East West University

"Clinical and Laboratory characteristics of Sepsis in under 5 year pneumonia children with Diarrhoea"

A thesis report submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of M. Pharm in Clinical Pharmacy and Molecular Pharmacology.

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Declaration by the Candidate

I, Ashiqur Rahman Akand (2014-3-79-017), hereby declare that the dissertation entitled **"Clinical and Laboratory characteristics of Sepsis in under 5 year pneumonia children with Diarrhoea"**, submitted by me to the Department of Pharmacy, East West University, in the partial fulfilment of the requirement for the degree of Masters of Pharmacy is a genuine & authentic thesis work carried out by me during Fall 2015- Spring 2016 under the supervision and guidance of Dr. Sufia Islam, Associate Professor, Department of Pharmacy, East West University.

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Certificate by the Invigilator

This is to certify that the dissertation, **"Clinical and Laboratory characteristics of Sepsis in under 5 year pneumonia children with Diarrhoea",** is a thesis work done by Ashiqur Rahman Akand (2014-3-79-017) in partial fulfillment of the requirements for the degree of Masters of Pharmacy. We further certify that all the sources of information and laboratory facilities availed in this connection is duly acknowledged.

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Endorsement by the Chairperson

This is to certify that the dissertation, **"Clinical and Laboratory characteristics of Sepsis in under 5 year pneumonia children with Diarrhoea",** is a thesis work done by Ashiqur Rahman Akand (2014-3-79-017) in partial fulfilment of the requirements for the degree of Masters of Pharmacy We further certify that all the sources of information and laboratory facilities availed in this connection is duly acknowledged.

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Dr. Shamsun Nahar Khan

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Abstract

Sepsis is a potential complication of pneumonia among under 5-year-old children. This study aimed to determine the symptom, diagnosis, causes, treatment, management and prevention of sepsis in pneumonia children. In this study 208 under 5-year-old pneumonia children with sepsis (cases) and without sepsis (control) attending at icddr,b hospital in Bangladesh were included. The mortality rate(odds ratio [OR] = 3.02, 95% confidence interval [CI], 1.11-8.64, p < 0.027) is high among the children with sepsis (odds ratio [OR] = 3.04, 95% confidence interval [CI], 1.11-8.64, p < 0.05) specifically the children under age of 2 months (odds ratio [OR] = 2.48, 95% confidence interval [CI], 1.22-5.10, p < 0.05). Higher gestational age(weeks) (p<0.002) increases sepsis risk with bacteria in our study. In a multivariate logistic regression analysis showed that clinical dehydration (odds ratio [OR] = 1.89, 95% confidence interval [CI], 1.11-3.23, p < 0.05) is the common clinical sign and change of total wbc count(p<.004) , immature poly(p<.044), bacterial growth on blood culture(p<.037) are the laboratory characteristics of sepsis. Ampicilin and gentamicin injection is used as a first line treatment for sepsis at icddr,b, with an excellent survival rate of 96%. Severely ill patients needed fluid resustication and bubble CPAP.Coagulase-negative *staphylococci*was isolated in 8% of clinical sepsis followed by *Acinetobacter* species (2.4%). Imipenem has been shown 100% sensitive against bacterial isolates from blood culture of the children. In resource poor setting simple clinical and laboratory characteristics in these children will help to have prompt early diagnosis and treatment that will help to reduce mortality.

CONTENT

Page Number

CHAPTER 01

INTRODUCTION

1. Introduction

Mortality Rate of Child death specially new born child is high among all over the world due to severe infection. As a surrogate marker for sepsis, over 90% of worldwide deaths due to pneumonia, meningitis, and other infections occur in less developed nations (Dunser MW et al, 2012). Deaths of newborns within 28 days of birth are a major barrier for improving the survival of children aged less than five years (under-five children) in developing countries (Lawn JE, 2005). The World Health Organization (WHO) reported in 2005 that over 70% of deaths in children under age five occur within the first year of life and 40% occur within the first month (WHO, World Health Report 2005. Make every mother and child count. Geneva: WHO; 2005.p.2005).

Pneumonia causes almost 1 in 5 under-five deaths worldwide: more than 2 million children each year. It kills more children than any other disease - more than AIDS, malaria and measles combined. (Unicef, 2005)

The burden of pneumonia and sepsis is the highest in developing countries. Among the estimated 6.3 million worldwide deaths in under-five children 15% were attributable to pneumonia and over half of the deaths were due to sepsis and the bulk of these deaths occur in Asia and Sub-Saharan Africa (Chisti MJ, 2015).

There is an estimated 150 million new cases of childhood pneumonia each year globally; conditions of 11 to 20 million of those children with pneumonia were severe enough to be life-threatening, thus requiring hospitalization in developing countries. In Bangladesh, pneumonia accounts for about 14% and 12% of deaths from community-based and hospital-based study of under-5 children respectively. Some of the death cases in the community might be due to the inadequate access to the hospital facility (Ashraf H, 2014).

Childhood pneumonia has an estimated incidence of 0.29 episodes per child-year in pre-developed and 0.05 episodes per child-year in developed countries, making it the most common cause of pediatric sepsis; it is also the leading cause of mortality in children less than 5 year of age. Pre-developed countries with large populations of children bear the major burden of pediatric sepsis. Of the approximately 156 million new cases of pneumonia per year

worldwide, 151 million are estimated to be in the developing world. Contaminated water, poor sanitation, indoor air pollution, crowding, low birth weight, and insufficient immunization and nutrition allow pathogens to invade and multiply relatively unchecked in the body. (Rudan I, 2008)

The number of neonatal patients at risk of acquiring nosocomial infections is increasing because of the improved survival of very low birth weight infants and their need for invasive monitoring and supportive care. (Adams- Chapman *et al,* 2002)

The risk of Sepsis is high when children with pneumonia have the co-morbidity of severe acute malnutrition (SAM) and has been reported to be 15 times higher compared to deaths in children who did not have severe acute malnutrition (SAM). Children with severe wasting or severe under-nutrition, or nutritional edema were considered as SAM. Most of these pneumonia and diarrhoea related deaths in SAM children occur in the critical care wards of developing countries (chisti mj 2013). WHO reported that, about 45% of all child deaths are linked to malnutrition. (WHO, 2008)

Many developing countries have reported 25% reductions in pneumonia episodes per child-year over the past decade, yet pneumonia remains the leading cause of childhood mortality globally. The deaths were disproportionately higher among severe acutely malnourished (SAM) children, particularly in sub-Saharan Africa and in South-East Asia. A recent Lancet Nutrition Series reported that 15% of global and 16.7% of the South-East Asian childhood pneumonia deaths were attributable to severe wasting. Sixty-seven percent (67%) of the deaths due to severe pneumonia were reported to occur early during the course of illness, i.e. in the first 48–72 hours. (Chisti MJ, 2011)

2. Risk Factors of Sepsis

Some of risk factors for Sepsis include; prematurity or low birth weight, preterm labour, premature or prolonged rupture of membranes, maternal chorioamnionitis, foetal hypoxia, traumatic delivery, male gender and low socio-economic status.

2.1 Environmental risk factors

Sepsis is more common in colder months, both in the UK (35% higher in winter than in summer) and US (17.7% higher in fall than in summer). The case fatality rate for sepsis is also higher in winter, despite similar severity of illness. Respiratory infections, particularly pneumonia have the greatest seasonal change, with their highest incidence in colder months. (Mayr F B, 2014)

The incidence is increased during the colder months in temperate climates for unknown reasons. It is presumed that person-to-person transmission of respiratory droplets enhanced by indoor crowding, impaired mucociliary clearance, and the peak of viral infections that led to viral pneumonias with secondary bacterial pneumonias are the cause of this peak. In tropical climates, peaks of respiratory infections are seen sporadically throughout the year. (Schlaudecker EP, 2010)

Environmental factors such as dust, unhealthy household condition, and high room temperature during hot summer months, cold allergy, and winter seasons were perceived as the causes of pneumonia in the present study. In rural Bangladesh, child usually comes in contact with smoke especially produced while cooking food, which is a known risk factor for pneumonia. (Ferdous F & Chisti mj,2014)

Air pollution, maternal illiteracy, and unfamiliarity with respiratory illnesses are the risk factors for childhood pneumonia. (Ferdous F & Chisti mj,2014)

Table 1 Highlights the risk factors of sepsis in neonates and older children and teens.

(Schlaudecker EP, 2010)

Risk Factors of sepsis

Risk factor for children	**Risk factor for neonates**
• Sex: M:F = 1.25:1–2:1	**Early-onset**
• **Socioeconomic/environmental factors:**	• Prolonged rupture of the fetal membranes (>18 hours)
○ Lower socioeconomic status (family size, crowding)	• Maternal amnionitis
○ Low maternal educational level	• Premature delivery
○ Poor access to care	• Fetal tachycardia
○ Indoor air pollution	• Maternal intrapartum fever
○ Malnutrition	
○ Lack of breastfeeding	**Late-onset**
○ Cigarette smoke (active and passive smoke exposure)	• Assisted ventilation (4 times higher in intubated than in nonintubated)
○Alcohol, drugs, and cigarettes use (increased risk of aspiration) in teens	
• **Underlying cardiopulmonary disorders and medical conditions:**	• Anomalies of the airway (eg, choanal atresia, tracheoesophageal fistula, and cystic adenomatoid malformations)
○ Congenital heart disease	• Severe underlying disease
○ Bronchopulmonary dysplasia and chronic lung disease	• Prolonged hospitalization
○ Diabetes mellitus	• Neurologic impairment resulting in aspiration of gastrointestinal contents
○ Cystic fibrosis	
○ Asthma	• Nosocomial infections due to poor hand washing or overcrowding
○ Sickle cell disease	
○ Neuromuscular disorders (especially those associated with altered mental status)	
○ Some gastrointestinal disorders (eg, gastroesophageal reflux, tracheoesophageal fistula)	
○ Congenital and acquired immunodeficiency disorders	

3. Bacterial Causes of Sepsis

Bacteria are almost always the cause of sepsis in newborns and infants. The causative organisms include a wide variety of gram positive and gram negative organisms. These include *staphylococcus aureus*, coagulase negative *staphylococcus (*CONS*), Escherichia coli (Ecoli)*, *Listeria monocytogenes*, *Klebsiella pneumoniae*, Group B *streptococcus (*GBS*)*, *Acinetobacter*, *Serratia*, *Pseudomona*s, *Haemophilus influenzae*, *Enterobacter, Candida* and anaerobes.

Streptococcus pneumoniae and *Haemophilus influenzae* type B were the most important primary bacterial pathogens and were associated with 33% and 16% of the pneumonic deaths respectively. (Chisti MJ, 2015)

Mycobacterium tuberculosis is also believed to be an important cause of pneumonia in severely malnourished children. The risk of disease after primary infection with TB is as high as 50% in infants below the age of one year, 10-20% in children aged 1-2 year(s), 5% in children aged 2-5 years. (Chisti MJ et al. 2013)

Pseudomonas sepsis often occurs in patients with burns, malignancy, or immunodeficiency or in preterm infants. Most of these infections are nosocomially acquired. *Pseudomonas* infection is clinically indistinguishable from other forms of Gram-negative bacterial infection. For this reason, patients with *Pseudomonas* infection often receive empirical antibiotics that are not sufficiently active against *Pseudomonas*, especially before culture results and antibiotic sensitivities become available. Despite recent improvements in therapy, *Pseudomonas* bacteremia remains fatal in more than 20% of cases. In a recent large multicentre study of all age groups, *Pseudomonas* bloodstream infection (BSI) was multidrug resistant (MDR) and associated with crude mortality rates of 39% in all patients and 48% in intensive care unit patients. (Farhana Akram & Chisti MJ, 2014)

A study among One hundred and forty-eight patients in Washington Hospital Center showed that 77 (52%) patients with 24 (16%) patients having polymicrobial infections. The most common pathogens were *Streptococcus pneumoniae* (19%), followed by *Staphylococcus aureus* (18%), *Haemophilus influenzae* (14%), *Klebsiella pneumoniae* (11%), and *Pseudomonas aeruginosa* (7%). Infection with *P aeruginosa* or *Acinetobacter* species carried a very high mortality (82%). (Paul E. Marik, 2000)

In many hospitals gram positive organisms cause up to 70% of nosocomial infections in neonates with coagulase negative *Staphylococci* accounting for more than half of these. (Van der Zwet WC *et al,* 2005)

In developing countries gram negative organisms may be far more prevalent as neonatal pathogens. Neonatal surveillance in developed countries generally identifies Group B Streptococcus (GBS) and *E.coli* as the dominant early onset sepsis pathogens and Coagulase-negative *Staphylococcus* (CONS) as the dominant late onset sepsis pathogen followed by Group B Streptococcus (GBS) and *Staphylococcus aureus*. (Vergnano *et al,* 2005)

A retrospective study at neonatal intensive care unit in Australia showed that the common causes of sepsis were Coagulase-negative *Staphylococcus* (38.8%), Group B Streptococcus (20.1 %)and gram negative bacilli (20.1%). (Sanghvi *et al,*1996)

In a prospective study over a 5 month period showed that the predominant organisms were gram negative (73.6 percent of isolates) with *klebsiella* species topping the list at 31 percent (Musoke *et al*,2000).

