Chapter 1. Background of the study
1.1 Introduction:

1.1.1 Definitions and overview:

The word “Pneumonia” is derived from the Greek word “περιπλευμονή” meaning “condition about the lung”; it refers to a clinicopathological state mainly characterized by some degree of fever, cough, chest pain, and difficulty in breathing (Duffin, 1993). Sir William Osler described pneumonia as "captain of the men of death" in 1918 (Osler, 1920) as death rate was very high compared to other infectious diseases.

Pneumonia is an infectious disease of the pulmonary alveoli, distal airways, and interstitium of the lung causing consolidation of lungs and alveoli gets filled with WBC, RBC and fibrin (Marrie et al., 2005).

Pneumonia can be broadly classified into community-acquired and hospital-acquired (Marrie et al., 2005). Hospital-acquired pneumonia (HAP) or nosocomial pneumonia occurs after 48 hours of hospital admission but patient is not ventilated the time of admission whereas Ventilator-associated pneumonia (VAP), a variant of nosocomial pneumonia, occurs after 48-72 hours of endotracheal intubation. As per American Thoracic Society (ATS) nosocomial pneumonia is subdivided into early-onset (within the first 4 days of the hospitalization) and late-onset (after the fifth hospital day). Prognosis of early-onset nosocomial pneumonia is better than late-onset nosocomial pneumonia; the latter tends to be associated with multidrug-resistant (MDR) organisms with higher mortality rates (Cunha, 2014).

Community-acquired pneumonia is usually caused by *Streptococcus pneumoniae* and more common among elderly patients who are staying in institutionalized settings (Glover and Reed, 2005).

1.1.2 Etiology and Pathophysiology:

Inhaled gram-negative bacteria colonizes in the upper respiratory tract or respiratory support equipment of the patient. Stomach is also an important source of gram-negative bacilli that can ascend and colonize the respiratory tract. Aspiration of such colonized upper respiratory tract secretions in immunologically compromised patients usually leads to the development of hospital-acquired pneumonia (Tarsia et al., 2005, Cunha, 2014).

Most common bacteria involved in nosocomial pneumonia include the *Pseudomonas aeruginosa*, *Klebsiella* species, *Escherichia coli*, *Acinetobacter* species, *Staphylococcus*
*S. aureus* (especially methicillin-resistant *S. aureus* [MRSA]), *Streptococcus pneumoniae* and *Haemophilus influenzae* (Cunha, 2014).

Early-onset hospital-acquired pneumonia is usually caused by *Streptococcus pneumoniae*. Up to 9% of pneumonias in elderly patients in nursing homes is due to *Streptococcus pneumoniae*. Some early-onset hospital-acquired pneumonia also may be due to *Haemophilus influenzae* (Cunha, 2014).

Pathogens that are less commonly found in nosocomial pneumonia may include *Serratia* species, *Legionella* species, Influenza A virus, Parainfluenza virus and Adenovirus. *Enterobacter* species, *Stenotrophomonas maltophilia* (formerly *Pseudomonas maltophilia*) *Burkholderia cepacia*, *Candida* species and Oropharyngeal anaerobes are very rarely found in nosocomial pneumonia.

1.1.3 Risk factors and prognosis:

Several comorbid conditions and other factors may increase the risk of development of pneumonia as described in Table 1.

**Table 1. Risk factors for the development of pneumonia (Glover and Reed, 2005, Tarsia et al., 2005)**

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<tr>
<th>Type of Pneumonia</th>
<th>Microorganism</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Community-acquired (CAP)</td>
<td></td>
<td>Age &gt;65 years, diabetes mellitus, asplenia, chronic cardiovascular, pulmonary, renal and/or liver disease, smoking and/or alcohol abuse</td>
</tr>
<tr>
<td>Hospital-acquired (HAP)</td>
<td><em>Staphylococcus aureus</em></td>
<td>Coma, head injury, influenza infection, i.v drug use, diabetes mellitus, renal insufficiency</td>
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<tr>
<td></td>
<td><em>MRSA</em></td>
<td>Prior history of antibiotic use, prolonged mechanical ventilation</td>
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Prognosis of patients with hospital-acquired pneumonia depends on several factors, in general early-onset HAP has a better prognosis than the late-onset. Factors which may adversely affect the outcome of HAP are prolonged (>48 hours) mechanical ventilation, duration of hospital/ICU stay, “Acute Physiology and Chronic Health Evaluation (APACHE)” score, presence of acute respiratory distress syndrome (ARDS) and comorbid illness. Mechanical ventilation (MV) is one of the main risk factors responsible for hospital-acquired pneumonia. About 9 to 24% of patients intubated for longer than 48 hours acquire ventilator-associated pneumonia (VAP) which accounts for one third of the total nosocomial infections. Due to mechanical ventilation the incidence of acquiring pneumonia is increasing by around 6-20 fold.

