), followed by *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Mycobacterium tuberculosis*. The less common bacterial causes are *Staphylococcus aureus,*

Bordetella pertussis, Pneumocystis jiroveci (previously known as *Pneumocystis carinii),* and *Niserria meningitidis.* In older children, when a bacterial cause is found, it is most commonly *Streptococcus pneumoniae* followed by *Mycoplasma* and *Chlamydia* (BTS, 2002). Viruses are the most common causes of pneumonia in younger children (infancy, pre-school and school age children), except neonates (BTS, 2002). In neonates, the most common causes are *Group B streptococcus beta haemolyticus* (GBB), *Escherichia coli,* *Klebsiella pneumoniae, Chlamydia trachomatis* (3-19 weeks), *Cytomegalovirus (CMV),* and the less common causes are *Staphylococcus aureus, Listeria monocytogenes,* and *Pseudomonas.* The common viruses are Respiratory Syncytial Virus (RSV), influenza, and parainfluenza viruses, adenovirus, and human metapneumovirus (HMV).

The spectrum and frequency of causative agents of bacterial pneumonia in severely malnourished children often differs in pneumonic children without severe malnutrition (Chisti et al., 2009).

Table 1. Causes of CAP according to various age groups and SAM

All age groups
Bacteria are the major causes of CAP in children

1. *Streptococcus pneumoniae*: commonest
2. *Haemophilus influenzae* (including Hib & nontypable strains)
3. *Staphylococcus aureus*
*Atypical bacteria**
4. *Mycoplasma pneumoniae** (> 5 years)
5. *Chlamydia pneumoniae**
6. *Chlamydia trachomatis** (3-19 weeks)
7. *Moraxella catarrhalis*
Gram-negative bacteria**
8. *Klebsiella pneumoniae***
9. *Escherichia coli***
10. *Pseudomonas***
Viruses***
11. Respiratory syncytial virus (RSV)***
12. Influenza A or B***
13. Parainfluenza virus types 1, 3***
14. Adenovirus***
15. Human metapneumovirus (HMV)***
16. Rhinovirus***
17. Coronavirus***
18. Enterovirus***
19. CMV***
20. *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii)*

0-2 months
1. *Group B streptococcus*
Gram-negative bacteria**
2. *Klebsiella pneumoniae***
3. *Escherichia coli***
4. *Pseudomonas***
5. *Staphylococcus aureus*
6. *Chlamydia trachomatis**
7. *Listeria monocytogenes*
8. Viruses***
9. *Ureaplasma urealyticum*
10. *Bordetella pertussis*

2 months-5 years
1. Viruses***
2. *Streptococcus pneumoniae*
3. *Haemophilus influenzae* (including Hib & nontypable strains) (Common in developing countries where vaccination is still not widely used)
4. *Staphylococcus aureus*
5. *Mycoplasma pneumoniae**

Above 5 years
1. *Streptococcus pneumoniae*
2. *Haemophilus influenzae* (including Hib & nontypable strains)
3. *Staphylococcus aureus*
*Atypical bacteria**
4. *Mycoplasma pneumoniae**
5. *Chlamydia pneumoniae**
6. Viruses***

SAM
1. *Klebsiella pneumonia** (26%)
2. *Staphylococcus aureus* (25%)
3. *Streptococcus pneumoniae* (18%)
4. *Escherichia coli** (8%)
5. *Haemophilus influenzae* (including Hib) (8%)
6. *Salmonella species**
7. *Pseudomonas***
8. *Acinetobacter* species**
9. Methicillin-resistant *Staphylococcus aureus* (MRSA)
10. *Pneumocystis jiroveci* (previously known *Pneumocystis carinii*)
11. CMV***
12. Candida

(N.B.   * indicates atypical bacteria   ** indicates gram-negative bacteria *** indicates viruses)

Risk factors for CAP

Some risk factors for CAP are shown below (Zar et al., 2005; Chisti et al., 2009)

Host factors
- Infancy (Age <1 year)
- Prematurity
- Low birth weight (including low weight for age)
- Malnutrition
- Immunosuppression