In some cases of, pneumonial sepsis in newborns, bacteria enter the baby's body from the mother during pregnancy, labor, or delivery. Some pregnancy complications that can increase the risk of pneumonial sepsis for a newborn include:

- maternal fever during labor
- premature rupture of the amniotic sac (before 37 weeks of gestation)
- rupture of the amniotic sac very early in labor (18 hours or more before delivery)

Some bacteria, in particular Group B Streptococcus (GBS) can be acquired by the newborn during delivery — 15% to 30% of pregnant women carry the bacterium for GBS in the vagina or rectum, where it can be passed from mother to child during delivery. (kidshealth, 2016)

4. Clinical Features

Neonates with sepsis may have nonspecific signs and symptoms and the initial manifestations may have limited symptomatology. Some of the features include temperature instability, hypotension, tachycardia, bradycardia, apnoea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distension and jaundice. (Nelson Textbook of Paediatrics, 17th edition, 2004)

The common morbidities noted during the follow-up visits at Radda Clinic were cough (28%), fever (20%), and rapid breathing (13%) while less common symptoms were difficult breathing (5%), feeding difficulty (4%), and chest wall-indrawing (4%). (Ashraf H, Chisti MJ,2012)

Hypoxemic severe acute malnourished children with pneumonia attended the hospital more often with convulsions. Convulsions is a warning sign of severe/very severe pneumonia which might be related to cerebral ischemia either from hypoxemia or impaired cerebral perfusion secondary to consequence of sepsis.(Chisti MJ, 2013)

Data from Chisti MJ suggested that under-five SAM children with pneumonia/sepsis who had hypoxemia, clinical dehydration, abdominal distension at admission, and those who require blood transfusion for the management of crystalloid resistant systolic hypotension during the course of hospitalized treatment are at higher risk of death. (Chisti MJ,2013)

A study report about Common signs of children's pneumonia/sepsis in Kumudini Women's Medical College and Hospital mentioned by mother that chest retractions, difficulty in breathing, noisy breathing, and the child stopping taking breast milk or uncontrolled crying are the signs and symptoms of pneumonia. Children are taken to the hospital because the child had at least two signs and symptoms such as severe cough with running nose, common cold, sneezing, noisy cough, noisy breathing, difficult or rapid breathing, chest retractions, fever with shivering, lethargy, and high fever with convulsion. (Ferdous F, Chisti MJ, 2014)

In a field trial at 39 villages in India, recording signs of sepsis as pneumonia showed that, simultaneous presence of any 2 of 7 signs (reduced or stopped sucking; weak or no cry; limbs becoming limp; vomiting or abdominal distension; baby cold to touch; severe chest indrawing) predicted sepsis death with sensitivity 100%, specificity 92%. The criteria identified 10.6% of the

neonates in the community as suspected sepsis, at a mean of 5.4 days before death. The criteria remained valid in the postintervention period. Any 1 of the 5 maternally observed danger signs (reduced sucking, drowsy or unconscious, baby cold to touch, fast breathing and chest indrawing) gave 100% sensitivity and identified 23.9% neonates for seeking care. (Bang AT, 2005)

4.1 Respiratory changes: The earliest clinical sign of sepsis is often a rapid respiratory rate. This may be driven by pyrexia, lactic acidosis, local lung pathology, pulmonary oedema , cytokine-mediated effects on the respiratory control centre or a combination of several of these factors. Hypoxaemia occurs as a result of pulmonary pathology, shunting of deoxygenated blood through the lungs (cytokine mediated) or pulmonary oedema secondary to capillary leak. (sepsisforum.com, access- 2016)

4.2 Circulatory changes: The release of bradykinin and production of cytokines cause normally 'tight' endothelial junctions to become loose resulting in increased vascular permeability with accompanying plasma leak i.e. capillary leak. This leads to hypovolaemia and reduced preload. Bradykinin and some cytokines also cause peripheral vasomotor failure: peripheral blood vessels dilate and diastolic blood pressure falls. The combination of reduced intra-vascular volume and vasodilatation often produces hypotension.
The body attempts to compensate by increasing the heart rate and mobilizing fluid from the interstitial space or blood from the splanchnic circulation, but this is inefficient due to cytokine mediated effects. (ihi.org, 2016)

4.3 Impaired tissue utilization: Although the cardiac output may rise in sepsis there is an unhinging of tissue oxygen delivery and requirements. There may be shunting of blood in the micro-circulation, by-passing cells which become hypoxic. There is also cytokine mediated disturbance of mitochondrial oxygen handling. (Advancesinsepsis.com, access-2016)
Proinflammatory cytokines induced by inflammation can stimulate anemia of inflammation by limiting serum iron and increasing cellular iron stores by modulating the expression and activity of various iron regulatory proteins including hepcidin, FPN, ferritin, and the iron importer divalent metal transporter 1 (S.Islam, 2015). This blocks the progress of oxygen down the

normal cascade. These both lead to lactic acidosis, organ dysfunction and ultimately multiple organ failure. (Advancesinsepsis.com, access-2016)

4.4 Criteria for Systemic Inflammatory Response Syndrome (SIRS) : Systemic inflammatory response syndrome (SIRS) is characterized by specific physiological alterations, including temperature, white blood cell count, heart rate, and respiratory rate, caused by a broad spectrum of noninfectious and infectious triggers. (S.Islam, 2015)

The original 1991 ACCP/SCCM diagnostic criteria for SIRS and sepsis are still considered the standard of diagnosis with a few caveats. (Levy MM, 2003)

- Body temperature <36°C or >38°C
- Heart rate > 90 beats/minute
- Respiratory rate > 20 breaths/minute *or* $PaCO_2$of < 32mmHg
- An alteration in WBC count, such as a count > 12,000 cells/cu mm or < 4,000 cells/cu mm, or the presence of more than 10% immature neutrophils

Pediatric age-specific SIRS criteria					
	Heart Rates, Beats/Min *b,c*			Leukocyte Count	
Age Group	Tachycardia	Bradycardia	Respiratory Rate	Leukocytes X 103/mm *3b,c.*	Hypotension, mm Hg**3**
0 days to 1 wk	>180	<100	>60	>34	<59
1 wk to 1 mo	>180	<100	>50	>19.5 OR <5	<75
1 mo to <2 yrs	>180	<90	>35	>17.5 OR <5	<75
2-5 yrs	>140	Not applicable	>30	>15.5 OR <6	<75
6-12 yrs	>130	Not applicable	>20	>13.5 OR <4.5	<83
>12 yrs	>110	Not applicable	>20	>11 OR <4.5	<90

5. Diagnosis

Neonatal sepsis in pneumonia is clinically diagnosed by a combination of clinical signs, nonspecific laboratory tests and microbiologically confirmed by detection of bacteria in blood by culture. Blood culture is the gold standard for diagnosis of septicaemia. (Marchant *et al,* 2013)

Clinical manifestations:

- BP, heart rate, and O_2 monitoring
- CBC with differential, electrolyte panel and creatinine, lactate
- Invasive central venous pressure (CVP), PaO_2, and central venous O_2 saturation ($ScvO_2$) readings
- Cultures of blood, urine, and other potential sites of infection, including wounds in surgical patients

5.1 Radiographic Imaging

The presence of infiltrates on chest radiograph in a child with fever and respiratory distress confirms the diagnosis of pneumonia; however, the absence of chest x-ray findings does not rule out pneumonia if there is high clinical suspicion. This is due to several factors: the radiographic findings may lag behind the clinical picture, dehydrated children may not have an infiltrate initially, and it is impossible to differentiate atelectasis from pneumonia on a single chest radiograph (an infiltrate that resolves in less than 48-72 hours is more likely atelectasis than pneumonia). (Bradly JS,2011)

An initial chest radiograph may be indicated in the following situations:

1. Severe disease, hypoxemia, or significant respiratory distress that requires hospitalization.
2. Inconclusive clinical findings.
3. To rule out other causes of respiratory distress (eg, foreign body, heart disease, underlying cardiopulmonary conditions).
4. Prolonged fever and worsening symptoms despite adequate antibiotic coverage to rule out complications (parapneumonic effusion, pneumothorax).
5. As part of the workup of a young infant with fever without a source and leukocytosis.

Follow-up chest radiographs are routinely indicated in children who are severely affected. Follow-up radiographs are indicated in complicated pneumonias that are clinically unstable, in patients receiving adequate antibiotic coverage for 48 to 72 hours with poor clinical improvement or worsening, and in recurrent pneumonias that involve the same lobe to rule out a suspected anomaly, chest mass, or foreign body.

Children with complicated pneumonia (sepsis) treated with chest tube placement or video-assisted thoracoscopic surgery (VATS) require routine daily chest radiography if they are clinically unstable.

Chest radiographs should be obtained in the posteroanterior upright position in children younger than 4 years and in the supine anteroposterior position in younger children. A lateral view is preferred, and a lateral decubitus view (with affected side down) should be obtained when a pleural effusion is suspected.

Bedside ultrasonography of the chest was studied and compared with chest radiographs. In one prospective cohort study of 200 patients, ultrasonography had an overall sensitivity of 86% (95% CI, 71%-94%) and a specificity of 89% (95% CI, 83%-93%). Specificity increased to 97% in children with consolidation greater than 1 cm by chest radiographs. The authors concluded that bedside ultrasonography was found to be a highly specific, noninvasive, radiation-free test that can be used by clinicians to diagnose pneumonia. (Shah VP, 2013)

5.2 Laboratory Testing

Routine laboratory testing is indicated to diagnose pneumonia with suspected sepsis, particularly in children who are hypoxic, and have suspected community-acquired pneumonia (CAP) and are candidates for inpatient treatment. Patients with hypoxemia, severe respiratory distress, possible complicated pneumonia, or associated comorbid conditions may need further workup.

5.2.1 Blood Tests

A complete blood cell count with differential is typically performed in children who are candidates for hospitalization. Peripheral eosinophilia suggests *Chlamydia trachomatis* in infants with afebrile pneumonia of infancy. Acute phase reactants, such as erythrocyte

sedimentation rate, C-reactive protein, and serum procalcitonin are other diagnostic tests. Other blood tests might include serum electrolytes to assess for degree of dehydration and to rule out hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion. (Virkki R,2002)

5.3 Microbiologic Tests

5.3.1 Blood Cultures: Blood culture is the gold standard for diagnosis of sepsis.

- Routinely indicated in the inpatient setting in children who have toxic effects and fully nonimmunized
- In patients with parapneumonic effusion or empyema the yield increases to 30% to 40%.
- Should be obtained in children hospitalized with severe disease, who fail to demonstrate response despite adequate antibiotic coverage, or in children with complicated pneumonia.
-
- Follow-up blood cultures are necessary in patients.

5.3.2 Sputum Cultures

- Difficult to obtain and induce in young children (<5 years) and in outpatient setting.
- Should be obtained in older hospitalized children, children who are in intensive care, those who have complicated pneumonia, or those who do not respond to empiric therapy; good-quality sputum samples can be obtained.
- An adequate sputum specimen for examination is one with:
    - 10 or fewer epithelial cells
    - And 25 or more polymorphonuclear leukocytes under low power (×100).
    - A predominant microorganism and/or intracellular organisms suggest the etiologic agent.