1.1.4 Epidemiology of hospital-acquired pneumonia:

Pneumonia is the most common infectious disease in United States with highest mortality, where annual incidence of disease is approximately 4 million cases and cost of $23 billion burden to the health care system. The incidence of HAP is approximately 0.5–2.0% among all hospitalized patients and it is the most common nosocomial infection with mortality rate ranging from 30-70%. Incidence of pneumonia further increase in patients with mechanical ventilation, which alone represents >80% of overall HAP in the USA (Richards et al., 1999, Tablan et al., 2004).

The incidence of hospital-acquired pneumonia in the developing countries like India varies from hospital to hospital. The incidence of HAP reported in various Indian studies varies between 9.38-29% (Trivedi et al., 2000, Chandrakanth et al., 2010). Pneumonia is the fifth

<table>
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<th><strong>Pseudomonas aeruginosa</strong></th>
<th>Prolonged ICU stay, corticosteroids, structural lung diseases (bronchiectasis, cystic fibrosis), malnutrition</th>
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<tr>
<td><strong>Anaerobes</strong></td>
<td>Aspiration, recent abdominal surgery</td>
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<tr>
<td><strong>Acinetobacter species</strong></td>
<td>Antibiotics before onset of pneumonia and mechanical ventilation</td>
</tr>
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leading cause of death (Ramanakumar, 2005) in India. Among elderly patients, nosocomial pneumonia is still the major cause of morbidity and mortality and nearly 50% of the pneumonia related hospitalizations occur in patients above 65 years of age (Vila-Corcoles et al., 2009).

Hospital-acquired pneumonia that develops in ICU patients is responsible for high morbidity and mortality, as these patients are already seriously ill. Mortality rate in ventilator-associated pneumonia is very high; 50–70% crude mortality rates have been reported in several studies. However many patients with VAP are critically ill with several comorbid conditions which could cause death even if VAP do not occur. According to a cohort study attributable mortality due in HAP is more than 25%. (Marrie et al., 2005).

1.1.5 Treatment of hospital-acquired pneumonia:

Most patients with hospital-acquired pneumonia require ventilatory support and supplemental oxygen therapy at some point of time.

Antibiotic selection for empirical therapy of HAP should be mainly based on the risk for multi-drug resistant (MDR) organism infection. Combination therapy is needed if patients are likely to be infected by MDR organism, and monotherapy can be used in severe cases where chances of infection with MDR pathogens are less (Tarsia et al., 2005). Usually hospital-acquired pneumonia patients are prescribed with appropriate antibiotics for 14 days. (Cunha, 2014).

1.1.6 Epidemiological studies and severity prediction in pneumonia:

Epidemiological studies are required to study the incidences of pneumonia caused in patients in the community and hospital settings. The risk factors which are responsible for the outcome of HAP need to be analyzed in each hospital settings for implementation of preventive strategies to reduce patient morbidity, mortality, and hospital costs (Vila-Corcoles et al., 2009).

Prediction research plays important role in identifying the suitable factors that determine the outcome of the patients. It includes both diagnostic prediction studies and prognostic studies. In prediction research single variable or multiple variables that independently influence the outcome are analysed using suitable statistical methods. Based on this, suitable model can be developed and can be validated for ICU settings. Several international organizations have developed guidelines or scoring system to assess the severity of community-acquired pneumonia and basic idea of these scoring system is to enhance the appropriateness of admission and to lower unnecessary admission rates (BTSSCC, 2001, Mandell et al., 2000, Rainer et al., 2003).
Predicting the outcome in ICU setting plays important role in the decision making strategies of the physician. Outcome of the HAP patients mainly depends on the presence or absence of several risk factors like age, sex, severity at the time of admission, comorbidities like diabetes, hypertension, renal impairment, acquired immunodeficiency syndrome (AIDS), patients who are receiving the immunosuppression therapy etc. Very limited studies are available on severity and mortality prediction with respect to HAP patients. Availability of such prediction models for HAP could help the physicians to assess risks and improvement regarding patient conditions during the hospitalization (Fine et al., 1997, Mehr et al., 2001).