Social/environmental
- Overcrowding
- Air pollution
- Inadequate housing
- Low socioeconomic status
- Passive exposure to tobacco smoke
- Indoor fuel exposure
- Winter season
- Lack of breast feeding
- Failure to complete immunization
- Attendance at day-care centres
- Presence of coughing sibling (s) at home

Pneumonia in SAM

The WHO defines malnutrition as "the cellular imbalance between the supply of nutrients and energy and the energy and the body's demand for them to ensure growth, maintenance, and specific functions (de Onis et al., 1993). Among the four principal causes of deaths in young children worldwide, undernutrition has been ascribed to be the cause of death in 60.7% children with diarrhoeal diseases, 52.3% of those with pneumonia (Caulfield et al., 2004). More than half of all the childhood deaths are associated with malnutrition (Rice et al., 2000). Pneumonia is common in malnourished children and frequently associated with fatal outcome (Bryce et al., 2005; Rice et al., 2000; Loeb & High, 2005; Nannan et al., 2007). Of children with malnutrition requiring hospital admission, up to two-thirds are diagnosed with pneumonia (Shimeles & Lulseged, 1994; Ahmed et al., 1999). A most recent systematic review revealed those children with pneumonia and moderate or severe malnutrition are at higher risk of death (Chisti et al., 2009). For SAM, the relative risks ranged from 2.9-121.2 with odds ratios ranged from 2.5-15.1. For moderate malnutrition, the relative risks ranged from 1.2-36.5 (Chisti et al., 2009). The clinical classification of pneumonia based on the diagnostic criteria according to the WHO guidelines should be carefully evaluated in children with SAM. A Gambian study evaluated that the respiratory rate cut-off required in malnourished children should be taken approximately 5 breaths per minute less than that in well nourished children and this finding may be related to the lower body temperatures found in severely malnourished children with pneumonia (Falade et al., 1995). Similarly, intercostal indrawing was more common and lower chest wall indrawing was less common in severely malnourished children (Falade et al., 1995; Chisti et al., 2010). In addition, lower chest wall indrawing is not sufficiently sensitive as predictors of pneumonia in SAM and no

visible clinical signs are consistently reliable for the diagnosis of pneumonia in SAM. Malnourished children may not have the strength to manifest some of these physical signs in the same manner as well nourished children (Falade et al., 1995; Chisti et al., 2010). Moreover, data from a recent systematic review suggest that a reliance on simple clinical signs will underestimate the burden of the disease and potentially delay the diagnosis of pneumonia in severely malnourished children (Chisti et al., 2009). Therefore, WHO recommends that children with SAM who present with cough, fast or difficult breathing irrespective of having clinical signs of pneumonia or not, should be treated with appropriate antibiotics to save the lives of these high-risk group of children (Falade et al., 1995).

Occult pneumonia is another entity characterized by the absence of the clinical signs and may be diagnosed by performing a chest radiograph; it may occur in SAM with dehydrating diarrhoea (Hall & Simon, 1987; Murphy et al., 2007; Bachur et al., 1999). The typical clinical signs of pneumonia may be absent in SAM due to sub-optimal inflammatory responses, reduced power of the respiratory muscles, and depletion of potassium and magnesium (Suskind et al., 1990). SAM also contributes to immune deficiency and reduced host defense.

Pneumonia with dehydrating diarrhoea

The clinical classification of pneumonia based on the diagnostic criteria according to WHO should be carefully evaluated in children presenting with dehydrating diarrhoea caused by *Vibrio cholerae*, *ETEC*, as well as rotavirus. If a child presents with severe or some degree of dehydration, then s/he would likely to have acidosis, which is responsible for the development of tachypnoea and it would be very difficult to distinguish clinically whether the increased respiratory rate is due to pneumonia, or due to acidosis, or both. In this situation, it is generally recommended to fully rehydrate the child first with IV/oral fluid (according to the type of dehydration present) within 4-6 hours and then count the respiratory rate for detecting pneumonia according to the standard WHO guideline. It is also recommended to perform a chest radiograph after full hydration of the patient for confirming the diagnosis of pneumonia.

