Ventilator Associated Pneumonia in A Neonatal Intensive Care Unit

Thesis

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in Clinical & Chemical Pathology

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Introduction

Ventilator-Associated Pneumonia (VAP) is pneumonia in mechanically–ventilated patients in intensive care units that develops later than or at 48 hours (hrs) after the patient has been placed on mechanical ventilation; VAP is the second most common hospital-acquired infection among pediatric and neonatal intensive care unit (NICU) patients. Empirical therapy for VAP accounts approximately 50% of antibiotic use in NICUs. Surveillance studies of nosocomial infections in NICU patients indicate that pneumonia comprises 6.8 to 32.3% of nosocomial infections in this setting **(Gauvin et al., 2003)**.

The incidence of VAP-attributable mortality is difficult to quantify due to the possible confounding effect of associated conditions, but VAP is thought to increase the mortality of the underlying disease by about 30%. VAP is also associated with considerable morbidity, including prolonged ICU-length of stay, prolonged mechanical ventilation, and increased costs of hospitalization **(Tejerina et al., 2006)**.

Neonates have unique characteristics predisposing them to nosocomial infections. The immature immune system; the skin and mucous membranes are more permeable and are less effective barriers to infection; abnormal granulocyte migration, and defective phagocytosis in these patients have been demonstrated. Additionally, decreased the activity of complement particularly opsonization and hypogamma-globulinemia **(Pessoa-Silva et al., 2004)**.

Low birth weight has been shown to be another risk factor for the development of nosocomial pneumonia. A 41-month surveillance study demonstrated a significant association between a birth weight of less than 1,500 g and a higher rate of

nosocomial pneumonia; however, low birth weight may be a marker for an increased duration of mechanical ventilation **(Cordero et al., 2002)**.

Ventilator-Associated Pneumonia (VAP) can be diagnosed by the following criteria: fever exceeding 38.5^{o}C, tachypnea and/or otherwise unexplained increased oxygen requirement, elevated white blood cell count (>15 x 10^{9} cells/liter), an isolated pathogen from endotracheal aspirate (ETA) and blood culture together with a positive gram stain, and increased leukocyte count, plus an infiltrate on chest radiographs persisting for 48 hrs or more **(Foglia et al., 2007)**.

Although, delayed diagnosis of VAP and subsequent delay in initiating appropriate therapy may be associated with worse outcomes; however, an incorrect diagnosis may lead to unnecessary treatment and subsequent complications related to therapy. Therefore, early, accurate diagnosis is a fundamental in the management of patients with VAP **(Rello et al., 2002)**.

Aim of Work

The aim of this work is to find the incidence of Ventilator-Associated Pneumonia (VAP), and to identify its associated risk factors in a newborn intensive care unit.

Healthcare-Associated Pneumonia

Healthcare-Associated Pneumonia (HAP) is a Lower Respiratory Tract (LRT) infection that appears during or after hospitalization in a patient who was not incubating the infection on admission **(Rotstein et al., 2008)**.

Healthcare-Associated Pneumonia (HAP) is the second most common nosocomial infection with a crude overall rate of 6.1 per 1000 discharges **(American Thoracic Society, 2005)**. By comparison, the infection rate for nosocomial urinary tract infection, the most common hospital-acquired infection, is 11 per 1000 discharges. The incidence of HAP varies depending on the hospital environment. The incidence of HAP is greater among patients in the intensive care unit (ICU); generally, approximately 30% of HAP occurs in critical care settings **(Yuan et al., 2007)**.

For any patient, the criteria must meet at least one of the following:

- Fever (>38°C or >100.4°F) with no other recognized cause.
- Leukopenia (<4000/mm^3) or leukocytosis ($\geq$12,000/mm^3).
- Altered mental status with no other recognized cause.
- And;

(1) Rales or dullness to percussion on physical examination of chest and any of:

- New onset of purulent sputum or change in the character of sputum;
- Organism isolated from blood culture;

- Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy.
- Isolation of virus or detection of viral antigen in respiratory secretions;
- Diagnostic single antibody titre (IgM) or four-fold increase in paired serum samples (IgG) for pathogen.

(2) Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation or pleural effusion **(CDC, 2004)**.