1.1.7 Antibiotic selection and utilization studies in HAP:

Selection of antibiotics is the crucial factor affecting the treatment outcome. Organizations like “World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC)” have very less information on the resistance pattern of the locally implicated organisms of pneumonia in developing countries like India. Thus in the absence of the local antibiotic sensitivity data, selection of empirical therapy is a difficult task. Antibiograms are often used by clinicians to assess local susceptibility rates, as an aid in selecting empiric antibiotic therapy, and in monitoring resistance trends over time within an institution. Thus development of local sensitivity data will help in the rational selection of antibiotics and reduce the incidence of treatment failure (Joshi, 2010).

The irrational use of antibiotics may lead to emergence of antibiotic resistance. High consumption of antibiotics leads to economic burden causing heavy devastation of economic sources. Drug utilization evaluation studies gives an insight by identifying the prescription pattern among the patients which help to provide useful information for appropriate and effective use of antibiotics in ICU (Suraj et al., 2008).

The defined daily dose (DDD) of antibiotics is the average maintenance dose per day for a antibiotic used for its main indication. The DDD calculated per 100 days can provide useful information regarding the antimicrobial agents used and its relationship with the resistance development and cost effectiveness (WHO, 2003).

Resistance results from the interplay of microorganisms, patients, and the hospital environment including antibiotic use and infection control practices. The emergence of antibiotic resistance in common respiratory pathogens may jeopardize the effectiveness of empiric treatment causing increased morbidity and mortality with infections and contributes substantially to rising costs of care resulting from prolonged hospital stays and need for more expensive drugs.
Antibiotics that are highly effective against specific organisms with less chance of development of resistance and controlled costs are needed at this juncture. But emergence of antimicrobial resistance has increased intensively within the past decade and has become obstacle to effective antibiotic selection. These trends have caused more difficulties especially in the ICUs. Bacteriologic records of throat swab culture results may be made useful as they provide guidance for empiric therapy before sensitivity patterns are available.

The antibiogram development for the hospital set up gives the periodic summary of antimicrobial susceptibilities of local bacterial isolates that are available from the clinical microbiology department of the hospital. Antibiograms are often used by clinicians to assess local susceptibility rates which are helpful in selecting empirical antibiotic therapy as well as monitoring resistance patterns over a period of time within the institution. Antibiograms can also useful in tracking the new local emerging resistance and changes in the resistance pattern of different classes of antibiotics against different microorganisms (Joshi, 2010). The antibiogram has its own limitations as we are not able to identify the cross-resistance and changes in the minimum inhibitory concentration of any antibiotics over a period of time.
1.2 Objectives of the study:

- **General Objective:**
  To study the risk factors associated with mortality, antibiotic resistance pattern and antibiotic utilisation pattern in hospital-acquired pneumonia (HAP).

- **Specific objective:**
  1. Identification of risk factors associated with mortality in HAP and development of mortality prediction model for HAP using multivariate analysis.
  2. Analysis of antibiotic resistance pattern in microorganisms isolated from HAP patients and development of model antibiogram.
  3. Analysis of antibiotic utilisation pattern and cost of antibiotic therapy in HAP.
1.3 Need for the study:

In order to understand the true burden of pneumonia, a detailed epidemiological study needs to be done in various circumstances. In addition, this will enable us to recognize the nature of disease patterns, to evaluate preventive measures and to allocate relevant health care and resources. Patient’s demographical data and clinical characteristics play an important role in deciding initial treatment.

Pneumonia is an infection of the lung parenchyma with significant morbidity and mortality. It occurs in persons of all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill. Pneumonia is often misdiagnosed, mistreated, and under estimated. The incidence of HAP is approximately 0.5–2.0% among all hospitalized patients and is the most common nosocomial infection with 30-70% mortality. Among them VAP constitutes more than 80% of HAP (Richards et al., 1999, Tablan et al., 2004). The incidence of HAP varies from hospitals to hospitals and different wards of the same hospital considerably. In an Indian study conducted by Trivedi et al., (Trivedi et al., 2000) incidence of nosocomial pneumonia was 9.38% and in another study (Chandrakanth et al., 2010) it was found to be 29%.

The outcome in the pneumonia patients is still not clear. Presence of risk factors such as advanced age, male sex, time of onset of the disease, type of wards, mechanical ventilation may adversely affect the outcome in HAP patients. The risk factors responsible for higher mortality in HAP patients must be recognized in order to provide extended care. Studies from past have identified many risk factors like prolonged mechanical ventilation >48 hours, large volume of aspiration, GCS rating <9, emergency interventions, cardiopulmonary resuscitation, severity of underlying illness that may increase the mortality in HAP patients (Tarsia et al., 2005). In this context prognosis of the patients in the ICU setting is very challenging and often depends on the various factors. The role of risk prediction models in the prognosis of the patients is already well-established in community-acquired pneumonia, like PSI scores and CURB- 65. But there are no studies available to predict the outcome or prognosis in the HAP patients especially in ICU settings (Moons et al., 2009, Royston et al., 2009).