Diagnosis of CAP

The diagnosis of CAP should be considered in any child who has an acute onset of respiratory symptoms, particularly cough, fast breathing, or difficulty in breathing. Diagnosis includes clinical evaluation, radiographic evaluation and etiological investigations to: (i) establish whether pneumonia is present; (ii) assess the severity of pneumonia; (iii) determine the clinical type of pneumonia; and (iii) determine the causative organism. In general, diagnostic investigations to determine the cause of pneumonia are indicated only in children requiring hospitalization (Zar et al., 2005). Bacterial pneumonia cannot be reliably distinguished from viral pneumonia on the basis of any single parameter: clinical, laboratory, or chest radiographic findings.

- Clinical evaluation
- Radiographic evaluation
- Aetiological investigations
- Pulse oximetry

The best objective measurement of hypoxaemia is by pulse oximetry which avoids the need for arterial blood gases. Oxygen saturation (Sao_2) measurements provide a non-invasive estimate of the arterial oxygenation (BTS, 2002). The human eye is poor in recognizing

hypoxaemia. Even under ideal conditions, skilled observers cannot consistently detect hypoxaemia until the oxygen (O_2) saturation is below 80% (Comroe & Bothello, 1947). Pulse oximetry is probably one of the most important advances in monitoring the respiratory problems and these instruments have a reasonable degree of accuracy (Jurban, 1999). The pulse oximeter is easy to use and requires no calibration. However, it requires a pulsatile signal from the patient. When using paediatric wrap around probes, the emitting and receiving diodes need to be carefully opposed. It is also highly subject to motion artifacts. To obtain a reliable reading (i) the child should be resting, still and quiet, not crying or irritable (Zar et al., 2005; BTS, 2002); (i) a good pulse signal (plethysmograph) should be obtained; and (iii) once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate stable trace is obtained (Zar et al., 2005; BTS, 2002). Pulse oximetry as a potentially useful diagnostic tool for the detection of hypoxaemia as an indicator of severe pneumonia; have not been sufficiently evaluated for the diagnosis of children with SAM (WHO, 2005). Widespread use of pulse oximetry is now recommended for monitoring children with severe pneumonia in the developing countries. Perhaps the major challenge facing pulse oximetry is whether this technology can be incorporated effectively into the diagnostic and management algorithms that can improve the efficiency of clinical management of CAP in the developing countries (Jurban, 1999).

Significance of hypoxaemia with CAP and its management
Assessment of oxygenation is important in the evaluation of a child with pneumonia and pulse oximetry should be performed in every child admitted to a hospital with CAP (Zar et al., 2005; BTS, 2002). Hypoxaemia is defined as the arterial oxygen saturation of less than 90% in room air at sea level as recorded by the pulse oximetry, which is the most serious manifestation of childhood pneumonia (Weber et al., 1997). In white patients, an S_PO_2 target of 92% resulted in a satisfactory level of oxygenation, whereas a higher S_PO_2 target of 95% was required in black patients (Jurban, 1999; Jurban & Tobin, 1990). Alternatively, no hypoxaemia is defined as the arterial oxygen saturation of ≥90% in room air as recorded by the pulse oximetry. The median prevalence of hypoxaemia in WHO-defined pneumonia requiring hospitalization (severe and very severe pneumonia) was 13% but the prevalence varied widely (Subhi, 2009). This corresponds to at least 1.5 to 2.7 million annual cases of pneumonia with hypoxaemia presenting to the health-care facilities (Subhi, 2009). WHO recommends for children older than 2 months, the use of oxygen in severe/very severe pneumonia, as ascertained by the presence of a number of clinical indicators of hypoxaemia, including cyanosis, inability to drink, severe lower chest wall indrawing, respiratory rate greater than 70 breaths per minute, grunting respiration, or head nodding (WHO, 2005). Head nodding is a movement of the head synchronous with each breath, which is caused by increased use of auxiliary muscles of respiration and therefore indicates severe respiratory distress and an important clinical sign predicting hypoxaemia (Weber et al., 1997). Only one Gambian study showed that hypoxaemia could be predicted in only half of the children by the presence of a combination of three clinical signs, such as extreme respiratory distress, cyanosis, and severely compromised general status (Weber et al., 1997). Agitation may be an indication that the child is hypoxaemic (BTS, 2002). Hypoxaemia is also a good indicator for detecting the severity of pneumonia (Wang et al., 1995; Hall et al., 1979; Shann et al., 1989). It is a common complication of childhood infections, particularly ALRI, and case fatality rate of pneumonia is inversely related to the arterial haemoglobin oxygen saturation (SaO_2)