5.3.3 Pleural Fluid

- When pleural fluid is more than minimal in amount, it should be obtained through a diagnostic (and possibly therapeutic) thoracentesis and sent for Gram stain and culture ideally before administration of antibiotics.

- Because most children have already received antibiotics by the time the pleural fluid is sampled, thereby significantly reducing the yield of conventional cultures, antigen testing and PCR may be helpful in identifying the causative agent.

- Studies such as pH, glucose, protein, and lactate dehydrogenase rarely change management and are not recommended, except for white blood cell count with differential to differentiate bacterial from mycobacterial causes and from malignancy. (Puligandla PS,2008)

5.4 Invasive Studies

Invasive studies to establish the cause of pneumonia in children are reserved for the critically ill child or the child with significant comorbidity whose initial diagnostic workup is inconclusive and in whom the risk of establishing the diagnosis outweighs the risk of the invasive procedure. Invasive studies include the following:

- Bronchoscopy with Bronchoalveolar lavage (BAL) - Quantitative culture techniques differentiate true infection from upper airway contamination.

- Morning gastric lavage through a nasogastric tube for acid fast *Bacilli* strain and culture is used in the diagnosis of tuberculosis.

- The Bronchoalveolar lavage (BAL) technique for obtaining cultures in intubated patients uses a catheter inside , avoiding sampling the upper airway and directly obtaining cultures from the alveoli. Because of the anatomy of the lungs, samples are obtained from the right lower lobe.

- Computed tomography or ultrasonography-guided percutaneous needle aspiration of the affected lung tissue.

- Lung biopsy either by a thoracoscopic or thoracotomy approach is rarely used in United States, but open biopsy yields diagnostic information that may affect medical management in up to 90% of patients. In one study, open lung biopsy confirmed the infectious cause in 10 of 33 patients, 8 of whom had a prior nondiagnostic BAL. Lung biopsy is commonly used in immunocompromised patients. (Shah S, 2007)

5.5 Differential Diagnosis

When the clinician is faced with a child presenting with fever, tachypnea, cough, respiratory distress, and infiltrates on chest radiograph, the diagnosis of pneumonia is highly likely. Other diagnoses, however, must be considered. In a neonate with respiratory distress, congenital anatomical cardiopulmonary anomalies must be ruled out for tracheoesophageal fistula, congenital heart disease, and sepsis. In infants and young children, foreign body aspiration (even if no history of any witnessed aspiration), bronchiolitis, heart failure, sepsis, and metabolic acidosis may all cause tachypnea. In these cases, a careful history and physical examination and a supportive imaging study can distinguish pneumonia from other conditions. (Rani S, 2013)

Children who present with respiratory distress and wheezing may have community-acquired pneumonia (CAP); however, first-time wheezing of asthma with or without bronchiolitis can be the true diagnosis. A patient with asthma or bronchiolitis may have a radiographic picture that is normal or has infiltrates that could potentially be due to atelectasis. (Esposito S, 2012)

5.6 Diagnosis Test at ICDDR, B

5.6.1 Clinical Procedure

Chest radiography is done for all study children, following the hospital's standard of care, and other investigations included a tuberculin skin test (TST), a blood culture, and microscopy and culture of gastric lavage and induced sputum (a single sample of each from each child). (Chisti MJ,2014)

A standard procedure of TST was followed and induration measured at 72 hours. Both sputum sampling procedures were performed after the children had fasted for 4 hours. Gastric lavage fluid was collected early in the morning before the children were ambulant, using an appropriate sized nasogastric tube introduced in the previous night. Samples were collected from gastric lavage and induced sputum following standard protocols, into sterile tubes and immediately sent to the TB laboratory for processing. Gastric lavage is an established procedure at icddr,b while sputum induction was introduced for this study following training under a concurrent study that examined the aetiology in child pneumonia. (Chisti MJ,2014)

In ICU Unit, Arterial oxygen saturation (SpO_2) is measured using a portable pulse oximeter (OxiMax N-600, Nellcor, Boulder, CO) and blood glucose is estimated using a bedside Gluco-check machine (STADA, Bad Vilbel, Germany). (Chisti MJ,2013)

5.6.2 Laboratory Procedures

Sputum samples were decontaminated according to the standard Petroffs' method in the tuberculosis laboratory of icddr, b as described earlier. (Chisti MJ,2014)
Acid fast *Bacilli* (AFB) were detected by light microscopy on sputum smear following Ziehl-Neelsen staining and decontaminated samples were inoculated on Löwenstein-Jensen slants for mycobacterial culture. (Chisti MJ,2014)

The Xpert MTB/RIF assay became available during the study period in November 2011 and this investigation was incorporated into the study following approval of the amended protocol by the Ethical Review Committee (ERC). The gastric lavage sample was split into two separate

sterile containers, and two sterile mucous extractors were used for sample collection following sputum induction. In each case, one sample was for smear microscopy and mycobacterial culture, and the other was for analysis by real-time PCR using the Xpert MTB/RIF assay following the standardized procedures . (Nicol MP, 2011)

Drug susceptibility testing (DST) is done for all positive cultures. In each lot of DST, a strain of H37Rv was used as the sensitive control strain and a known Multi drug resistant (MDR) strain is used as the resistant control strains. Mycobacterial species were identified by molecular testing. Blood cultures are processed using the BACTEC system (BioMerieux, Marcy L'Etoile, France). (Chisti MJ, 2010)

The laboratory tests of interstitial lung disease (ILD) included: Blood for total and differential white blood cell (WBC) count, blood culture and sensitivity, serum electrolytes, creatinine, and a chest X-ray to diagnose pneumonia. (Chisti MJ, 2013)

6. Treatment

Pneumonia can be treated through simple interventions but without early treatment, it can be fatal. The statistic that only 54% of children in Bangladesh with pneumonia are taken to qualified healthcare providers as well as the fact that it is the world's leading cause of death for children speaks for itself. (unicef.org, 2005)

6.1 Antimicrobial, Fluid and Vaccine Management

In almost every case of sepsis including pneumonia, patients need to be hospitalized, treated with appropriate intravenous antibiotics, and given therapy to support any organ dysfunction. Sepsis can quickly cause organ damage and death. Most cases of sepsis are treated in an intensive-care unit (ICU) of the hospital. (medicine.net)

There cannot be a single recommendation for the antibiotic regimen of sepsis for all settings. The choice of antibiotics depends on the prevailing flora in the given unit and their antimicrobial sensitivity. The decision to start antibiotics is based on clinical features and or positive septic screen. (Sankar *et al*, 2008) Additionally, early and efficient fluid resuscitation in children with sepsis help to reduce deaths. (Biban P,2012)

6.1.1 Antibiotic Administration

The importance of rapid initiation of antibiotic therapy for life-threatening infections has become increasingly apparent in the last few decades, as demonstrated by improved outcomes in patients with community-acquired pneumonia who receive antimicrobials early rather than later in the course of their disease. It has been shown from different retrospective studies that there is a strong positive relationship between prompt antimicrobial administration and improved outcome in severe sepsis or septic shock. The most commonly quoted study shows that in the first 6 hours after development of septic shock every hour of delay in initiating antibiotic therapy was associated with a 7.6% increase in mortality. This led the international Surviving Sepsis Campaign to recommend that patients with severe sepsis and septic shock receive rapid initiation (beginning in less than 1 hour) of antimicrobials. (Sweet D, 2012)

A study among 183 paediatric sepsis patients in the intensive care unit (ICU) and longer-stay unit (LSU) of the Dhaka Hospital of icddr,b showed that, One hundred and eighty-one patients had received a combination of injection of ampicilin and gentamicin, and two patients had received the combination injection of ceftriaxone and gentamicin. Only 25% patients required a change of antibiotics to the combination of intravenous ceftriaxone plus gentamicin after non-response of injection of ampicilin and gentamicin combination; 4% patients died who received injection ampicilin and gentamicin whereas none died among the other two patients who received injection of ceftriaxone and gentamicin. Observation of this study is, 99% of under-five children with clinical sepsis received injection ampicilin and injection gentamicin as the first-line antibiotics, with an excellent survival rate of 96%. The combination of injection ampicilin and gentamicin as the first-line antibiotics for the management of sepsis in children even beyond the neonatal age is very effective, resulting in lower mortality. WHO has also recommended this combination therapy as the treatment of choice for children with clinical sepsis at inpatient facilities. (Bibi S & Chisti MJ, 2012)

Third-generation cephalosporins, such as ceftriaxone, have a broad-spectrum activity and further-increased activity against Gram-negative organisms. This may be particularly useful in treating Gram-negative bacteria causing severe forms of sepsis where a combination of injection ampicilin and gentamicin is ineffective. A combination of intravenous ceftriaxone and gentamicin should be preserved as the second-line therapy, if the first-line therapy (injection ampicilin and gentamicin) fails (on the basis of no clinical improvement in 48 hours after initiation of therapy or clinical deterioration within 24 hours after initiation). (Bibi S & Chisti MJ, 2012)

A German study suggested that, Infections in intensive care unit (ICU) patients like severe pneumonia, e.g. nosocomial (NP) and community-acquired pneumonia (CAP), or septicemia must be treated promptly and effectively because of the ensuing high mortality. Treatment is thus empirical and starts before the results of microbiological cultures are known (Bodmann KF, 2005).

The risk factors affecting mortality include severity of illness, virulence of etiologic pathogens and the use of inappropriate antibiotic therapy. Several studies have shown that modifying

initially inadequate therapy, according to microbiological results, does not result in a better outcome. Due to this, antibiotic treatment requires agents which have an appropriate spectrum covering the likely pathogens causing these infections. In critically ill patients, the need for empirical first-line treatment covering a broad spectrum of Gram-negative and Gram-positive bacteria, as recommended in international guidelines (e.g. those of the American Thoracic Society or the Infectious Diseases Society of America), is justified in the presence of resistant organisms commonly documented in these patients. To choose an appropriate, initial antibiotic regimen, local and national resistance data have to be considered. With respect to new German resistance trends in Gram-negative and Gram-positive bacteria, the Paul Ehrlich Society of Chemotherapy has recently published guidelines for the treatment of infections in hospitalized patients. Especially in ICU patients with severe pneumonia (NP or CAP) or septicemia and risk factors like underlying diseases, antibiotic pretreatment or mechanical ventilation, agents with an appropriate spectrum encompassing *Pseudomonas aeruginosa* as well as other Gram-negative bacteria like *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. and Gram-positive bacteria (e.g. *Staphylococcus aureus*, *Pneumococci* and *Streptococci*) are recommended as treatment of choice. Combination therapy with an anti-pseudomonal beta-lactam and a fluoroquinolone or an aminoglycoside are recommended for these patients to provide the necessary spectrum of activity and to prevent the emergence of resistant organisms. On the other hand, clinical trials and meta-analyses have shown the efficacy, tolerability and cost-effectiveness of monotherapy regimens even in critically ill and immunocompromised patients. Appropriate beta-lactam antibiotics recommended in international and German guidelines for the treatment of severe community-acquired pneumonia, nosocomial pneumonia and septicemia, either as monotherapy or as combination therapy, are the 4th generation cephalosporin cefepime, the carbapenems imipenem and meropenem, and the acylamino-beta-lactamase inhibitor combination piperacillin-tazobactam.(Bodmann KF, 2005)

Although there are several key components to the early management of septic patients, none may be as simple or as important as early initiation of antibiotics. The development of systems that allow clinicians to deliver antimicrobials within minutes of identifying septic patients is

likely the single greatest lifesaving improvement that many emergency departments can implement.

6.1.2 Fluid Resuscitation

The early administration of fluids and antibiotics is the cornerstone of management for patients with sepsis.

