Bushehr University of Medical Sciences
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Final Report of Research Project (Thesis of Medical Degree)

Ventilator-associated Pneumonia: A Study of Patients admitted in Internal Intensive Care Unit of Ali Asghar Hospital, Shiraz

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In the Name of God

Dedication

I dedicate this thesis to my best friend

in life,

my husband Mohammad Javad &

also

to my father, mother & brother who

helped me a lot in my life

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Abstract

Introduction: Ventilator-associated pneumonia is defined as a pneumonia occurring in patients within 48 hours or more after intubation with an endotracheal tube or tracheostomy tube and which not present before. The main objective of this study was to determine prevalence, predisposing factors and outcomes for ventilator associated pneumonia in an internal intensive care unit in a tertiary hospital.

Material and Methods: In this retrospective review, all adult intensive care unit admitted patients at Ali Asghar Hospital with clinically and radiologically suspected ventilator-associated pneumonia between March 2009 and May 2010 were considered. The following data were recorded for each patient: demographic data, culture densities, chest radiological findings, pathogen(s), age, white blood cell count (WBC), presence of comorbid diseases, duration of hospital stay prior to diagnosis, and hospital survival. Data was assessed with SPSS software version 15 compatible for windows.

Results: There were 49 patients in this study and most of the patients (69.3%) were males. Most of the patients (65.3%) were in more than 60 years age group of whom males were dominant. The most common risk factor was smoking, nasogastric tube, prolong duration of hospitalization, hospital admissions more than 2 times, prolong duration of intensive care unit admission, decreased level of consciousness and prolong ventilator support. The most common organism isolated was acinetobacter. Most of the patients were died (59.1%) of whom most were males.

Discussion and conclusion: This study demonstrated that ventilator associated pneumonia is an important nosocomial infection among patients receiving mechanical ventilation in a community hospital and it is associated with greater hospital mortality rates and longer lengths of stay in the intensive care unit and hospital. Prevention is better than cure. Ventilator associated pneumonia is a well preventable disease and a proper approach decreases the hospital stay, cost, morbidity and mortality.

Key Words: Ventilator-associated pneumonia, endotracheal tube, intensive care unit, pathogen

Chapter 1:

Introduction

1.1. Ventilator-Associated Pneumonia:

Most research on Ventilator-Associated Pneumonia (VAP) has focused on illness in the hospital setting. However, the information and principles based on this research can be applied to Healthcare-Associated Pneumonia (HCAP) not associated with ventilator use as well. The main rationale for the new designation HCAP is that the pathogens and treatment strategies for VAP are more similar to those for Hospital-Acquired Pneumonia (HAP) than to those for pure CAP. The greatest difference between VAP and HCAP/HAP—and the greatest similarity of VAP to CAP—is the return to dependence on expectorated sputum for a microbiologic diagnosis, which is further complicated by the frequent colonization with pathogens among patients in the hospital or other health care–associated settings (1).

1.1.1. Etiology:

Potential etiologic agents of VAP include both multi drug resistance (MDR) and non-MDR bacterial pathogens. The non-MDR group is nearly identical to the pathogens found in severe CAP; it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors for HCAP, MDR pathogens are a consideration, even early in the hospital course. The relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution. Many hospitals have problems with P. aeruginosa and MRSA, but other MDR pathogens are often institution-specific (1).

Table 1-1 Microbiologic Causes of Ventilator-Associated Pneumonia	
Non-MDR Pathogens	**MDR Pathogens**
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	MRSA
Haemophilus influenzae	*Acinetobacter* spp.
MSSA	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	*Enterobacter* spp.
Escherichia coli	ESBL-positive strains
Klebsiella pneumoniae	*Klebsiella* spp.
Proteus spp.	*Legionella pneumophila*
Enterobacter spp.	*Burkholderia cepacia*
Serratia marcescens	*Aspergillus* spp.

Note: ESBL, extended-spectrum -lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

Less commonly, fungal and viral pathogens cause VAP, most frequently affecting severely immunocompromised patients. Rarely, community-associated viruses cause miniepidemics, usually when introduced by ill health care workers (1).

1.1.2. Epidemiology:

Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia—VAP in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. Once a ventilated patient is transferred

to a chronic care facility or to home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia (1).

Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and compromise of the normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors (1).

Table 1-2 Pathogenic Mechanisms and Corresponding Prevention Strategies for Ventilator-Associated Pneumonia

Pathogenic Mechanism	**Prevention Strategy**
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose patients[a]
Gastroesophageal reflux	Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of gastrointestinal bleeding due to prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b]
Cross-infection from other colonized patients	Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation[a]

Prolonged duration of ventilation	Daily awakening from sedation,[a] weaning protocols[a]
Abnormal swallowing function	Early percutaneous tracheostomy[a]
Secretions pooled above endotracheal tube	Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and patient transport
Altered lower respiratory host defenses	Tight glycemic control[a]; lowering of hemoglobin transfusion threshold; specialized enteral feeding formula

[a]Strategies demonstrated to be effective in at least one randomized controlled trial.

[b]Strategies with negative randomized trials or conflicting results.

The most obvious risk factor is the endotracheal tube (ET), which bypasses the normal mechanical factors preventing aspiration. While the presence of an ET may prevent large-volume aspiration, microaspiration is actually enhanced by secretions pooling above the cuff. The ET and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the ET surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged during suctioning and can reinoculate the trachea, or tiny fragments of glycocalyx can embolize to distal airways, carrying bacteria with them (1).