Risk factors for HAP:

(1) Condition of patient:

- Severely ill, e.g. septic shock
- Age (elderly or neonate)
- Surgical operation (chest/abdomen)
- Major injuries
- COPD
- Extensive cardiopulmonary disease
- Cerebro-vascular accidents
- Coma
- Heavy smoker

(2) Therapy:

- Sedation
- General anesthesia
- Tracheal intubation
- Tracheostomy
- Prolonged artificial ventilation
- Enteral feeding
- Broad-spectrum antibiotic therapy
- H2 blockers
- Immunosuppressive and cytotoxic drugs

(Johanson and Dever, 2003)

Sources of HAP:

HAP may be caused by infectious agents from endogenous or exogenous sources;

- Endogenous sources due to aspiration from oropharynx, trachea, nasal, sinuses or gastric fluids.
- Exogenous sources due to inhalation from healthcare-workers, ventilatory circuits and neubulizers **(Sherman et al., 2006)**.

Etiologic agents of HAP:

The timing of HAP is an important epidemiologic variable, risk factors for pathogens, and outcome in patients with HAP. HAP is subdivided into pneumonia that occurs at the word and those arise in the ICU. The term "early-onset" used if pneumonia occurs within 96 hrs of admission and the "late-onset" if pneumonia arises beyond this time **(Napolitano, 2003)**.

Incidentally, this division assists in the microbiological identification of pathogens that cause HAP; it has been suggested that patients with late-onset healthcare-associated pneumonia are associated with an increasing prevalence of resistant pathogens **(Leroy and Soubrier, 2004)**.

Healthcare-Associated Pneumonia is caused by a spectrum of bacterial pathogens, may be polymicrobial and rarely due to viral or fungal pathogens **(Hentschel et al., 2005).**

Common pathogens including:

• Bacterial:

1) Aerobic gram-negative bacilli (e.g., *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterobacter species*, and *Serratia marcescens)*.
2) Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae*.
3) *Anaerobes*, *Mycobacterium tuberculosis* or *Legionella pneumophila* **(Alcon et al., 2003)**.

- Viral: e.g., *Influenza A and B*, and *Respiratory syncytial virus (RSV).*
- Fungus: e.g., *Aspergillus species*, and *Candida species*.
- Protozoa: e.g., *Pneumocystis carinii* **(Babcock et al., 2003)**.

Neonatal Ventilator-Associated Pneumonia

Definition of VAP:

Ventilator-Associated Pneumonia (VAP) is defined as an infection occurring > 48 hours after hospital admission in a mechanically ventilated patient with a tracheostomy or endotracheal tube **(Bouza et al., 2008)**.

Ventilator Associated Pneumonia (VAP) is a subset of healthcare-associated pneumonia and includes all patients receiving mechanical ventilation at the time of infection and it occurs exclusively in the ICU and represents approximately 86% of all ICU-healthcare-associated pneumonia **(Aly et al., 2008)**. It is the most widespread infection encountered in the intensive care unit and is associated with significant morbidity, mortality and cost **(Rosbolt et al., 2009)**.

Mechanical ventilator:

Ventilator is a device to assist or control respiration continuously; inclusive of the weaning period, through a tracheostomy or by endotracheal intubation **(Dollinger, 2007)**.

Goals of mechanical ventilation are to achieve and maintain adequate pulmonary gas exchange, minimize the risk of lung injury, reduce patient work of breathing, and to optimize patient comfort **(Guthrie et al., 2005)**.

Lung expansion devices such as Intermittent Positive Pressure Breathing (IPPB); Nasal Positive End Expiratory Pressure (PEEP) and Continuous Nasal Positive Pressure (CPAP, hypo-CPAP) are not considered ventilators unless

delivered via tracheostomy or endotracheal intubation (e.g ET-CPAP) **(Leblebicioglu et al., 2007)**.

The most common neonatal respiratory disorders requiring receiving ventilation are *Respiratory distress syndrome (RDS)*, *Meconium aspiration syndrome*, congenital *pneumonia*, *Persistent Pulmonary Hypertension of the Newborn (PPHN)*, and *Bronchopulmonary Dysplasia* **(Reyes et al., 2006)**.

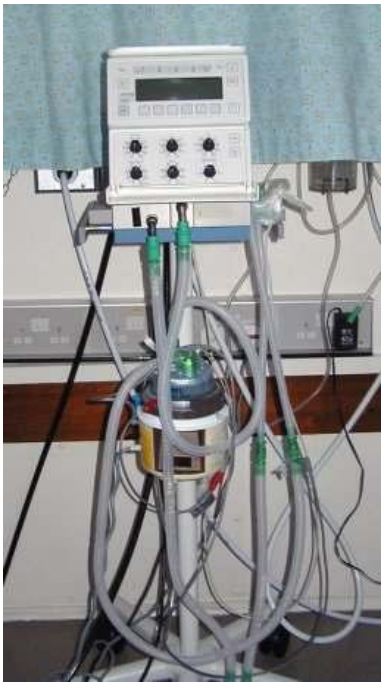

Figure (1): Neonatal ventilator.