(Onyango et al., 1993). In pneumonia - a disease that disproportionately impacts the developing countries, hypoxaemia is an important risk factor for death (Onyango et al., 1993; Duke et al. 2000), as hypoxaemic children are five times more likely to die than non-hypoxaemic children. In patients admitted with pneumonia to a general medical service, it was found that O_2 saturation <90% of at least 5 minutes duration occurred in 26% of the patients (Bowton et al., 1994). On follow-up over the next 4-7 months, those patients experiencing hypoxaemia during the first 24 hour of hospitalization had more than a threefold higher mortality than patients who did not desaturate (Bowton et al., 1994).

In the critical care setting especially for evaluating the progress of children suffering from severe pneumonia, pulse oximetry is also used as one of the most commonly employed monitoring modalities in the critical care setting especially for evaluating the progress of children suffering from severe pneumonia (Jurban, 1999). Moreover, hypoxaemia is also an important risk factor for failure to the day-care management as well as the need for future follow-up admissions (Ashraf et al., 2010). Therefore, measurement of oxygen saturation should be routinely done in all children with severe pneumonia with pulse oximetry, and those with hypoxaemia requiring prolonged oxygen therapy for more than six hours should be referred to a hospital for long-term oxygen therapy (Ashraf et al., 2010). Results of that study were consistent with earlier reports that hypoxaemia in pneumonic children are predictors of severe disease and is a risk factor for death (Onyango et al., 1993; Duke et al., 2000). Hypoxaemia has been overlooked in world-wide strategies for pneumonia control and reducing child mortality (Subhi, 2009). It is also often overlooked in the developing countries, mainly due to the low accuracy of clinical predictors and the limited availability of pulse oximetry, despite of its more accurate detection of hypoxaemia and oxygen therapy for treatment (Subhi, 2009). Many more people do not have access to the health care facilities. Oxygen therapy in developing countries continues to be a low priority on the child health agenda (Subhi, 2009). Oxygen was never mentioned in the recent publication by the WHO and UNICEF efforts to control pneumonia (Wardlaw et al., 2006). The accurate detection of hypoxaemia is important as delivery of oxygen to the hypoxaemic children may improve the outcome. Especially in a setting where oxygen has to be bought in cylinders, a pulse oximeter might be a cost effective purchase, as it allows identification of children who are in need of oxygen, and the amount of oxygen given can be titrated to the actual need of the patient, thus avoiding unnecessary wastage of valuable oxygen (Weber et al., 1997). There is now evidence that ensuring ample supplies of oxygen and promoting a routine and systematic approach of screening for hypoxaemia by using pulse oximetry is associated with improved quality of care and reduced mortality, and that the technology required to do so is affordable and sustainable in district level hospitals and day-care centres in the developing countries (Duke et al., 2000, Dobson et al., 1996; Duke et al., 2008; Dobson, 1991; Steinhoff & Black, 2007; Matai et al., 2008). Pulse oximetry would enable accurate identification of hypoxaemia and might increase the safety and cost effectiveness of this recommendation and this diagnostic tool should be included. This was demonstrated by our recent study reporting successful day-care case management of severe pneumonia using pulse oximetry as an important part of the treatment algorithm (Ashraf et al., 2008). Hypoxaemia is a very common and treatable complication of childhood pneumonia in developing countries and it is a recognized predictor of severe disease and a risk factor for death and correlates with disease severity. For home management to be safe and ethical, it is essential that only children without hypoxaemia are managed outside health-care facilities (Subhi et al., 2009).