Therapeutic priorities for patients with sepsis include:

- Early initiation of supportive care to correct physiologic abnormalities, such as hypoxemia and hypotension.
- Distinguishing sepsis from systemic inflammatory response syndrome (SIRS) because, if an infection exists, it must be identified and treated as soon as possible. (Dellinger RP, 2008)

EARLY MANAGEMENT OF SEPSIS— The first priority in any patient with severe sepsis or septic shock is stabilization of their airway and breathing. Next, perfusion to the peripheral tissues should be restored and antibiotics administered. (Dellinger RP, 2013)

Stabilize respiration — Supplemental oxygen should be supplied to all patients with sepsis and oxygenation should be monitored continuously with pulse oximetry. Intubation and mechanical ventilation may be required to support the increased work of breathing that typically accompanies sepsis, or for airway protection since encephalopathy and a depressed level of consciousness frequently complicate sepsis. (Sessler CN, 2004)

Once the patient's respiratory status has been stabilized, the adequacy of perfusion should be assessed:

6.1.2.1 Monitoring

6.1.2.1.1 Static Monitoring

In sepsis, it is important to identify which patients will respond to volume resuscitation. In the critically ill, this means identifying the patient whose cardiac output will improve with fluid administration, called preload responsiveness. Traditionally, static indicators such as Central venous pressure (CVP) have guided therapy. However, historic and recent evidence suggest CVP

is a poor predictor of fluid responsiveness. In a systematic review on the usefulness of the CVP, Marik et al. concluded that it is neither a good indicator of volume status nor a predictor of responsiveness to fluid therapy (Marik et al. 2008). It has been suggested that CVP no longer be used to guide fluid therapy; although it remains in the surviving sepsis guidelines, some authors suggest that these recommendations should be revisited. In fact, recent evidence suggests CVP guided fluid resuscitation leads to venous congestion increasing the incidence of pulmonary complications in septic shock. However, removal of CVP parameters from the guidelines may result in inadequate volume resuscitation and many centres continue to use static CVP measurement, despite evidence that it is an unhelpful guide for fluid administration. Furthermore, respiratory variation in the CVP is useful for predicting fluid responsiveness in spontaneously breathing patients. (S. Magder, 1992)

6.1.2.1.2 Dynamic Monitoring

The most useful indicators of preload responsiveness are phasic changes in stroke volume and systolic blood pressure during positive pressure mechanical ventilation. Stroke volume variation (SVV) is the ratio of maximal stroke volume difference during several respiratory cycles and the mean stroke volume over the same period. Since the arterial pulse pressure depends on the amount of blood ejected during each systole (stroke volume), the pulse pressure variation (SPV) covary with Stroke Volume Variation (SVV). During positive pressure ventilation, inspiration increases the intrathoracic pressure reducing the right ventricular (RV) filling and right ventricular output if the RV is volume responsive. This causes the left ventricular filling and left ventricular (LV) output to decrease over successive beats if the LV is also volume responsive. A SVV of >15% in patients receiving a tidal volume of >8 mL/kg or an SVV of >10% in patients receiving a tidal volume of 6 mL/kg accurately predicts preload responsiveness in patients with a closed chest. (D. A. Reuter, 2002)

6.1.2.1.2 Indicators of Tissue Perfusion

The ultimate goal of fluid resuscitation is adequate tissue perfusion. However, dynamic monitoring does not measure tissue perfusion. Indicators of adequate perfusion include SVO_2, $ScVO_2$, and lactate. The surviving sepsis group recommends targeting $ScVO_2$ of 70% within the

first 6 hours of recognition of sepsis. In contrast, hyperlactatemia is a more consistent finding in sepsis. Normalization of lactate can be a useful target, alongside other hemodynamic parameters. Jansen et al. demonstrated reduced hospital mortality when targeting normalisation of lactate in a multicentre clinical trial (MRCT). (T. C. Jansen, 2010)

3-hour bundle - The below actions are to be taken within the first 3 hours of resuscitation upon initial recognition for pediatric patients within 60 minutes upon initial recognition

1. Serum lactate measured within 3 hours of presentation.
2. Blood Cultures obtained prior to antibiotic administration to determine all potential site and source of infection.
3. Initial fluid administration of 20 ml/kg crystalloid in children.

6- hour bundle - The actions below are to be taken within the first 6 hours of resuscitation upon initial recognition for pediatric patients within 60 minutes upon initial recognition
The recommended bundle elements include:

1. Vasopressor therapy for persistent hypotension despite initial fluid administration.
2. Re-measure lactate if the initial value was elevated.

(Dellinger, 2012)

6.1.3 Choice of crystalloid for resuscitation of sepsis

Raghunathan et al have demonstrated some survival benefit from "balanced" crystalloid in a retrospective cohort. A meta-analysis of similar vintage found the same association, but the confidence of recommendations was rather low, owing to heterogeneity. Overall, a large randomised controlled trial is being called for further decision . (Raghunathan et al, 2014)

6.1.3.1 Utility of albumin in sepsis

The studies published to date have somehow served to encourage both those people who like to use albumin, and those who don't.

SAFE study is often quoted in support of the use of albumin in sepsis.

- The improvement in mortality in the septic subgroup did not reach statistical significance (the group was not powered to detect a subtle treatment effect).
- However, the study did demonstrate that albumin was *as safe as saline*; the lack of evidence for harm was enough to encourage people.

ALBIOS trial is the more recent entry into the scene; again albumin did not appear to be associated with any mortality benefit.

- Albumin appears to improve mortality of septic shock patients once hemodynamic stability has been achieved, and was associated with some haemodynamic advantages (eg. a higher arterial pressure (MAP), a lower positive fluid balance, and a lower heart rate).
- As some critics have pointed out, those differences were statistically significant but *clinically insignificant*- the increase in MAP, for instance, was by 1-2mmHg.

Overall, a recent meta-analysis did not find enough evidence to recommend the use of albumin in sepsis.

Trial Study: 14 studies (18 916 patients) were included with 15 direct comparisons. Network meta-analysis at the 4-node level showed higher mortality with starches than with crystalloids (high confidence) and lower mortality with albumin than with crystalloids (moderate confidence) or starches (moderate confidence). Network meta-analysis at the 6-node level showed lower mortality with albumin than with saline (moderate confidence) and low-molecular-weight starch (low confidence) and with balanced crystalloids than with saline (low confidence) and low- and high-molecular-weight starches.(Bram Rochwerg, 2014)

A recent review cited several studies associating NS (normal saline) infusions with the development of a hyperchloremic metabolic acidosis, in addition to other findings of questionable clinical importance. Recently, other studies demonstrated that NS leads to more adverse events and worse patient outcomes compared with resuscitation with a balanced fluid. (Jones et al. 2010)

In a prospective, open-label study of consecutive patients admitted to an intensive care unit (ICU), those that received balanced crystalloids had a decreased incidence of acute kidney injury (OR 0.52 CI 0.37-0.75; *P*<0.001) and less need for renal replacement therapy(OR 0.52 CI0.33-0.81; *P*=0.004). (Duus et al., 2015)

In a meta-analysis more relevant to emergency medicine, septic patients that received balanced fluids had a trend towards a lower mortality than those that received NS (OR 0.78 95% credibility intervals 0.58-1.05). The authors evaluated multiple fluid resuscitation strategies (among them balanced versus unbalanced crystalloids) with a primary endpoint of 90-day mortality. While the complete analysis included 14 studies and 18,916 patients, no trial that was included directly compared balanced with unbalanced crystalloid solutions. (Morgan TJ, 2005)

Crystalloids that are "balanced" have the presence of an organic anion (such as lactate) and a lower chloride content that more closely resembles the composition of plasma. The difference between the strong cations and the strong anions (the positives and the negatives) in "balanced fluids" is 24-28. In plasma, the actual difference between the sodium (Na) (142 mEq/L) and chloride (Cl) (103 mEq/L) is approximately 39. (Jones et al. 2010)

6.1.4 Resuscitation process of ICDDR, B

A retrospective case-control study among 454 children (cases = 50 and controls = 354) in ICU of ICDDR, B with history of cough or difficult breathing and radiologic pneumonia, Both cases and control children received antibiotics therapy and micronutrients supplementation following hospital guidelines based on local evidence. The cases additionally received fluid resuscitation i.e. 20 ml per kg of body weight per hour of physiological saline over 2 hours and Children without sepsis (the controls) did not receive any fluid resuscitation. Non-invasive respiratory support was provided using bubble CPAP among the study children who had severe pneumonia

and hypoxemia and/or grunting respiration and invasive respiratory support using mechanical ventilation was given who developed respiratory failure.(Chisti MJ, 2015)

Justification for use of IV physiological saline in severe sepsis: Isotonic fluid is the choice of fluid in managing severe sepsis is isotonic. As physiological saline/normal saline is considered as one of the isotonic fluids, and clinicians in the Dhaka hospital of icddr,b routinely practice infusion of normal saline as the choice of resuscitation fluid in severe acute malnutrition (SAM) children following our hospital guideline that is based on robust data from Bangladesh published in the Lancet by Ahmed T et al. in 1999. Although, WHO specifically recommended few resuscitative fluids in SAM children, in spite of the physiological saline, lack in experimental evidence is the main flaw of this recommendation. (Chisti MJ, 2015)

Out of the 50 cases, 29 (58%) did not respond to fluid resuscitation, required inotrope (s) support, and regarded as septic shock; 29 of the total 404 study children (7%) had septic shock. The case-fatality rate in children with severe sepsis was 40% (20/50) and that among children with septic shock was 69% (20/29).(Chisti MJ,2015)

6.1.5 New Invention of Chisti MJ & his Team at ICDDR, B (Bubble CPAP)

A new way to deliver oxygen to children with severe pneumonia, called bubble-continuous positive airway pressure (bubble-CPAP), has been shown to have better outcomes than low-flow oxygen therapy which is standard in resource-poor settings.

Results of open, randomised trials of the new method, conducted by scientists of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) and the University of Melbourne, published in *The Lancet* last month (August), showed decreased mortality rate among under-five children on bubble-CPAP.

Md. Jobayer Chisti, a scientist at icddr,b who developed bubble-CPAP, tells *SciDev.Net* that the low-cost method holds promise for the treatment of children with severe pneumonia and

hypoxaemia (low levels of blood oxygen) in areas with limited medical facilities.

The simple device — the trials involved no more than a discarded, plastic shampoo bottle and ordinary respiration tubes linked to an oxygen concentrator — works by maintaining sustained oxygen pressure to prevent lung collapse.

Regular CPAP equipment has been in use in middle and high-income countries for many years, but its high cost has kept it out of reach for most healthcare facilities in developing countries. In contrast bubble-CPAP is cheap and can be set up anywhere.

The team randomly picked 225 under-five children for the study that was conducted between August 2011 and July 2013. Subjects were placed into three study groups – one on bubble-CPAP, a second on standard low-flow oxygen and a third on high-flow oxygen therapy. Mortality in children placed on bubble-CPAP therapy was significantly lower (four per cent) compared to those given standard low-flow oxygen therapy (15 per cent).

“If the death rate for severe pneumonia exceeds 10 per cent in our hospital and others, then we need to keep researching for better alternatives of treatment,” Chisti tells *SciDev.Net*. “This intervention with bubble-CPAP therapy could be a solution.” (scidev.net, 2016)

Study Result: Some children will have both type I (hypoxemic) and type II (hypercarbic) respiratory failure. Together this accounts for high case-fatality rates in most populations with severe pneumonia. Standard oxygen supplementation by nasal prongs (low flow) can be lifesaving, but is not always sufficient to manage respiratory failure. In recent years continuous positive airway pressure (CPAP) has been used to relieve hypoxemia and reduce the work of breathing. There are several ways to give positive airway pressure; one is bubble CPAP (BCPAP), another is high flow nasal cannula (HFNC) oxygen therapy.