Severity or mortality prediction scores are developed to categorise the critically ill patients based on the severity of the disease. Depending on the severity of the disease an increasing score is assigned to each patient (Rao et al., 2008). Based on the set of given variables and modeling equation these scores predict the outcome of the patient. Majority of the severity
scoring systems are developed using multivariate regression analysis to identify the most relevant factors for prediction of outcome or mortality. Availability of such severity or mortality prediction model for HAP can quantify severity of illness and aid in making decisions about ICU care and also for evaluating the suitability of patient for novel therapy (Rao et al., 2008).

Although treatment guidelines are important in patient management, it is also important that physician has to emphasize on the sensitivity and resistance pattern of locally implicated pathogens. Determination of the incidence of hospital-acquired pneumonia, etiological pathogens and their resistance pattern play an important role in the planning of treatment strategies (Lacy et al., 2004).

The prevention of infection in the ICU requires an intimate knowledge of the source of infection and antimicrobial resistance patterns of the invading organisms. Development and spread of antibiotic resistance starts right from hospitals, especially the intensive care units. Emergence of antibiotic resistance responsible for increased morbidity and mortality in infectious disease and increases total cost of treatment due to prolonged hospital stay and use of costly drugs (Struelens, 1998). Antibiotic selection within the hospital environment demands greater care because of constant changes in antibiotic resistance patterns in vitro and in vivo (Shlaes et al., 1997). The association between irrational antibiotic usage and emergences of resistance is well evident and is supported by number of studies (Goossens et al., 2005).

Important complementary steps for the containment of antimicrobial resistance are surveillance methods and reducing unnecessary and inappropriate use of antibiotics. Surveillance provides local antibiotic susceptibility data for selection of empirical therapy, information about the extent of resistance, changes in resistance rates, emergence and spread of new resistances. Information generated can be utilized to design policy and intervention aimed at reducing antibiotic resistance and hence indirectly improving the treatment outcome. This can be done by the development of an antibiogram. Hospital antibiogram plays an important role in identifying the susceptibility pattern and provide the physician to guide the local susceptibility pattern of the microorganisms. Antibiograms are commonly referred by the physician to assess local susceptibility rates and there by selecting effective empiric antibiotic therapy and also in monitoring resistance trends over a period of time within the institution. Antibiograms will also help in developing the local empirical antibiotic protocol which will benefit in reducing the treatment failure due to resistance (Joshi, 2010, Zapantis et al., 2005).
Very little informations are available on the resistance pattern of the locally implicated pathogens of HAP, in developing countries like India. Thus in the absence of the local antibiotic sensitivity/resistance data, empirical therapy is a difficult task.

Drug utilization studies helps in minimizing the development of antibiotic resistance. The main objective of the antibiotic utilization study is to facilitate the rational use of antibiotics in patient populations. It is not only to promote the rational antibiotic use but also to ensure the adherence to the local sensitivity pattern. The total consumption of antibiotics is represented in terms of DDD/100 bed days. The significance of calculating DDD of antibiotics indicates the rational usage of the specific antibiotic in a proper dosage according to the WHO guidelines. It also help in calculating the cost of total units of antibiotic consumed (WHO, 2012, Suraj et al., 2008, Shankar et al., 2003)

Many studies have proven that antibiotics play a major role in the total heath related costs. Cost studies will help in identifying effective combination which will be economical to the patients with better outcome and less side effects. In many cases single antimicrobial agent add higher cost than the combination therapy. Drugs used in combination not only reduced the total DDD but also total cost of the antibiotic. So cost studies will also help in not only reducing the total cost of antibiotic but also help in identifying the effective antibiotic regimen that can be used in the management of infectious disease (Shankar et al., 2005, Shankar et al., 2003, Suraj et al., 2008).
1.4 Review of Literature:

1.4.1 Definition and diagnostic criteria for HAP:

Pneumonia is an infection of the pulmonary parenchyma. The word ‘Pneumonia’ refers to a clinicopathological state that arises in several different yet specific disease patterns (Duffin, 1993). Pneumonia is still a major cause of mortality in this millennium despite the availability of extended spectrum antibiotics and improved medical care. The term ‘Pneumonia’ is derived from a Greek word which means “condition about the lung” (Duffin, 1993).

Nosocomial infection also called as ‘Hospital-acquired infection’ is an infection that occurs in a patient who was hospitalised for a reason other than that infection (Ducel et al., 2002). Pneumonia is considered to be “Hospital-acquired or ‘Nosocomial” when it occurs after 48-72 hours of hospitalization. After urinary tract infections (UTI), hospital-acquired pneumonia is the most common infection that occurs after hospitalisation with highest mortality.