Children with hypoxaemic pneumonia requiring prolonged oxygen therapy for more than six hours, need to be identified (which is often difficult using only clinical signs), admitted, and given supplemental oxygen for prolonged duration, and close monitoring (Ashraf et al. 2010). The measurement of SpO_2 as a regularly measured vital sign by using pulse oximetry should be incorporated as an important part of the treatment algorithm for improving the diagnosis of hypoxaemia, and categorizing the severity of pneumonia (Onyango et al., 1993; Steinhoff & Black, 2007; Lozano et al., 1994; Weber & Mulholland, 1998). For treating children with pneumonia, there is an urgent need to increase the widespread availability as well as use of pulse oximetry for monitoring patients with severe pneumonia and effective oxygen delivery systems in the developing countries.

Classification of hypoxaemia

There are two ways of classifying hypoxaemia in children: (i) WHO classification and (ii) British Thoracic Society (BTS) classification as defined below:

(i)   WHO classification of hypoxaemia

Experts from WHO often classifies hypoxaemia as mild, moderate and severe as defined below:

- Mild hypoxaemia: when the arterial oxygen saturation lies between 85 to 90%, the patient is known to have mild hypoxaemia.
- Moderate hypoxaemia: when the arterial oxygen saturation lies between 80 to 85%, the patient is known to have moderate hypoxaemia.
- Severe hypoxaemia: when the arterial oxygen saturation is less than 80%, the patient is known to have severe hypoxaemia.

(ii) BTS classification of hypoxaemia

Similarly, experts from paediatric respiratory medicine in developed countries including BTS often categorized hypoxaemia as mild, moderate and severe as defined below:

- Mild hypoxaemia: when the arterial oxygen saturation lies between 88 to 92%, the patient is known to have mild hypoxaemia.
- Moderate hypoxaemia: when the arterial oxygen saturation lies between 85 to 88%, the patient is known to have moderate hypoxaemia.
- Severe hypoxaemia: when the arterial oxygen saturation is less than 85%, the patient is known to have severe hypoxaemia.

Indications for oxygen therapy
1. Hypoxaemia (oxygen saturation <90% in room air at sea level)
2. Central cyanosis
3. Severe lower chest-wall in-drawing
4. Grunting respiration
5. Restlessness (due to hypoxaemia)
6. Inability to drink or feed
7. Respiratory rate >70 breaths/min
8. Head Nodding

Management of hypoxaemia

- Oxygen should be available at any health care facility where sick children are seen regularly. Oxygen therapy reduces mortality associated with severe pneumonia. It should be given to children who are restless, who had tachypnoea with severe lower chest wall in-drawing, head nodding, cyanosis, or not tolerating oral feeds. The SpO_2 should be maintained above 92%.
- If oxygen is required infrequently then cylinders are the most practical source of oxygen. Cylinders also allow oxygen therapy to be used while the patient is transferred to a facility with more resources.
- If oxygen is used more frequently, then oxygen concentrators are the preferred source of oxygen.
- In hospitals with oxygen supplies, wall oxygen units should be available.
- Low flow meters must be available to give appropriate oxygen flow to children. In most hospitals these will be variable orifice units, but fixed orifice units may be more practical in some units.

Key messages about hypoxaemia in relation to CAP (WHO, 2009)

- Hypoxaemia is a common complication in ALRI in children, and is a strong risk factor for death.

- At least 13% of children presenting to hospitals with severe or very severe pneumonia have hypoxaemia, and the rates are much higher in some hospitals; some exceeding 50%.

- The prevalence of hypoxaemia is higher in referral hospitals than in primary care settings. Hypoxaemia is more common at higher altitude, in younger ages and in certain geographical regions.

- SpO_2 <90% is the most clinically useful definition of hypoxaemia and is considered by most clinicians as an appropriate indication for giving oxygen.

- If pulse oximetry is available only at the time of admission, screen all patients if time allows, or those patients with any clinical signs of hypoxaemia, including all children with emergency or priority signs.

- If oximetry is used at outpatient triage, screen all children with any emergency or priority signs.

- Any child with an SpO_2 <90% should receive oxygen.

- Use oximetry, at least daily, to check any patients who are already on oxygen, and screen any patient who develops any emergency signs or shows other clinical signs of deterioration.

- Explain the meaning of oximetry to parents. This will help them understand the importance of oxygen and other treatments and will involve them in their child's care.