13 relevant studies were identified. Ten evaluated the efficacy of BCPAP among 3164 children, and three described the same for HFNC in 255 children. In all studies the entry criteria was

severe respiratory distress. The study methodologies, the outcomes recorded and results were heterogeneous. The age range of the children in the studies was from the immediate newborn period on day 1 of life up to the age of 12 years. They evaluated the outcome of our review in two aged categories and found: children 0-28 days for 8 studies and > 28 days for 2 studies. In 3 studies of children aged 0-28 days and 2 studies of older children had clinical features consistent with severe pneumonia and those who among them were treated with immediate BCPAP therapy had better outcome ($p<0.01$ or CI < 1) compared to those who were treated with delayed BCPAP, or historical control one each, or standard flow flow (LF) oxygen therapy (in two studies). Primary outcomes were comparable between BCPAP and ventilator driven CPAP in three studies and between BCPAP and low flow oxygen or variable flow nasal CPAP in two studies (95% CI contain 1) of children aged 0-28 days. Children treated with HFNC compared to those who did not receive HFNC in three relevant studies, all of them in older children had better outcome ($p<0.05$). (Chisi MJ, 2014)

6.1.6 Monitoring Serum Lactate Clearance

Lactate production is a byproduct of anaerobic metabolism. Currently, serum lactate clearance shows the most promise as a reasonable biomarker alternative to invasive resuscitation monitoring. Studies have found that septic patients who do not clear serum lactate by 10% in the first 2 to 6 hours have an increased mortality.(Nguyen HB, 2004)

Two recently published studies examined the association of targeting lactate clearance as a resuscitation goal with mortality. In 2010 Arnold and colleagues published results of a multicentre trial in which patients were randomized to conventional invasive monitoring (EGDT) or a therapy target guided by serial lactate clearance of 20% every 2 hours in addition to conventional invasive monitoring.(Arnold RC,2009)

They found a significantly reduced ICU length of stay and both ICU and hospital mortality in the lactate clearance group when adjusting for predefined baseline mortality risk factors. Also in 2010, Jones and colleagues published results of a multicentre noninferiority trial comparing two groups of patients: one assigned to normalization of CVP, MAP, and ScvO2 according to EGDT

protocols, and one to normalization of central venous pressure (CVP), mean arterial pressure (MAP) and a lactate clearance of 10% in the first 6 hours.(Jones AE, 2010)

Although the authors found no significant difference in in-hospital mortality rates between the groups (i.e., noninferiority), suggesting that lactate clearance may be used instead of central venous oxygen saturation as a resuscitation target in sepsis, the study had two limitations. First, caregivers could not be blinded to the treatment groups of patients.

Second, after normalization of CVP and MAP, very few patients required further therapy to normalize their ScvO2 or to clear their lactate—that is, the planned intervention was not much different between treatment groups, which could explain why outcomes did not differ between groups. While there is growing evidence for resuscitation with a target of lactate clearance, and the use of this biomarker is simple and appealing, further research needs to be conducted before lactate clearance can be recommended as a resuscitation biomarker in sepsis.

Patients with sepsis and evidence of global hypoperfusion may require 6 to 10 L of crystalloid in their initial resuscitation. Several recently published studies suggest that there is a danger of overresuscitation in this patient population, as there is with patients undergoing burn resuscitation.(Boyd JH, 2011)

Although some patients may require several litres of crystalloid early in their disease, it remains unclear at which point fluid administration may cause increased morbidity. Furthermore, optimal (meaning both safe and effective) fluid resuscitation may not require all of the invasive monitoring used in the original EGDT protocol. Accordingly, researchers and clinicians seek better targets for resuscitation that are less invasive than ScvO2, such as circulating biomarkers to titrate resuscitation.

Three large government-funded RCTs are now underway and each is designed to determine the ideal method of sepsis resuscitation: ProCESS (Protocolized Care for Early Septic Shock, NCT00510835 at www.clinicaltrials.gov), a US trial; ARISE (Australasian Resuscitation in Sepsis Evaluation, NCT00975793 at www.clinicaltrials.gov); and ProMISe (Protocolised Management in Sepsis), a UK trial. These trials will be performed in different countries, but the groups have

planned for a prospective combined meta-analysis that they hope will provide a final answer to this hotly debated question.

6.1.6.1 Lactate as a prognosticator in early sepsis management

A diagnostic tool that is presently uncommon but may be seen in the future is the lactate monitor. Looking and operating much like blood glucose monitors, lactate monitors are a reliable method for determining circulating blood lactate levels. Lactate is released by hypoxic tissues and is a reliable early indicator of hypoperfusion. Lactate levels above 4 mmol/L suggest hypoperfusion and sepsis. These meters have been effectively used in prehospital settings for identifying patients who have severe sepsis.[8] Because early recognition of sepsis correlates with decreased mortality, it makes sense to consider using lactate meters for early sepsis recognition.(Stephen W, 2011)

In 2004 and 2008 sepsis guidelines, Dellinger et al. recommended measurement of lactate on initial presentation, with an elevated value signifying tissue hypoperfusion and necessitating aggressive resuscitation (Dellinger RP et al, 2013).

Although their guidelines suggested measuring lactate only upon presentation, many clinicians and researchers have attempted to capitalize on the test's theoretical diagnostic and predictive value by including additional measurements during the resuscitation process. For example, it was shown that lactate clearance greater than 10 % from initial measurement during the first 2 to 6 h of resuscitation predicted survival from sepsis and that protocols targeting lactate clearance of at least 10 % produced similar short-term survival rates to protocols using $ScvO_2$ monitoring. Moreover, it was demonstrated that for every 10 % increase in lactate clearance, there was a corresponding 11 % decrease in in-hospital mortality. Similarly, septic patients with lactate clearance of greater than 20 % during the initial 8 h of resuscitation had a 22 % decline in the relative risk of mortality, compared with patients having lactate clearances of less than 20 %. (Jansen TC, 2010)

Since these initial studies are evaluating lactate as a marker of recovery in sepsis, further research has evaluated the role of lactate monitoring during the early resuscitative period. For

example, Puskarich et al. studied resuscitation during the initial 6 h of treatment and demonstrated that achieving an $ScvO_2$ goal ≥70 % without obtaining a lactate clearance goal ≥10 % was associated with higher mortality than reaching the lactate clearance goal without the $ScvO_2$ goal. Furthermore, these same authors showed that early lactate normalization (within 6 h) was a predictor of survival in patients being treated for sepsis and septic shock. (Pukarich MA et al., 2011)

Nguyen et al. investigated the addition of lactate clearance within the first 12 h of resuscitation to the sepsis resuscitation bundle and showed that including lactate clearance leads to an almost twofold increase in relative risk reduction of death. In response to the convincing literature supporting the utility of lactate clearance in early sepsis, the newest surviving sepsis guidelines for early goal-directed therapy (EGDT) now includes lactate clearance during the first 6 h of resuscitation as a goal of early resuscitation. (Nguyen HB et al., 2007)

Thus, research regarding lactate monitoring as a marker of recovery in sepsis has proven fruitful but has primarily focused on the early resuscitation period.

Furthemore, Rivers et al. warn against using only lactate clearance as a marker of sepsis recovery and state that lactate clearance, central venous oxygen saturation ($ScvO_2$), and other markers are complementary and not mutually exclusive end points. (Rivers EP et ai, 2011)

6.1.6.2 Lactate as a late prognosticator in sepsis management

Literature evaluating the clinical and predictive value of lactate measurements beyond the initial 6-h resuscitation period in the medical management of sepsis is significantly less robust. In a study of 137 surgical intensive care unit (SICU) patients, Husain et al. showed elevated initial and 24-h lactate levels to be significant predictors of mortality, with mortality ranging from 10 to 67 % depending on whether lactate levels normalized or failed to normalize at 24 h, respectively. (Husain FA, 2003)

In another study investigating SICU patients, Bakker et al. showed that lactate clearance measured 24 h after admission was a significant predictor of in-hospital mortality and that the duration of persistent lactic acidosis was more predictive of mortality than the initial lactate value. (Bakker J, 1996)

Similarly, Friedman et al. showed in a 35-patient study that survivors of sepsis admitted to the medical intensive care unit (MICU) or SICU had significantly lower lactate values at 24 h of resuscitation than nonsurvivors. (Friedman G, 1995)

Finally, Manikis et al. followed lactate measurements every 8 h for >72 h in 129 trauma patients and demonstrated serial lactate measurements and the duration of hyperlactemia to be reliable indicators of morbidity and mortality following trauma. (Manikis P, 1995).

In a 94-patient SICU sepsis study, Marty et al. measured lactate at time$_0$ (T), T_6, T_{12}, and T_{24} and showed that the best predictor of death was the T_{24} clearance. These authors concluded that during the first 24 h in the ICU, hyperlactemia, even after the "golden hours," is associated with increased mortality, and lactate clearance-directed therapy should be considered for the first 24 h of treatment. (Marty P, 2013)

Similarly, in an 81-patient study, Herwanto et al. investigated the role of 6-, 12-, and 24-h lactate clearance in patients with sepsis and found only the 24-h lactate clearance measurements to be associated with mortality. (Herwanto V, 2014)

6.1.7 Clinical Effects of Statins & Corticosteroids in Sepsis

Many, but not all studies, have demonstrated the benefits of statins in patients with sepsis. Liappis *et al*. demonstrated that patients on statins had greater than 7 times greater chance of survival with sepsis. (A. P. Liappis et al, 2001)

Almog *et al*. showed in an ICU that only 2.4% of patients on a statin developed bacterial sepsis compared with 19% ($p < 0.001$) who were no at statin.(Y. Almog, 2004)

Van de Garde *et al*. showed a significant reduction of the risk of pneumonia among patients with diabetes mellitus. (Van de Garde *et al, 2010)*

Kruger *et al*. studied a cohort of bacteriemic patients and found a significantly lower incidence of mortality and bacteraemia-related mortality with statin therapy.(Kruger P,2006)

Furthermore, in patients with sepsis, bacteremia or community acquired pneumonia and in patients admitted to the intensive care unit with Acute Physiology and Chronic Health Evaluation II scores of ≥20, statins prevented sepsis from becoming severe or decreased 28-day, 30-day, or 31 - 180-day mortality, hospital mortality, or bacteremia-related mortality. Mortensen E. M, 2005)

Patiens who received statins had a lower risk of death due to influenza, pneumonia, or chronic obstructive pulmonary disease in one study and a lower risk of fatal pneumonia in another study. (Schielenger R. G, 2007)

In another hand, in a study which compared the outcomes of inmunocompromised patients who received or not statins, the prior use of them was not associated with an increase of the survival . (Viasus D, 2011)

Other investigations haven't demonstrated benefits with statins in patients with sepsis, as Fernandez *et al*., who found that the hospital mortality was even higher in patients receiving statins and mechanical ventilation,(Fernandez R et al , 2006) or Yang *et al*. who conducted a retrospective study and found no differences in mortality between the two groups. (Yang K. C et al, 2007)

Evaluating the effects of statins in sepsis caused by concrete microorganisms, we can observe how, in a clinical study, patients who received statins had significantly lower overall and attributable mortality associated with bacteremic infections caused by gram-negative bacilli and *S. aureus* than did those not receiving statins. Fluvastatin might have a potential role in the treatment of tuberculosis as a result of the enhacement of the host T-helper response agaisnt *M.tuberculosis*. (Chisti mj, 2013)

However, Kopterides *et al*., in a critical review of 22 studies with 177,260 patients (7 prospective cohorts, 12 retrospective cohorts and 1 aleatorized clinic assay), concluded that the

majority of studies show that statins have a beneficial effect over the result of the infection. Kopterides P et al, 2009)

A nine-month old boy admitted at icddr, B with very severe pneumonia (confirmed by radiology), severe hypoxaemia, severe malnutrition, and Down's syndrome. The patient was treated according to the hospital protocol for the management of pneumonia and malnutrition. But treatment was unsuccessful for a hospital-acquired pneumonia, the problems further expanded to include interstitial lung disease (ILD). The patient was treated with prednisolone for 6 months, along with antitubercular drugs. He fully recovered from ILD, hypoxaemia, and pneumonia both clinically and radiologically. This data suggested that prednisolone (statin) is effective to Pneumonia with ILD.(Chisti mj, 2013)

6.1.8 Prevention in the era of conjugate vaccines

Acute bacterial attack is an important cause of morbidity among children, especially in developing countries. Despite the increasing availability of potent antimicrobials and sophisticated intensive care units, mortality rates due to bacterial infection still reach high levels, leading to significant neurological sequelae. (Oostenbrink R., 2012)

The advent of the conjugate vaccines during the last decade was a remarkable achievement, launching a new era in the history of modern vaccinology. In contrast to the first generation of the purified polysaccharide vaccines, the conjugate vaccines produce a T-dependent response and result in the development of an immunological memory, leading to clinical protection in children less than 2 years old. This age group is at high risk for invasive diseases caused by the three most important agents of bacteria *Haemophilus influenzae*, *Streptococcus pneumoniae.(* Heath P.T. 2008)