Factors which may promote and facilitate the spread of infections among hospitalized patients include (Ducel et al., 2002):

- Immunosuppression among patients
- ICU interventions like endotracheal intubation and mechanical ventilation
- Spread of drug-resistant bacteria among hospital patients
- Inadequate infection control systems in hospitals

Diagnosis of HAP is confirmed by using the definition adapted by the “Centers for Disease Control” (CDC, 1989). The criteria includes:

- Onset of pneumonia 48-72 hours after hospital admission or mechanical ventilation
- A chest radiograph with new or progressive infiltrates, consolidation or pleural effusion
- Any of the following:
  - Onset of purulent sputum or any change in sputum characteristics
  - Isolation of etiological organisms from cultured blood
  - Isolation of an etiological organism from tracheal aspirate, bronchial brushing, bronchoalveolar lavage or biopsy

1.4.2 Epidemiology

In spite of tremendous improvements in diagnosis and treatment, hospital-acquired pneumonia remains as an important cause of morbidity and mortality (Bowton, 1999). HAP is usually of bacterial origin and it is the most common hospital-acquired infection in United States (Cunha,
2014). It occurs in patients who are on mechanical ventilation at a rate of 1 to 3% per day (George, 1995). In most of the studies the prevalence of HAP varies between 10-65% and associated mortality was more than 20% (George, 1995, Kollef, 1999). The mortality rates and duration of ICU stay is higher in patients who develop ventilator-associated pneumonia compared to other types of pneumonia.

Incidence of HAP is most common in medical and surgical ICUs. Study reports from various Asian hospitals suggest that the proportion of ICU-acquired respiratory infections is from 9-23% (Rozaidi et al., 2001). A prospective study done at the National University Hospital, in Singapore showed that 17.7% (24/136) of patients admitted to a medical ICU developed HAP and among them incidence of VAP was 12% (Stebbings et al., 1999).

The incidence of HAP varies considerably from hospital to hospital and different wards of the same hospital. The main predisposing factors are advanced age, type of hospital and type of ward (Tarsia et al., 2005). In a study done at King Edward VII Memorial Hospital, Mumbai, 16.7% of the patients admitted to the ICU developed HAP (Merchant et al., 1998). In another Indian study done on 328 ICU patients incidence of HAP was 53.9%, and out of that 81.7% were VAP (Mukhopadhyay et al., 2003). A study done over one year period in another Indian hospital shows that 9.4% (89/948) of patients admitted to ICU, developed HAP (Trivedi et al., 2000). Incidence of ventilator-associated pneumonia was most common in surgical and trauma ICU and incidence increases with number of ventilator days (Edwards et al., 2007).

Patients with HAP have higher mortality compared to those who are without HAP, however numerous studies have demonstrated that severe underlying illness, interventions, and patient conditions have an impact on the mortality. Uncontrolled cardiac and pulmonary disorders may account for the high mortality associated with nosocomial pneumonia. Prognosis of early-onset HAP is better compared to late-onset, as latter is usually associated with MDR pathogens and mortality is high (Cunha, 2014). A study conducted on HAP patients, in India reveals that 40% of the fatality (with overall crude mortality of 67.4% in ICU patients) is attributable to infection alone (Merchant et al., 1998). In a study conducted on HAP patients in Philippines crude reveals that mortality rate and attributable mortality rate was 42.4% and 30.1% respectively. (Berba et al., 1999).

1.4.3 Etiology and Pathogenesis:

HAP and VAP occur when a sufficiently large number of organisms are delivered to the lower respiratory tract so that host defences are overwhelmed (e.g., by aspiration or contaminated
respiratory therapy equipment), when host defences are impaired (e.g., by immunodeficiency or steroids), or if particularly virulent organisms are involved (McEachern and Campbell Jr, 1998). Gram-negative bacteria (GNB) account for 55% to 85% of HAP infections, and Gram-positive cocci account for 20% to 30% (Lynch, 2001). Aspiration of gram-negative bacteria colonised oropharyngeal secretion is one of the important causes of HAP (McEachern and Campbell, 1998). The oropharynx of hospitalized patients becomes colonized by GNB in as many as 35% of moderately ill and 73% of critically ill patients, often within the first 4 days of admission. With the introduction of these new pathogenic organisms into the oropharynx, the previously benign event of micro-aspiration now becomes a mechanism whereby virulent organisms are introduced into the lower respiratory tract and cause pneumonia (McEachern and Campbell, 1998).