Figure (2): Adult ventilator.

Incidence of VAP:

Ventilator-Associated Pneumonia (VAP) is the most frequent intensive care unit (ICU)-hospital acquired infection among patients receiving mechanical ventilation and accounts for more than 15% of all hospital acquired infections **(Kollef, 2005)**. VAP is affecting 8 to 20% of ICU-patients and up to 27% of mechanically ventilated patients **(Beardsley et al., 2006)**. It has been shown that these infections prolong both the duration of ventilation and the duration of ICU-stay **(Agbaht et al., 2007)**.

VAP is the second most common hospital acquired infection among pediatric and neonatal intensive care unit (PICU) (NICU) after blood stream infection (BSI) **(Calaghan, 2007)**. VAP rates within the neonatal population range anywhere from 6 to 40% **(Wall et al., 2008)**. It has been shown to increase length of stay and mortality especially in the extremely low birth weight infant **(Keith et al., 2004)**.

These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP **(Dellinger et al., 2004)**. However, a precise and universal evaluation of such over costs is very difficult; cost analysis is indeed dependent on a wide variety of factors which differ from one country to another, including healthcare-system, organization of the hospital and the ICU, the possibility of patients being treated by private practitioners, cost of antibiotics, and confounding factors such as the responsible pathogen or the severity of the underlying disease **(American Thoracic Society, 2005)**.

Interestingly, approximately 50% of all antibiotics prescribed in an ICU are administered for respiratory tract infections **(Foglia et al., 2006)**. Because several studies have

shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals **(Colardyn, 2005)**.

Mortality:

VAP was the most common hospital acquired infection contributing to death **(Evans, 2005)**. The mortality rate for VAP ranges from 20% to 50% and can reach 70% when lung infection is caused by high-risk pathogens; in contrast to infections of other frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1% to 4% **(Bradley et al., 2004)**.

The infant's mortality depended on birth weight, duration on ventilator and virulence of pathogen; the mortality rate increased in infants with a birth weight less than 1,500g; among infants who died, those with VAP had longer duration on a ventilator **(Kollef, 2005)**. The causes of death was attributed directly to multi-resistant strains of *Acinetobacter*, *Klebsiella* and *Pseudomonas* which are difficult to treat and are implicated in a wide spectrum of hospital-acquired infections, predominantly in the ICU **(Koksal et al., 2006)**.

Risk factors:

Intubation with mechanical ventilation is the most important risk factor for the development of VAP. For this reason, intubation should be used only when medically necessary **(Lista et al., 2004)**. However, most phases of respiratory support have been linked to respiratory infection. These include; mechanical ventilation bags, ventilators, aerosolized medications, water supply, bronchoscope, suction catheters and respiratory support personnel **(Singh et al., 2006)**.

Clinical interventions for monitoring and therapeutic purposes can increase infants' risk of VAP such as that which may occur during reintubation, physical movement out of the ICU, and bronchoscopy **(Dunn and Reilly, 2003)**. Placement of the enteral tube might enhance nasopharyngeal and gastric colonization with gram-negative bacilli **(Wolf and Arnold, 2005)**.

General risk factors for developing VAP in the newborn include: prematurity, immature immune system (defective chemotaxis and phagocytosis, poor antibody production and reduced cellular immunity), congenital abnormalities, prenatal asphyxia and medications associated with the development of VAP are NADP, steroids, and histamine-type 2 receptor blockers **(Beck et al., 2007)**.

Infants with respiratory distress syndrome need prolonged use of mechanical-ventilatory support, which potentiates exposure to contaminated respiratory equipment and contact with contaminated or colonized hands of healthcare-workers in the NICU **(Finer et al., 2004)**.

The design of the NICU may also have an effect on the incidence of nosocomial infections and specifically VAP. A 5-year prospective study of nosocomial infections in a NICU was performed; the NICU-location was moved from cramped quarters adjacent to a busy medical ward to a new facility. The new nursery had a 50% increase in staffing and improved infection control features. In the old nursery, 16 of 492 patients had pneumonia, where as in the new nursery, only 1 patient of 419 had pneumonia **(Goldmann et al., 2003)**.