The development of a conjugate vaccine against type b *H. influenzae* (Hib) in the early 1990's, and its implementation for routine immunization, have contributed directly to changes in the epidemiological profile of the invasive diseases caused by Hib in some developed countries by reducing mortality rate.(Ada G. 2011)

7. Reason of Sepsis Development

7.1 Antibiotic Resistance

Resistance to antibiotics is a global problem. Reports of multiresistant bacteria causing neonatal sepsis in developing countries are increasing and this may be explained by the wide availability of over the counter antibiotics and the inappropriate use of broad-spectrum antibiotics in the community. (Jyothi *et al,* 2013)

Most gram negative bacteria are now resistant to ampicillin and cloxacillin and many are becoming resistant to gentamicin. A retrospective study carried out by Iregbu *et al* in the Department of Clinical Microbiology and Parasitology of a tertiary hospital in Nigeria in the year 2006 showed that 89% of staphylococcus aureus were sensitive to amoxicillin- clavulanic acid while 85%, 45%, 71% and 64% were sensitive to cefuroxime, ciprofloxacin, chloramphenicol and erythromycin respectively. The only three isolates tested against tetracycline were all susceptible to the drug. The resistance to penicillin was 90%.Resistance to ceftazidime, ceftriaxone and gentamicin were 71% ,64% and 60% respectively. (Vergnano *et al*, 2005)

The resistance of the isolated *Klebsiella pneumoniae* to ceftazidime, ceftriaxone and cefotaxime was 85%, 87.5% and 94% respectively. Resistance to amoxicillin and ampicillin-sulbactam was 100%, and 85% for amoxicillin-clavulanic acid. All (100%) of the *Klebsiella pneumoniae* isolates tested against imipenem were susceptible while 75% were susceptible to amikacin. (Iregbu *et al,* 2006)

Recent data among 407 children suggest that the range of bacterial pathogens causing pneumonia in children is different; Gram negative bacteria play a much more significant role and are also associated with higher deaths. Additionally, organisms, especially gram-negatives causing severe pneumonia in these children are often resistant to penicillin and ampicillin, and also gentamicin, but have better susceptibility to extended spectrum cephalosporin such as ceftriaxone and also to fluoroquinolones, including ciprofloxacin. Penetration of ceftriaxone and ciprofloxacin in the pneumonic lung is also considerably better than that of ampicillin or gentamicin. WHO guidelines do not differentiate antibiotic treatment for hospitalised SAM children (penicillin/ampicillin and gentamicin) with those who have pneumonia, and also with those who have danger signs of severe pneumonia, such as hypoxemia, cyanosis, grunting,

convulsion, inability to drink or persistent vomiting. The WHO guidelines recommend that children with severe pneumonia who fail to respond to these initially administered antibiotics may be treated with ceftriaxone. The switching-over to ceftriaxone only after treatment failure in children with danger signs of severe pneumonia may result in significant delay in appropriate treatment and leading to poor outcomes.(Chisti MJ 2015).

Infection with antibiotic resistant organisms results in delay in starting effective antibiotic therapy, fewer possible treatment options and increased morbidity and mortality with prolonged hospital stay and greater costs of hospitalisation. The slow pace in the development of newer drugs and rapidity in resistance development are major areas of concern. (Shah *et al,* 2012).

7.2 Lack of bacillus Calmette-Guérin (BCG) vaccination

A research from April 2011 to July 2012 were enrolled (n = 405) in icdd,b. Comparison was made between pneumonic SAM children with (cases = 18), and without (controls = 387) bacteraemia. The death rate was significantly higher in cases than controls (28% vs. 8%, P < 0·01). In logistic regression analysis, after adjusting for potential confounders, the SAM children with pneumonia and bacteraemia more often had a history of lack of bacillus Calmette-Guérin (BCG) vaccination (odds ratio 7·39, 95% confidence interval 1·67-32·73, P < 0·01). The results indicate the importance of continuation of BCG vaccination which may provide benefit beyond its primary purpose. (Chisti MJ,2015)

7.3 Blood Transfusion

A data from Chiti MJ observed that blood transfusion used for the management of refractory systolic hypotension revealed as the independent predictor for death in under-five SAM children with pneumonia – a very important information for clinicians in critical care wards of developing countries. WHO recommends blood transfusion in severely malnourished children who do not recover from septic shock even after infusion of consecutive two boluses of isotonic fluid . The protocolized management of such children in our hospital followed this recommendation. Systolic hypotension, in addition to features of sepsis (defined by our local guideline) are used as the marker of septic shock in SAM children, especially in resource limited

settings. Children with systolic hypotension and unresponsive to crystalloid received blood transfusion but did not receive diuretics and had frequent fatal outcome. Death in this special population is often very high even with adequate treatment not only in developing countries but also in developed countries. (Chisti MJ, 2013).

7.4 Lack of Breast Feeding

Total 107 infants were enrolled in a study at icddr, b of whom 73 were breast-fed and 34 were non-breast fed . In this study, all hypoxemic infants received oxygen therapy. The median (inter quartile) duration of hypoxemia (hours) in non-breast fed infants was longer compared to those in breast-feds [12.0 (0.0, 21.75) vs. 0.0 (0.0, 12.0); $p = 0.021$]. The lowest SpO_2recorded at admission for the non-breast-fed and breast-fed infants were 63% and 70% on air respectively. They observed a higher incidence of hypoxemia among non-breast-fed infants than breast-fed infants presenting with pneumonia and diarrhea. It is a novel and interesting finding which have no ready explanation. Cessation of breast feeding in the neonatal period or non-breast feeding since birth is strongly associated with pneumonia. Hypoxemia is one of the common sequels of severe pneumonia . Non-breast-fed infants often have reduced immunity resulting from prolonged deprivation of highly immunogenic breast milk. Breast milk contains certain factors, especially transforming growth factor (TGF)-β1 that is related to production of elastin which is needed for normal structural and functional development of the lungs. It is possible that non-breast-fed infants in that study had under developed and less well functioning lungs and pneumonia caused further deterioration of lung function leading to ventilation perfusion mismatch, the end result being hypoxemia. Obstructive sleep apnea-related hypoxemia that has a strong association with cessation of breast milk in neonatal period could not be ruled out as one of the potential contributing factors for this observation. The lowest observed SpO_2 at admission was recorded in a non-breast-fed infant and non-breast-fed infants in our study more often remained hypoxemic than breast fed infants after O_2 supplementation, which could also be due to their under developed and poorly functioning lungs. From an observational study, and a well designed mechanistic future study is likely to provide an explanation for this findings.(Chist MJ, 2011)

7.5 Inadequate Knowledge

In developing countries including Bangladesh, mothers or primary caretakers of pneumonic children had inadequate knowledge about pneumonia. Most of them could not recognize whether their child had pneumonia or not. When the mothers detected that their child either was not breathing properly or had high fever or convulsion or was unable to take or stopped taking or was reluctant to receive the feed, they brought their child to the health facility. Majority of them did not have prior knowledge about the clinical features of pneumonia. Those mothers who had knowledge about clinical features especially early danger signs of pneumonia, they even could not identify properly that their children were suffering from pneumonia. They brought their child to the hospital when the child developed late danger signs with severe form of the disease or associated complications. (Chisti mj, 2011)

7.6 Believe in Myth

A group of mothers believed that if they have cough and cold, their child would also develop cough through breastfeeding while sucking breast milk. There is no adequate data on spread of pneumonia from the infectious cough of breastfed mothers, although breastfed mothers with active tuberculosis are one of the risk factors for developing tuberculosis in children. Proper breastfeeding can prevent the severity of pneumonia such as hypoxemia. This finding implies that mothers have lack of appropriate knowledge about pneumonia and its prevention. Childhood pneumonia is associated with poverty and results from suboptimal child rearing and care seeking practices compounded by lack of access to healthcare. Previous studies reported that hand hygiene practices are vital in minimizing the spread of most organisms responsible for pneumonia, which can reduce the incidence of acute respiratory infections and pneumonia by up to 50 percent. (Ferdous F & Chisti MJ, 2014)

7.7 Inefficient Healthcare Personnel

Appropriate health care for pneumonia in rural community is very critical due to inadequate number of healthcare facility. Moreover, lack of knowledge about the danger signs and symptoms of pneumonia among the primary caregivers is another cause of delayed seeking care for childhood pneumonia, which could even be life threatening. Several studies have examined the prevalence, health consequence, and clinical management of pneumonia however, inadequate number of literatures has reported the perception, especially of rural community mothers about pneumonia and its signs and symptoms. A recent hospital based published data revealed that only 7% caregivers of pneumonic children had a good understanding and 51% had poor understanding about the clinical signs of pneumonia. However, community based information is needed regarding mothers' ideas about causes of childhood pneumonia, and the healthcare seeking behaviors of mothers for their child's pneumonia.(Chisti MJ, 2011)

7.8 Sclerema

The major observation of chisti mj, 2009 case report is the development of sclerema in association with septic shock on two occasions in two successive hospitalizations in this severely-malnourished young infant who was also treated successfully with blood transfusions in addition to appropriate antibiotics, intravenous fluid, inotropes, correction of electrolyte imbalance, supplementation of micronutrients, vitamins and minerals, and therapeutic diet.

Sclerema is defined as diffuse hardening of subcutaneous tissue, which usually spreads very rapidly to underlying structures; the skin in the involved areas cannot be picked up, and the subcutaneous tissue seems bound down to subjacent muscle and bone. It is a life-threatening condition which occurs in young infants with overwhelming sepsis, hypothermia, hypoxaemia, hyponatraemia, acidosis, and hypocalcaemia. The reported case fatality from sclerema in different series ranged from 30% to 100%, and deaths usually occur within hours to days of onset of the condition. Although sclerema no longer exists in developed countries, it still develops in young infants in resource-poor countries, like Bangladesh. (Chisti MJ, 2009)

8. Supportive management

The following supportive measures are recommended in the management of children sepsis and severe pneumonia; nursing in a thermo neutral environment to avoid hypo or hyperthermia, maintaining oxygen in the normal range, intravenous fluids if hemodynamically unstable and corticosteroids for adrenal insufficiency. Hyperbilirubinaemia should be monitored and treated with phototherapy and or exchange transfusion. By following timely sepsis care and maintaining emergency medical services' role as well as using modern technologies and Screening Process and also admitting educated health professionals in hospital, pneumonia with severe comalication can be managed successfully.

8.1 Day-Care Model Proposed by ICDDR, B

World Health Organization (WHO) has classified pneumonia as severe or very severe based on clinical presentation. Standard management of severe pneumonia requires hospitalization for supportive treatment including oxygen therapy, airway suctioning, fluid and nutritional management, antimicrobials, and careful monitoring.

Most of developing countries (including Bangladesh) do not have enough paediatric beds in hospitals to accommodate the demand for admission of all children with severe and very severe pneumonia. This inadequate capacity assuredly results in excess and unwanted death of children who, with proper care, would otherwise survive. Alternative treatment options, such as '' are, therefore, needed for those children who cannot be hospitalized but are too sick to be managed in the community through establishment of facilities at 'outpatient clinics' for the management of common childhood illnesses, thereby hoping to reduce morbidity and deaths. To address the issue of the day-care management of severe pneumonia, we tested this approach first in an uncontrolled, prospective study, followed by another randomized controlled trial; the results of both approaches demonstrated that it is possible to manage childhood pneumonia with antibiotics, feeding, and supportive care.

Majority (≈90%) of the children who suffered from severe and very severe pneumonia can comply with follow-up scheduled fortnightly for 3 months after discharge from the day-care clinic. There was a low incidence (15%) of minor illnesses during the follow-up period, with an even lower requirement of medication (8%) following recovery from severe and very severe pneumonia. It may be mentioned that the illnesses during follow-up period and hospitalization had no relationship with initial pneumonia episode.

This study showed a great importance of follow-up after discharge from the day-care clinic as some children developed morbidity, which might had chances to lead to a fatal outcome if not documented in time; others needed hospitalization, and a small number died. This results also indicate the necessity of establishing routine follow-up system for children following successful treatment for severe or very severe pneumonia in healthcare facilities for detecting medical problems early, understanding appropriate intervention and, thus, preventing death. Such follow-ups should be ideally done at the same healthcare facility from where children had received their initial treatment but a community follow-up system may be feasible, if adequately trained and motivated community health workers and other resources are available (Chisti MJ, 2014)

8.2 Proper Follow-up Procedure

A study by Chisti MJ described That among 86 children discharged that had been diagnosed with tuberculosis, of which 27 were microbiologically confirmed. It was planned that all children discharged receiving anti-tuberculosis treatment were followed until completion of the course i.e. for 6 months.