1.4.4 Risk factors and outcome in hospital-acquired pneumonia:
Knowledge about the different risk factors present in HAP patients offers better prognostic information about the outcome in individual patients and will enable effective and rational preventive measures. Mortality is the most common outcome in most cases of HAP, however exact contribution of pneumonia to mortality is still not clear (Rello and Valles, 1998). Mortality from HAP mainly depends on the severity of the underlying illness, type of causative pathogen, presence of endotracheal intubation and mechanical ventilation. Finally the outcome of the patient depends on virulence of the pathogen responsible, immune status of the patient and appropriate antibiotic therapy. In a study evaluating the incidence of HAP in ventilated patients crude mortality was 42% compared to ventilated patients without pneumonia (38%) (Rello et al., 1991).

Large volume aspiration, Glasgow coma scale rating <9, emergency interventions, cardiopulmonary resuscitation and respiratory or cardiac arrest have been identified as risk factors which may have an impact on the outcome. Also patients with underlying conditions like cardiovascular diseases, respiratory diseases, surgery, gastrointestinal diseases, central nervous system diseases, trauma, burns, sepsis, and metabolic diseases were more prone to HAP and may have an impact on the outcome of the patient (Rello et al., 1999).

1.4.5 Severity and mortality prediction models in pneumonia:
Prediction research plays important role in identifying the suitable factors that determine the outcome of the patients. The risk factors responsible for higher morbidity and mortality in HAP must be recognized in order to provide extended care.
Severity prediction models (PSI scores, CURB-65) are available for community-acquired pneumonia where as such severity predictions models are not available for HAP.

The pneumonia severity index (PSI) or PORT Score is a clinical prediction tool used for assessing the probability of morbidity and mortality among CAP patients. PSI prediction rule considers factors such as age, patient’s medical history and abnormal physical findings (such as a respiratory rate of \( \geq 30/\text{minute} \) or a temperature of \( \geq 40^\circ\text{C} \)), and abnormal laboratory findings (such as a pH 7.35, a blood urea nitrogen (BUN) concentration \( \geq 30 \text{ mg/dL} \) or a sodium concentration \( <130 \text{ mmol/L} \)) at presentation (Fine et al., 1997). PSI can be used for assessing the risk of death within 30 days of presentation for CAP patients.

CURB-65, is a clinical prediction tool developed for predicting the mortality in community-acquired pneumonia (Lim et al., 2003). The CURB-65 is based on the earlier CURB score (Lim et al., 2001) and is recommended by the “British Thoracic Society” for the assessment of severity of pneumonia (BTSSCC, 2001). The score is an acronym for each of the risk factors measured ranging from 1 to 5, with 1 being the lowest and 5 being the highest.

- Confusion of new onset
- Blood Urea nitrogen greater than 7 mmol/l (19 mg/dL)
- Respiratory rate of 30 breaths per minute or more
- Blood pressure less than 90 mmHg systolic or diastolic blood pressure 60 mmHg or less
- age 65 or older

España et al., (España et al., 2006) developed a clinical prediction rule for identifying patients with severe community-acquired pneumonia. In the multivariate analyses, eight independent predictive factors were correlated with severe community-acquired pneumonia: arterial pH <7.30, systolic blood pressure <90 mm Hg, respiratory rate >30 breaths/min, altered mental status, blood urea nitrogen >30 mg/dL, oxygen arterial pressure <54 mm Hg or ratio of arterial oxygen tension to fraction of inspired oxygen <250 mm Hg, age \( \geq 80 \) years, and multilobar/bilateral lung affectation. This prediction model can be used as practical diagnostic decision aid, and predicts the development of severe community-acquired pneumonia.

Mehr et al., (Mehr et al., 2001), developed a prediction model for 30-day mortality in nursing home residents with lower respiratory tract infection (LRTI). The model was developed by
logistic regression using parameters like: serum urea nitrogen, white blood cell count, body mass index, pulse rate, activities of daily living status, absolute lymphocyte count of less than 800/μL, male sex, and deterioration in mood over 90 days.

APACHE II ("Acute Physiology and Chronic Health Evaluation" II) is a disease severity classification system developed by Knaus et al., (Knaus et al., 1985). APACHE II is used to find the risk of death of a patient who is admitted in ICU. The tests are carried out within 24 hours of the admission. The APACHE II scores are calculated from 12 physiological and biochemical parameters. The parameters used for calculating APACHE II scores are body temperature, mean arterial pressure, heart rate, respiratory rate, partial oxygen pressure (PaO₂), arterial blood pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood cell count and Glasgow Coma Scale (GCS). The sums of these 12 values are called Total Acute Physiology Score (A). It is added to age points (B) and chronic health points (example severe organ insufficiency or immunocompromised patients), to arrive at the APACHE II score.