•Children should not be discharged until their SpO_2 has been stable at 90% or more while breathing room air for at least 24 hours, until all emergency and priority signs have resolved, and until appropriate home treatment can be organized.

Methods of oxygen administration

- <u>Nasal prongs</u>: are recommended for most children. Nasal prongs give a maximum fractional concentration of inspired oxygen (F_1O_2) of 28-35% except in small infants when higher concentrations may be obtained. This method does not require humidification of oxygen and ensures that the child receives oxygen during feeding. Oxygen flow rates of 0.5-1 l/minute are required in children less than 2 months old and 2-3 l/minute in infants and children aged 2 months to 5 years.

- <u>Nasal catheters</u>: are usually well tolerated and humidification is not required, but they can be blocked by mucous. Oxygen via nasal catheters gives a maximum F_1O_2 of 35-40%.

- <u>Nasopharyngeal catheters</u>: have the advantage of requiring the lowest flow rate to achieve a given oxygen concentration in the airways. Infants under the age of 2 months can usually be treated with 0.5 minute and infants up to 1 year with 1 minute. However, humidification of oxygen is required and the catheter may be easily blocked. Further, potentially lethal complications including gastric distension, airway obstruction, apnoea, pneumo-orbitus and pneumocephalus may occur. Continuous skilled nursing is therefore necessary to prevent these complications. Consequently, oxygen administration via nasopharyngeal catheter is not recommended.

- <u>Headbox:</u> oxygen is well tolerated by young infants. Headbox oxygen requires no humidification but requires a high flow and a mixing device to ensure the correct F_1O_2 is delivered. This is the *least preferred* method as there is wastage of oxygen and delivered F_1O_2 is unpredictable.

- <u>Facemask:</u> oxygen is designed to deliver 28%-65% oxygen at a flow rate of 6-10 minutes.

- <u>Polymask</u>: In severely hypoxaemic infants who are not ventilated, oxygen should be administered using a polymask whereby F_1O_2 concentrations of 60-80% may be achieved. The flow rate should be regulated to keep the bag of the mask inflated during inspiration and expiration.

- Using the prone position for infants may improve hypoxaemia and the respiratory system compliance (Chaisupamongkollarp et al., 1999) and should be attempted if hypoxaemia is difficult to treat.

- Oxygen should be discontinued when the child is improving and the transcutaneous saturation is above 90% in room air, as recorded by the pulse oximetry.

Radiological diagnosis

Radiological changes may be vague or inconclusive or even absent despite the presence of clinical signs of pneumonia (Doherty, 1991; Hamid et al., 1996; Wafula et al., 1998: Chisti et al., 2009). Conversely, clinical signs of pneumonia can be absent in the presence of radiological signs of pneumonia (Murphy et al., 2007; Bachur et al., 1999; Chisti et al., 2009). There are two main clinical definitions of pneumonia based on the radiological findings:

Bronchopneumonia is defined as a febrile illness with cough, respiratory distress with evidence of localized or more than one or generalized patchy infiltrates on the chest x-ray.

Lobar pneumonia is defined as a febrile illness with cough, respiratory distress with an illness similar to that of bronchopneumonia, except that the physical findings (affected lobe reveals woody dull on percussion, rales, increased vocal resonance and/or bronchial breath sound on auscultation) and radiographic examination indicate lobar consolidation.

Occult pneumonia: It was observed that approximately 25% of the febrile children defined as the rectal temperature becoming more than 38^0 Celsius (Ashraf et al., 2010), with a WBC count >20,000/mm^3, but without any lower respiratory tract findings on examination, had radiographic evidence of pneumonia, known as occult pneumonia, commonly found in children with SAM and children with dehydrating diarrhoea (Murphy et al., 2007; Bachur et al., 1999; Chisti et al., 2009).