In a high percentage of critically ill patients, the normal oropharyngeal flora is replaced by pathogenic microorganisms. The most important risk factors are antibiotic selection pressure, cross-infection from other infected/colonized patients or contaminated equipment, and malnutrition (1).

How the lower respiratory tract defenses become overwhelmed remains poorly understood. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-

third of colonized patients develop VAP. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although several factors have been suggested. Hyperglycemia affects neutrophil function, and recent trials suggest that keeping the blood sugar close to normal with exogenous insulin may have beneficial effects, including a decreased risk of infection. More frequent transfusions, especially of leukocyte-depleted red blood cells, also affect the immune response positively (1).

1.1.3. Clinical Manifestations:

The clinical manifestations of VAP are generally the same as for all other forms of pneumonia: fever, leukocytosis, increase in respiratory secretions, and pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation (1).

1.1.4. Diagnosis:

1.1.4.1. Clinical Diagnosis:

No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates (1).

Application of clinical criteria consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) tracheal colonization with pathogenic bacteria in patients with ETs, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency

of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities, such as atypical pulmonary edema, pulmonary contusion and/or hemorrhage, hypersensitivity pneumonitis, ARDS, and pulmonary embolism. Clinical findings in ventilated patients with fever and/or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management (1).

This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The recent IDSA/ATS guidelines for HCAP suggest that either approach is clinically valid (1).

1.1.4.2. Quantitative-Culture Approach:

The essence of the quantitative-culture approach is to discriminate between colonization and true infection by determining the bacterial burden. The more distal in the respiratory tree the diagnostic sampling, the more specific the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, a quantitative endotracheal aspirate yields proximate samples, and the diagnostic threshold is 106 cfu/mL. The protected specimen brush method, in contrast, obtains distal samples and has a threshold of 103 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram's stain, differential cell counts, staining for intracellular organisms, and detection of local protein levels elevated in response to infection (1).

Several studies have compared patient cohorts managed by the various quantitative-culture methods. While these studies documented issues of relative sensitivity and specificity, outcomes were not significantly different for the various groups of patients. The IDSA/ATS guidelines have suggested that all these methods are appropriate and that the choice depends on availability and local expertise (1).

The Achilles heel of the quantitative approach is the effect of antibiotic therapy. With sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnostic threshold. Recent changes in antibiotic therapy are the most significant. After 3 days of consistent antibiotic therapy for another infection prior to suspicion of pneumonia, the accuracy of diagnostic tests for pneumonia is unaffected. Conversely, colony counts above the diagnostic threshold during antibiotic therapy suggest that the current antibiotics are ineffective. Even the normal host response may be sufficient to reduce quantitative-culture counts below the diagnostic threshold by the time of sampling. In short, expertise in quantitative-culture techniques is critical, with a specimen obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed (1).

In a study comparing the quantitative with the clinical approach, use of bronchoscopic quantitative cultures resulted in significantly less antibiotic use at 14 days after study entry and lower rates of mortality and severity-adjusted mortality at 28 days. In addition, more alternative sites of infection were found in patients randomized to the quantitative-culture strategy. A critical aspect of this study was that antibiotic treatment was initiated only in patients whose gram-stained respiratory sample was positive or who displayed signs of hemodynamic instability. Fewer than half as many patients were treated for pneumonia in the bronchoscopy group, and only one-third as many microorganisms were cultured (1).

1.1.4.3. Clinical Approach:

The lack of specificity of a clinical diagnosis of VAP has led to efforts to improve the diagnostic criteria. The Clinical Pulmonary Infection Score (CPIS)

was developed by weighting of the various clinical criteria usually used for the diagnosis of VAP (Table 251-7). Use of the CPIS allows the selection of low-risk patients who may need only short-course antibiotic therapy or no treatment at all. Moreover, studies have demonstrated that the absence of bacteria in gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative diagnoses possible in patients with suspected VAP, can prevent inappropriate treatment for this disease. Furthermore, data show that the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage when empirical antibiotic therapy is narrowed. Since the most likely explanations for the mortality benefit of bronchoscopic quantitative cultures are decreased antibiotic selection pressure (which reduces the risk of subsequent infection with MDR pathogens) and identification of alternative sources of infection, a clinical diagnostic approach that incorporates such principles may result in similar outcomes (1).

Table 1-3 Clinical Pulmonary Infection Score (CPIS)

Criterion	**Score**
Fever (°C)	
38.5 but 38.9	1
>39 or < 36	2
Leukocytosis	
<4000 or >11,000/L	1
Bands > 50%	1 (additional)
Oxygenation (mmHg)	
Pa_{O2}/FI_{O2} <250 and no ARDS	2
Chest radiograph	
Localized infiltrate	2
Patchy or diffuse infiltrate	1
Progression of infiltrate (no ARDS or CHF)	2
Tracheal aspirate	
Moderate or heavy growth	1

Same morphology on Gram's stain	1 (additional)
Maximal score[a]	12

[a]The progression of the infiltrate is not known and tracheal aspirate culture results are often unavailable at the time of the original diagnosis; thus, the maximal score is initially 8–10.

Note: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure.

1.1.5. Ventilator-Associated Pneumonia: Treatment:

Many studies have demonstrated higher mortality rates with inappropriate than with appropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the patterns of resistance of the most likely pathogens in any given patient (1).

1.1.5.1. Resistance:

If it were not for the risk of infection with MDR pathogens, VAP could be treated with the same antibiotics used for severe CAP. However, antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (MRSA and ESBL-positive Enterobacteriaceae) or for intrinsically resistant pathogens (P. aeruginosa and Acinetobacter spp.). Frequent use of -lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and ESBL-positive strains (1).