Extensive literature search indicates no attempt has been made to develop severity or mortality prediction model for CAP or HAP in India.

1.4.6 Common pathogens in HAP:

Gram-negative pathogens like *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, microorganisms belonging to the family Enterobacteriaceae (*Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia* species, etc.) and under certain conditions, microorganisms such as *Haemophilus influenzae* are the most frequent cause of HAP (Rello et al., 2005, Park, 2005). Gram-positive pathogens commonly isolated in HAP include *Staphylococcus aureus* and *Streptococcus pneumoniae* accounting for 35–39% of all cases (Spencer, 1996, Fluit et al., 2001).

In a study conducted, the distribution of the bacterial isolates from 426 positive specimens of patients with HAP showed that 96.2% (410/426) isolates were obtained from specimens of patients on ventilator and 3.8% (16/426) from those not on ventilators. Gram-negative organisms like *P. aeruginosa* followed by *E. coli* and *K. pneumoniae* were isolated more frequently than Gram-positive organisms which were isolated from patients with HAP not using ventilator (Mukhopadhyay et al., 2003).

A two phase prospective cohort study by Berba et al, reported that the incidence of nosocomial pneumonia in Philippine General Hospital over a one-year period was 28.2 %. Most pathogens
were gram-negative bacteria and 3 out of 7 major isolates were from the family *Enterobacteriaceae* giving an incidence of 15% (Berba et al., 1999).

Gram-negative bacterial infections are of particular concern as they are highly efficient at up-regulating or acquiring genes that code for mechanisms of antibiotic resistance, especially in the presence of antibiotic selection pressure. They often use multiple mechanisms against the same antibiotic or using a single mechanism to affect multiple antibiotics (Peleg and Hooper, 2010).

*S. aureus* is particularly important in mechanically ventilated patients in which higher rates of multiple drug resistant (MDR), methicillin resistant isolates often prevail together with MDR Gram-negative bacilli.

**1.4.7 Antibiotic resistance in HAP:**

Discovery of antibiotics during 20th century substantially reduced the mortality attributable to infectious disease. Antibiotics have saved the life of millions of people suffering from serious infectious disease and contributed immensely to increased life expectancy during the latter part of the last century. Ironically these gains are jeopardised by the emergence and spread of microorganism which are resistant to cheap and effective first-line antibiotics (WHO, 2002). These include penicillin-resistant *S. pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, multi-resistant salmonellae, and multi-resistant *Mycobacterium tuberculosis*.

Antibiotic resistance is a natural biological phenomenon triggered by variety of factors, including certain human practices. The overuse of antimicrobial agents forces microbes to either adapt or die in a phenomenon known as "selective pressure". Bacteria are particularly efficient at enhancing the effects of resistance as they are capable of transferring their resistance genes during their replication and to other bacteria through ‘conjugation’. As a consequence, the resistance can be spread to the entire bacteria population (WHO, 2002).

Many studies have proved that total consumption of antimicrobials is the key factor for the development of resistance. Studies have shown that early appropriate antibiotic therapy significantly decreases mortality in nosocomial pneumonia. Initial therapy with broad spectrum antibiotics should be started as soon as the diagnosis is made to cover all possible organisms. Choice of antibiotics initially is empiric, guided by time of onset of infection and the antibiotic susceptibility pattern of local microbes. Once culture and antibiotic susceptibility reports are available, it was recommended to modify the empirical therapy and to use antibiotics with
narrower spectrum. This so called de-escalation of antibiotic therapy (Sandiumenge et al., 2003) is done to limit the emergence of multi-drug resistant pathogens related to overuse of antimicrobial agents and to avoid the risk of super-infection with resistant microorganisms.

A study aimed to assess the feasibility of de-escalation in an Indian ICU showed that despite the high prevalence of antibiotic resistance, de-escalation was still possible in 68% patients where the organism could be isolated (Bajpai and Karnad, 2010).

De-escalation was possible in 64% of late-onset VAP where non-fermenters were isolated compared to 82% with early-onset VAP in a study by Rello et al., (Rello et al., 2004).

**1.4.8 Antibiotic use, emergence of resistance and their surveillance**

Antibiotic resistance increases the morbidity and mortality associated with infectious disease and increases the treatment cost by prolonging hospital stay and demanding for more expensive drugs (Gold et al., 1996). Multiple antibiotic resistance to useful antibiotics, including the penicillins, cephalosporins, aminoglycosides, and fluoroquinolones, has gradually increased among a number of gram-negative pathogens.