For this study, all care-givers were provided instructions verbally in local language regarding follow-up. They were requested to return to the hospital at 12 weeks following discharge but advised that if their children developed any symptoms or signs of illness at any time prior to this, then they should either return to the hospital or consult with a study physician by mobile phone at any time. The phone numbers of the study physicians were provided during discharge and all caregivers had access to mobile phones. No funding was provided for potential phone

call costs. If any of the caregivers did not attend the 12-week post-discharge follow-up, the study staff attempted to contact them via mobile phone. If any of the care-givers could not be contacted by mobile phone or still did not attend the follow-up after contact by mobile phone, then research assistants visited their home to ensure follow-up. Study participants were defined as “lost to follow-up” if research assistants visited the given address on at least two separate occasions and failed to identify them.

Verbal autopsy was requested when possible for those children that were identified as having died during the follow-up period. Verbal autopsy procedure followed the WHO standard questionnaire . Information obtained included the presence and duration of symptoms prior to death as well as treatment sought. Interviews were undertaken by the study physicians at icddr’b for the majority that were willing to attend, otherwise the interview was performed by mobile phone (n = 4). (Chisti MJ, 2014)

8.3 Timely Sepsis Care and Emergency Medical Services’ Role

In a retrospective cohort study of 2,731 adult patients with septic shock, Kumar et al. found that each hour of delay before the start of antibiotics after the onset of hypotension was associated with a 7.6% decrease in survival to discharge,(kumer et al. 2006) and in a prospective cohort study of 406 patients admitted to intensive care for sepsis, Garnacho-Montero et al. found that adequate initial antimicrobial therapy was crucial to patient outcome. (Garnacho-Montero et al. 2003)

In a prospective, randomized-control study of 263 sepsis patients by Rivers et al, patients receiving Goal Directed Therapy in the emergency department had 20% better sixty-day survival rates and fared significantly better on a number of other measures when compared with patients who did not receive Goal Directed Therapy. (Rivers et al, 2001)

In a retrospective study by Seymour et al, prehospital administration of fluids was found to improve patient outcomes, but not to a degree achieving statistical significance. However, out of 216 patients included in the study, only 25 received prehospital fluid resuscitation, and the

observed improvement in patient outcomes did approach statistical significance, so larger trial may have revealed a significant improvement. (Seymour et al, 2010)

8.4 Education

A. Nursing Staff – Severe sepsis recognition and treatment training is incorporated into new employee orientation and annual recertification requirements.

B. Resident, Licensed Independent Practitioner and Attending Staff – Severe sepsis recognition and treatment training: Residents are required to receive the training annually. LIPs and Attendings are required to receive the training prior to their reappointment. Exceptions to this educational requirement include Pathologists, Speech Pathologists, Audiologists and Psychologists.

C. Pharmacy, Respiratory, and Laboratory Staff - Severe sepsis recognition and treatmentn training is incorporated into new employee orientation and annual recertification requirements. (Dellinger,2012)

8.5 Use of Technology

Identification of Sepsis - SBUH is in the process of deploying an automatic Sepsis alert in the patient's electronic medical record based on recent patient vitals, querying the record for signs of SIRS. Nursing and physician clinical judgment, determinations and pending treatment plan is documented within the alert.

i. Electronic sepsis alert incorporates a perpetual 4 hour review of a patient's vital signs for abnormal or significantly changes.

ii. An electronic sepsis screening tool is fired to the bedside nurse when the patient meets SIRS criteria.

iii. Upon answering and completion of the alert, the electronic review will desist for an 8 hour period. (Goldstein, 2005)

9. Prevention of sepsis

Strategies to reduce rates of infection includes clean and safe deliveries, adherence to universal precautions in all patient contact, strict postnatal cleanliness, early and exclusive breastfeeding avoiding nursery overcrowding and limiting nurse to patient ratios(Haque *et al,*2003). Other measures include strict compliance to hand washing, decreasing the number of venepunctures and heel pricks and providing education to nursery personnel (Bang *et al,* 1999)

9.1 Home Medication

Home medication was relatively common in the present study; however, appropriate home management of ARI prevents serious consequences of pneumonia.Previous studies accounted that vitamin C has an effective role in pneumonia treatment in those who have less serum vitamin C, as it influences immune system and the metabolism of vitamin C is changed in infectious diseases including pneumonia, as indicated by decreased levels in plasma, leucocytes, and urine. In the present study mothers used lemon juice and tulsi leaf (green leaf) as both contain vitamin C. Previous studies reported that hand hygiene practices are vital in minimizing the spread of most organisms responsible for pneumonia, which can reduce the incidence of acute respiratory infections and pneumonia by up to 50 percent.(Ferdous F, chisti mj,2014)

9.2 Maternal Education

It is very important that rural mothers should have appropriate knowledge about the clinical features of pneumonia, because delays in detecting clinical signs including danger are the major obstacles to preventing deaths due to childhood pneumonia. It has been observed that mothers were unable to detect the severity of the illness of their child and brought the matter to the attention of adult family members or household head in order to get permission to take the child outside of home for treatment. A study in recent past in western Kenya reported that comorbidities, spread from upper respiratory tract and delay in seeking treatment, were the

common identified causes of severe pneumonia on presentation to health facilities. .(Ferdous F, chisti mj,2014; Onyango D, 2012)

9.3 Vaccination

The most effective prevention method based on strong evidence is active immunization of children against *H influenzae* type b, *S pneumoniae*, influenza, and pertussis. Influenza virus vaccine should be administered annually to all infants 6 months or older and to adult caretakers of infants younger than 6 months. The latter should also receive the pertussis vaccine. High-risk infants should receive the RSV-specific monoclonal antibody–based on the American Academy of Pediatrics recommendation. (Schlaudecker EP, 2010)

CHAPTER 2

OBJECTIVE OF THE STUDY

2. Objective of the study:

Mortality Rate of new born child is high among all over the world due to sepsis. Pneumonia is the main complication of sepsis. The reason of sepsis development is still unknown but it can be detected by observing clinical and laborotorical sign of patient.

To reduce the mortality from pneumonia and sepsis this study aimed to determine clinical and laboratory characteristics related to

- Clinical symptoms,
- Laboratory diagnosis,
- causes,
- management and
- prevention of sepsis in pneumonia children.

CHAPTER 03

MATERIALS AND METHOD

3. Methods and Materials

3.1 Study design

We performed unmatched case-control design. Children of either sex, aged 0–59 months, admitted to the study hospital from January 2016 through April 2016 with history of cough or difficult breathing and radiologic pneumonia, who were assessed for sepsis at admission constituted the study population. Children who were assessed to have sepsis constituted the cases, and those without sepsis constituted the controls. Sepsis was defined as tachycardia plus hypothermia (≤35.0°C) or hyperthermia (≥38.5°C), or abnormal WBC count plus poor peripheral perfusion (mean arterial pressure ≤50 mm of Hg and/or absent peripheral pulses or capillary refilling time ≥3 seconds) in the presence of clinical dehydration. Abnormal WBC count was defined if WBC count was >11000/cc or, <4000/cc or, band and neutrophil ration ≥ 0.1, or band>10%. (Chisti MJ, 2012)

Number of study unit: 3

Number of patients: 258

Study Unit1: Intensive Care Unit (ICU)

Study Unit 2: Longer Stay Unit (LSU)

Study Unit 3: Shorter Stay Unit (SSU)

Study Site: icddr, b

Duration of study: 4 months

Study type: Retrospective Study

Operational modality:

Indoor (3 unit) patients of sepsis from icddr.b were studied. Information like age , sex, biophysical characteristics, sign and symptoms, cause, type of sepsis, treatment pattern, drugs prescribed to treatsepsis, duration of treatment , hospital cost, family history were analyzed by using Microsoft word and Microsoft excel software.

CHAPTER 04

RESULTS AND DISCUSSION

4. Results and Discussion

4.1 Results

In total, 258 children were admitted to the Dhaka Hospital of icddr,b during the study period, and 151 of them were considered as cases and 107 were controls.

Table1 shows the clinical characteristics of under – five children with sepsis (cases) and without sepsis (controls). The case fatality rate was significantly higher among the cases when compared with the control (p=0.027). The cases more often were younger, and had SIRS syndrome, breathing difficulty, hypoxemia (Table 1) and abnormal WBC count, immature poly, bacterial growth on blood culture (Table 2) compared to the controls. During hospitalization, 4 cases and 1 controls required bubble CPAP oxygen therapy, 1 cases and no control received inotropes, and no cases and controls had mechanical ventilation for their severe illness. In logistic regression analysis, after adjusting for potential confounders the cases were independently associated with age less than 2 month, gestational age, clinical dehydration, lack of BCG vaccination (Table 5). There was no evidence of differences in distributions of sex; poor socio-economic condition; not use of vit-A capsule, no use of antibiotic before admission, hypothermia, oedemaus malnutrition at admission; and development of hospital acquired infection among the cases and the controls (Table 1). Table 3 and table 4 represents the causative bacteria and resistance drugs of sepsis respectively.

Table1: Clinical characteristics of under – five children with sepsis (cases) and without sepsis (controls)

Variables	Cases (n = 151)	Controls (n=107)	OR	95% CI	P value
Male gender	88(58)	59(55)	1.14	0.67-1.93	0.708
Age in months (Median, Range	5.0(0.1,59.0)	8.5(0.25,59.0)	-	-	-
< 2 Month of age	41(27)	14(13)	2.48	1.22-5.10	0.010
Gestational age (weeks) mean ± standard deviation	38.0±3.0	39.1±2.2	-	-	0.002
Not use of capsule vitamin –A within last 6 Months	83(55)	48(45)	1.26	0.73-2.18	0.442
History of measles with in last 6 Months	22/146(15)	18(17)	0.78	0.38-1.60	0.575
No use of antibiotic before admission	78/143/(55)	45(42)	1.65	0.97-2.83	0.068
Clinical dehydration (some / severe)	83(55)	42(39)	1.89	1.11-3.23	0.018
SIRS syndrome	80(53)	31(30)	3.49	1.88-6.18	0.002
Lack of BCG vaccination	45(30)	16 (15)	3.79	1.78-8.0	0.001
seizure	17(11)	10(9)	1.23	0.51-3.03	0.773
Hypoxemia (SPO2 < 90%	71(47)	48(45)	3.09	2.08-6.85	0.001
Hypothermia on or after admission (Temp) ≤ 35^0 C)	7(5)	1(1)	5.15	0.62-113.10	0.145
Oedematous Malnutrition	15(10)	11(10)	0.96	0.40-2.36	0.905
HAZ(<-3) z score)	48(32)	26(25)	1.43	0.79-2.61	0.260
WAZ (<-3z score)	64(42)	42(40)	1.09	0.63-1.86	0.850
WHZ (<-3 z score)	41(27)	20(19)	1.57	0.82-3.00	0.191
Outcome (Died)	23(15)	6(6)	3.02	1.11-8.64	0.027

Figures represent n(%) , unless specifid . Or: odds ratio . CI: confidence interval .