Limitations of chest radiography
- Less useful in discriminating the causative pathogens
- Cannot accurately discriminate viral from bacterial pneumonias (Swingler, 2000).
- Wide range of inter- and intra-observer variation in the interpretation (Swingler, 2001; Bada et al., 2007; Pauls et al., 2007; Sarria et al., 2003), not only among the paediatricians, but also among the radiologists, even paediatric radiologists
- Does not result in the improved outcome or change in the treatment of ambulatory settings (Swingler et al., 2000)

Indications for CXR
- To confirm the presence of pneumonia
- To detect clinical pneumonia, unresponsive to the standard ambulatory management
- To identify suspected cavitations or military mottling in PTB
- To identify suspected foreign body aspiration
- To identify hospitalized children for the detection of local complications of pneumonia, such as pleural effusion, pneumothorax, empyema thoracis, advanced stage of bronchiectasis, and lung abscess
- High fever, leukocytosis with no obvious focus of infections (26% such cases may have radiographic pneumonia) (Bachur et al., 1999).
- Children developing secondary heart failure
- Children with congenital problems, such as Congenital Heart Disease (CHD), cystic fibrosis, Down's Syndrome
- Children with re-current attacks of pneumonia

Indications for follow-up CXR

- Children with lobar collapse
- To document the resolution of a round pneumonia (as this may mimic the appearance of a Ghon focus)
- Children with ongoing respiratory symptoms
- Children with re-current attacks of pneumonia

General tests of infection

They may not be useful to differentiate bacterial from viral pneumonia (Nohynek et al., 1995; Toikka et al., 2000; Korppi et al., 2003)

● WBC count, neutrophil count (PMN leukocytosis suggests bacterial pneumonia (Marks & Klein, 1995; Klein, 1992) and lymphocytic leukopenia suggests viral pneumonia) (Austrian & Gold, 1964)

● C-reactive protein (>40 mg suggests bacterial infection)

● ESR

● Procalcitonin

● Copeptin

● Blood culture: to identify the causative bacterial pathogen, that is possible in only less than 30% (10-30%) of cases of CAP (Donowitz & Mandell, 1990), and to determine its sensitivity

● Pleural fluid: if present, should be aspirated and investigated for specific infectious agents

The C-reactive protein, ESR, procalcitonin, and copeptin are the non-specific markers for the diagnosis of pneumonia.

Indications for hospital admission

1. Hypoxaemia (oxygen saturation <90% in room air at sea level)
2. Toxic appearance
3. Respiratory rate >70/minute, or severe respiratory distress
4. Infants < 2 months
5. Impaired level of consciousness
6. Inability to drink or eat
7. Cyanosis
8. Stridor in calm child
9. Chronic lung disease
10. Systemic manifestation
11. Intermittent apnoea
12. Grunting respiration
13. Severe lower chest-wall indrawing
14. SAM
15. Family unable to provide adequate care/non-compliant parents
16. Failure to respond ambulatory care/no response to previous oral antimicrobial therapy
17. Clinical deterioration on treatment
18. Immunocompromised host/immunodeficiency
19. Recurrent pneumonia

Indications for transfer and admission to Paediatric Intensive Care Unit (PICU)
1. Needs ventilator support
2. Failure to maintain a saturation of >90% with oxygen therapy
3. Apnoea or slow irregular breathing
4. Severely acidotic patient
5. Exhaustion with rising respiratory rate and pulse rate
6. Patient is in shock

Differential diagnosis of a child with cough, or difficult breathing

Diagnosis	Points in favour
1. Pneumonia	Fast breathing Lower chest wall indrawing Crepitations on auscultation Bronchial breathing Nasal flaring Grunting respiration Head nodding
2. Cardiac failure	Tachycardia Tachypnoea Enlarged tender liver Dependent oedema Raised jugular venous pressure Central cyanosis Heart murmur Gallop rhythm
3. Pneumothorax	Sudden onset Sudden onset of unexplained tachypnoea and respiratory distress (disproportionate to the severity of pneumonia) Hyper-resonance chest on the affected side on percussion Shift of mediastinum (trachea, apex beat to opposite side) Diminished or absent breath sound on auscultation on the affected side
4. Pleural effusion, empyaema	Stony dull on percussion (it is difficult to elicit in young child) Diminished breath sound on the affected side of lesion Shift of mediastinum (trachea, apex beat to opposite side)
5. Pericardial effusion	Oedema feet Raised jugular venous pressure Apex beat not visible/not palpable Increased area of cardiac dullness

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