Pathogenesis:

The upper respiratory tract is normally colonized with non-pathogenic or "commensally" bacterial flora, but physical and immunologic host defenses generally ensure that bacteria that gain access to normally sterile sites (e.g., the LRT) are cleared **(Joanne and Langley, 2005)**.

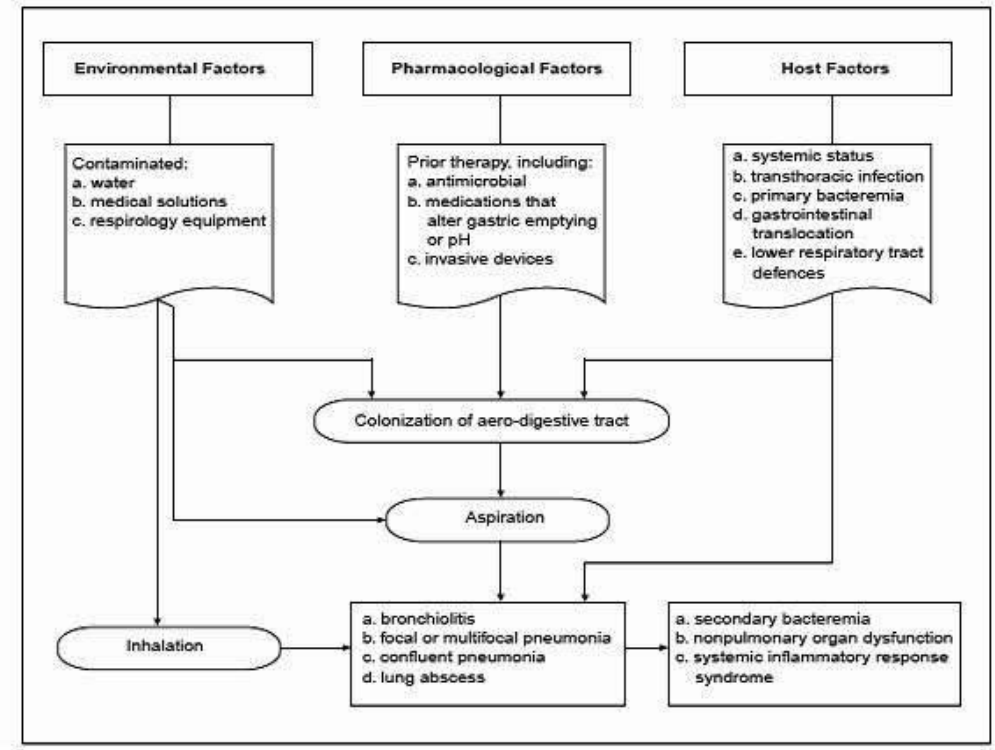

Figure (3): Pathogenesis of HAP and VAP **(**Quoted from **Rotstein et al., 2008)**.

Colonization of the oropharynx with Gram-negative bacilli occurs within a few days of ICU-admission in about 50% of patients (up to 80% of intubated patients) and increases the subsequent risk pneumonia. The source of these bacteria may be endogenous of (gastric overgrowth, fecal-oral, or sinuses) or exogenous (via the hands of healthcare-workers or contaminated equipment) **(Safdar et al., 2005)**.

Micro-aspiration in a hospitalized patient is serious and more likely to cause infection because the oropharyngeal secretions that are aspired are likely to contain organisms that are not present under normal circumstances but which frequently cause VAP **(Larson, 2005**). VAP develops when the aspiration or inoculations of microorganisms occur in patients with impaired defense mechanisms **(Smith et al., 2005)**.

Gram-negative bacilli colonize the oropharynx of hospitalized patient, often within the first 4 days of admission **(Stoller et al., 2003)**. Therefore, increased adherence of gram-negative bacteria, airway damage due to the presence of an endotracheal tube, nasogastric tube, repeated suctioning, and decreased normal flora as a result of antibiotic abuse are the mechanisms by which virulent organisms are introduction into the lower respiratory tract and cause pneumonia **(Topeli et al., 2004)**.

Mechanical ventilation is associated with high rates of VAP because the endotracheal tube bypasses upper respiratory tract defenses, allowing large number of organisms colonize the oropharynx to be delivered to the lower respiratory tract **(Osorio et al., 2005)**.

Since, some clinical interventions increase development of VAP, clinical guidelines for the treatment of VAP should be developed; clinicians should understand its epidemiology and participate in control measures, by reducing the risk of cross-contamination during mechanical ventilation, preventing colonization and aspiration, and caring for enteral tubes and umbilical catheters in sick infants **(Van Kaam and Rimensberger, 2007)**.