IQR: inter- quartile range . HAZ: height for age z score . WAZ: Weight for age z score. WHZ: weight for height z score; Spo2= transcutaneously measured blood oxygen concentration

Table2: Laboratory characteristics of under – five children with sepsis (cases) and without sepsis (controls)

Variables	Cases (N= 18)	Controls(n =72)	P value
Total WBC count (number/ cu.mm) median, IQR)	15,000(10,000,21,100)	12,000(9,0000,16,000	0.004
Immature poly ((number/ cu.mm) median, IQR)	00(00,1.00)	00(00,00)	0.044
Serum creatinine (micromole /L (Median, IQR)	82.35(65.00,162.00)	68.00(63.50,107.00)	0.164
Hyponatremia (mmo1/L)	38(25)	18(17)	0.148 1.66(0.85-3.26)*
Hyperkalaemia (mmo1/L)	16(11)	12(17)	0.964 0.94(0.40-2.33)*
Hypokalaemia (mmo1/L)	42(28)	35(33)	0.479 0.79(0.45-1.41)*
Hyperkalaemia (mmo1/ L	12(8)	7(7)	0.854 1.23(0.43-3.61)*
Radiological pneumonia	108/140(77)	82/102(80)	0.653 0.82(0.42-1.61)*
Hypoglycemia (RBS< 3mmo1/L)	20(13)	7(7)	0.118 2.21(0.84-6.03)*
Growth on blood culture	23/123(19)	6/82(7)	0.037 2.91(1.06-8.44)*

Figures represent n(%) , unless specified . IQR: interquartile range.* OR(95% CI); RBS: Random blood sugar

Table 3: Isolated bacterial organisms of under five children presenting with sepsis (cases) and without sepsis (controls)

Organism	Clinical sepsis (123)	Without clinical sepsis (82)
Streptococcus pneumoniae	2 (1.7)	0
[a]CNS	10 (8.0)	3 (3.6)
Haemophylus influenzae	2 (1.7)	0
Salmonella Typhi	2 (1.7)	2 (2.4)
Klebsiella species	2 (1.7)	1 (1.2)
Acinetobacter species	3 (2.4)	0
Escherichia coli	1 (0.8)	0
Enterococcus species	1 (0.8)	0

[a]CNS= coagulase-negative staphylococci

Table 4: Antibiotic sensitivity, resistance and intermediate sensitivity of *bacteria* isolated from blood culture in under-five sepsis children

Drugs	**Sensitivity *n* = 31 (%)**	**Resistance *n* = 31 (%)**	**Intermediate sensitivity *n* = 31 (%)**
Ampicilin	12 (39)	19 (61)	0 (0)
Gentamicin	16 (52)	15 (48)	0 (0)
Ciprofloxacin	24 (77)	5 (16)	2 (7)
Ceftazidime	26 (84)	3 (10)	2 (7)
Imipenem	31 (100)	0 (0)	0 (0)
Netilmicin	22 (71)	8 (26)	1 (3)
Amikacin	22 (71)	7 (23)	2 (7)
Meropenem	27 (87)	2 (7)	2 (7)

Table 5: Results of logistic regression

Characteristics	OR	95% CI	P value
< 2 month of age	3.53	1.39-9.00	.008
Gestational age (weeks)	.90	.79-1.03	.122
Clinical Dehydration (some/severe)	.99	.53-1.84	.972
Growth on blood culture	3.58	1.26-10.17	.017
Total WBC count	1.00	1.00	.141
Immature poly	1.13	.98-1.30	.091
Lack of BCG	4.60	1.99–10.66	0.001

4.2 Discussion

The observation of significantly higher case-fatality sepsis in pneumona children with compared to those without sepsis is an important but understandable observation.

Pneumonia (without sepsis) is typically diagnosed based on a combination of physical signs and a chest X-ray. The World Health Organization has defined pneumonia in children clinically based on either a cough or difficulty breathing and a rapid respiratory rate, chest indrawing, or a decreased level of consciousness. A rapid respiratory rate is defined as greater than 60 breaths per minute in children under 2 months old, 50 breaths per minute in children 2 months to 1 year old, or greater than 40 breaths per minute in children 1 to 5 years old. In children, increased respiratory rate and lower chest indrawing are more sensitive. Grunting and nasal flaring may be other useful signs in children less than five (Rambaud-Althaus, 2015). However, those with potential complications, those not having improved with treatment, or those in which the cause is uncertain, a chest radiograph is recommended. Sputum culture should be considered, and culture for *Mycobacterium tuberculosis* should be carried out in persons with a chronic productive cough. If it is suspected as sepsis blood culture also recommended. Symptoms of sepsis include: 1.a fever above 101ºF or a temperature below 96.8ºF;2. heart rate higher than 90 beats per minute;3. breathing rate higher than 20 breaths per minute;4. probable or confirmed infection. (Schlaudecker EP, 2010) In our study We observed clinical and laboratorial sign of patient. Here we observed that clinical dehydration(55%), SIRS Syndrome (53%) and Hypoxemia (47%) are common clinical syndrome in cases (sepsis) than control (with out sepsis). Laboratorial sign includes in sepsis development patient is Change in Total WBC count(>12000) and bacterial growth on culture (19%).

The causative organisms of sepsis include a wide variety of gram positive and gram negative organisms. These include *staphylococcus aureus*, coagulase negative *staphylococcus (*CONS*), Listeria monocytogenes*, *Klebsiella pneumoniae*, Group B *streptococcus(*GBS*)*, *Acinetobacter*, *Serratia*, *Pseudomona*s, *Haemophilus influenzae*, *Enterobacter, Candida* and anaerobes. But The organisms most commonly involved are *Streptococcus pneumoniae*, *Haemophilus influenzae*,

and *Klebsiella pneumoniae*. Downie *et al* describe *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* species as the most common causes of community-acquired neonatal and infant bacteraemic infection in developing countries.(Downie L, 2013)

The high frequency of use of antibiotics with high levels of resistance required special attention. Inappropriateness of empirical antibiotic therapy can contribute to high level of mortality. Patients who received appropriate initial antimicrobial treatment have lower mortality than those of who didn't. The early administration of appropriate antibiotic therapy for serious infection is associated with lower mortality, shorter duration of hospitalization, and lower health care cost (Reade MC, 2009). In other hand, wrong or inappropriate use of antibiotic will contributed to the development of antibiotic resistance and multi drug resistance (MDR). The high incidence of MDR can reduce the opportunities of patients to get the appropriate antimicrobial that can affect to increase the risk of death. Raymond in his study have suggested a high mortality cases found in the patients with MDR and the study also showed that the patients received inappropriate empirical antibiotic and had severity of co-morbidity. (Raymond DP, 2003)

Meta-analysis of *in vitro* evidence shows that the WHO recommended antibiotic regimen for neonatal sepsis, penicillin and gentamicin, covers only just over half the isolates. The alternative of a third generation cephalosporin, often used because it is cheap and 'broad spectrum', does not improve coverage. (Lilian D, 2013) In an African Hospital shows the highest High resistance was seen against ampicillin (82.9%), ceftriaxone(75.2%), cefuroxime(72.6%). The resistance to gentamicin was 65.6%.
Klebsiella spp showed high sensitivity to meropenem(100%), piperacillin tazobactam(100%), Amikacin(100%). *Enterobacter spp* showed high sensitivity to levofloxacin(100%), imipenem(94.7%) and meropenem(94.4%). This study has shown that the organisms are more sensitive to the more expensive antibiotics such as meropenem, Teicoplanin. This poses a challenge since neonatal sepsis mostly affects those of low socioecomic status who may not be able to afford these cost (Krasinski KM, 2012). Our study also represents that multidrug resistance increases the mortality rate of sepsis. This studies shows that only imipenem (100%)

and ceftazidime (84%) shows sensitivity against bacteria. But the cost of these drug is very high and increases mortality rate among low socioeconomic society.

The emergence of microbial resistances were not by the availability of novel antimicrobial agents, which is marked by only four new classes of antibacterials have been discovered in the last 11 years. The strategies for limiting or modifying antibiotic use are needed to control resistance growth and to improve the rational use of antibiotics (Kollef MH, 2001). The seven strategies to prevent antibiotic resistance that were suggested by Kollef in 2005 are as follows: (1) Establishment of a formal protocol and guidelines, (2) Hospital formulary restrictions, (3) Use of narrow spectrum antibiotics when supported by clinical situation and culture data, (4) Combination antibiotic therapy, (5) Shorter courses of antibiotic treatment, (6) Antibiotic heterogeneity, and (7) Optimization of pharmacokinetic/pharmacodynamic principles.(Kollef MH, 2005) . Systemic review and meta analysis from 1950 to 2013 showed protection against infection of 27% compared with 71% who takes BCG vaccine.(A Roy, 2014)

Our observation of the association of lack of BCG vaccination with sepsis in malnourished pneumonic children is a novel finding, although the beneficial effects of BCG vaccination on non-tubercular illness has been well documented. Lack of BCG usually is a marker of lack of uptake of services that might be due to a lack of adequate knowledge of caregivers about the well known tubercular and non-tubercular advantages of BCG vaccination. BCG vaccination has been reported to reduce around 50% of deaths from non-tubercular infections such as pneumonia in developing countries with high childhood mortality.

The first line of management of sepsis in our hospital is the combination of parental ampicillin and gentamicin. Ampicilin and gentamicin injection is used as a first line treatment in our study popuation at icddr,b, with an excellent survival rate of 96%. The second line is the combination of ceftriaxone and gentamicin. Third and fourth lines of treatment of sepsis in our hospital are the combination of ceftazidime and amikacin or imipenem alone, respectively. In cases of hospital acquired infection, ceftazidime and amikacin together and imipenem are the first and

second lines of treatment. WHO has also recommended this combination therapy as the treatment of choice for children with clinical sepsis at inpatient facilities(WHO guidline, 2005).

Our study children with sepsis received fluid resuscitation following our hospital guideline that is based on robust hospital data from Bangladesh. Results of study conducted in Africa (FEAST trial) observed higher deaths in association with aggressive fluid therapy in children with features of sepsis. The FEAST trial did not include who receive any non-invasive or invasive respiratory support for those who developed respiratory failure, whereas all of our study population were malnutrition children and they had the opportunity to receive bubble CPAP. Thus, compared to the children in FEAST trial, our study children were sicker. However, the possible impact of WHO recommended relatively slower and less aggressive fluid resuscitation on case fatality in our study population remains unknown. Based on results of our study and within the afore-mentioned limitations, we may suggest that pneumonic SAM children with severe sepsis requiring fluid resuscitation in addition to standard antibiotic and other supportive therapy are likely to have higher case-fatality compared to those without severe sepsis. The results highlight the importance of randomized, controlled clinical trials in evaluating the efficacy of different fluid resuscitation strategies with or without inotropes support in order to reduce deaths in such children. (Chisti mj, 2013)

CHAPTER 05

CONCLUSION

5. Conclusion

Sepsis is a systemic infection that can lead to complications and death. The cause of sepsis is unknown but it is the second cause of death among under five year children. Death rate is even higher when children with sepsis also have pneumonia. While gram-negative bacteria were previously the most common cause of sepsis, in the last decade gram-positive bacteria, most commonly staphylococci, are thought to cause more than 50% of cases of sepsis. Other commonly implicated bacteria include Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella species *(Bloch, KC, 2010).* Early diagnosis is necessary to properly manage sepsis, as initiation of early goal directed therapy is key to reducing mortality from sepsis. The high use of antibiotics with high levels of resistance such as levofloxacin, ceftazidime, ciprofloxacin, cefotaxime, ceftriaxone, and erythromycin requires a policy to control the use of antibiotics.(Levy MM, 2012). Microbial culture and resistance pattern were obtained from the local sepsis patients can be used as data to choose appropriatness of empirical antibiotic therapy for reducing mortality and morbidity in the sepsis patients. Within the first three hours of suspected sepsis, diagnostic studies should include WBCs, measuring serum lactate and obtaining appropriate cultures before starting antibiotics, so long as this does not delay their use by more than 45 minutes. To identify the causative organism(s), at least two sets of blood cultures using bottles with media for aerobic and anaerobic organisms should be obtained (Delaloye, J, 2014). Fluids should be administered until the central venous pressure (CVP) reaches 8–12mmHg. Once these goals are met, the central venous oxygen saturation (ScvO2), i.e., the oxygen saturation of venous blood as it returns to the heart as measured at the vena cava, is optimized. If the ScvO2 is less than 70%, blood may be given to reach a hemoglobin of 10 g/dL and then inotropes are added until the ScvO2 is optimized. Crystalloid solutions are recommended initially(Rochwerg B, 2014). Crystalloid solutions and albumin are better than other fluids (such as hydroxyethyl starch) in terms of risk of death. CPAP also gives support for treatment of sepsis. Among various CPAP devices and delivery systems Bubble CPAP is one of the low cost nasal CPAP delivering systems with underwater seal. (Kondwani Kawaza, 2014)

CHAPTER 06
RERERENCES

6. References

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