Studies have shown that there is substantial geographic differences in the proportion of resistance to various classes of antibiotics (Goossens and Sprenger, 1998). In northern European countries rates of antibiotic resistance is low whereas the rates are alarmingly high in southern and central Europe. Irrational use of antibiotic is the main cause of emergence antibiotic resistance and selection pressure of antibiotic (Bronzwaer et al., 2002).

Monitoring the use of antibiotics and surveillance programs on antibiotic resistance is considered as most effective tools of nosocomial infection control programme (Haley et al., 1985). The importance of monitoring the development and spread of antibacterial resistance has led to the instigation of many surveillance studies which mainly involves Alexander Project, MYSTIC (Meropenem Yearly Susceptibility Test Information Collection), SMART (Study for Monitoring Antimicrobial Resistance Trends), PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin), ANSORP (Asian Network for the Surveillance of Resistant Pathogens and LASER (Latin American Surveillance and Epidemiology Research). The “European Surveillance of Antimicrobial Consumption (ESAC)” project, granted by the European Commission, is an international network of surveillance systems aiming to obtain comparable and reliable data about antibiotic use in Europe. Increased use of antibiotics and the spread of pneumococcal clones led to the launching
of Swedish Strategic Programme (Mölstad et al., 2008) for the “Rational Use of Antimicrobial Agents and Surveillance of Resistance”, which contributed to the decrease of antibiotic use.

1.4.9 Hospital antibiogram and their role in tracking antibiotic resistance:

The hospital antibiogram is a periodic summary of antimicrobial susceptibilities of local bacterial isolates submitted to the hospital's clinical microbiology laboratory. It is often used by physician to assess local susceptibility of microorganisms that assist in selecting empirical antibiotic therapy and in monitoring resistance pattern within the institution over a period of time (Lacy et al., 2004, Zapantis et al., 2005).

Many hospital laboratories routinely perform antimicrobial susceptibility testing for different pathogens. Cumulative susceptibility testing results are often organized into a summary table or antibiogram, which may be used by clinicians, pharmacists, infection control personnel and microbiologists as a reference guide to community or hospital-specific resistance patterns. Antibiograms lend information that can be used to raise awareness of resistance problems, support the use of optimal empiric therapy, and identify opportunities to reduce inappropriate antibiotic usage (Fridkin et al., 2001, Van Beneden et al., 2003). A typical antibiogram displays the total number of bacterial isolates tested against a range of antimicrobials and includes the percentage of bacterial isolates susceptible or resistant to each antimicrobial agent tested. The time period covered by most antibiogram is 6-12 months and it summarizes susceptibility testing results for an entire hospital by inpatient, outpatient, and intensive care units or by individual wards (Fridkin et al., 2001).

Aggregated antibiogram data is an accurate way for health departments to generate needed estimates of pneumococcal resistance.

Limitations of Antibiograms:

Antibiograms have only limited value for tracking antimicrobial resistance and guiding empiric therapy. Drawbacks to this method include the inability to evaluate resistance to multiple drugs. Relatively few drugs can be evaluated because of laboratory variations in antibiotics selected for susceptibility testing by antibiograms. Another limitation of antibiograms is the inability to distinguish between intermediate and high level resistance to penicillin. This distinction has become relevant for treatment of some infections (Van Beneden et al., 2003) Aggregating susceptibility data across an entire hospital can be misleading as hospital wide susceptibility data may hide trends in specific hospital wards or areas. Antimicrobial resistance is likely to be more prevalent in ICUs than in other areas of the hospital.
Reliability of antibiogram can be improved by including patient related clinical data. The hospital antibiogram cannot be used alone to select the optimal empiric therapy in an individual patient as specific patient factors need to be considered, including the type and severity of infection, the infecting organism, patient’s medical history and past antibiotic use.

1.4.10 Role of Drug Utilization studies in the HAP:
Drug utilization research was defined by WHO as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (WHO, 2003).

“Anatomical Therapeutical Chemical (ATC)” Classification and “defined daily dose (DDD)” are statistical measure of drug consumption, DDD is used to standardize the comparison of drug usage between different drugs or between different health care environments. Most of the surveillance systems use the number of DDD per 100 patient days to compare consumption rates over time and between hospitals, geographical regions and countries. It can be defined as average maintenance dose per day for a drug used for its main indication in adults.

Cost studies play an important role in nosocomial infections and they are carried out to check the economic burden on the patient. These studies helped in identifying the cost-effective regimen. Studies showed that antibiotic cost includes the major part of the treatment cost in the hospital. The major determinants of costs are length of hospital stay and ICU admissions (Shankar et al., 2005).