Role of Inhaled Antibiotics in Management of Ventilator-Associated Pneumonia

An essay

Submitted for partial fulfillment of Master degree in
General Intensive Care

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2016

بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (١٠٥)

*First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

*My profound thanks and deep appreciation to **Prof. Dr. Mohamed Hossam Shokeir**, Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine- Ain Shams University, for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.*

*I am deeply grateful to **Dr. Mayar Hassan Sayed Ahmed ElSersi,** Assistant Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine- Ain Shams University for adding a lot to this work by her experience and for her keen supervision.*

*I am extremely sincere to **my family** who stood beside me throughout this work giving me their support.*

*Words fail to express my love, respect and appreciation to **my wife** for her unlimited help and support.*

Khaled Reda Elsharnoby Ahmed Elnaggar

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List of Abbreviations

AA	:	Aerosolized antibiotics
AGNB	:	Aerobic Gram negative bacteria
APACHE	:	Acute physiology and chronic health evaluation
ARDS	:	Acute respiratory distress syndrome AS: Aerosolized
ATS	:	American thoracic society
BAL	:	Bronchoalveolar lavage
CDC	:	Centers of disease control and prevention
CF	:	Cystic fibrosis
CHF	:	Congestive heart failure
CMS	:	Colistimethate sodium
COPD	:	Chronic obstructive pulmonary disease
CPIS	:	Clinical Pulmonary Infection Score
ELF	:	Epithelial lining fluids
ESBL	:	Extended-spectrum beta-lactamase producing bacteria
ETA	:	Endotracheal aspirate
ETT	:	Endotracheal tube
FDA	:	Food and drug administration
FEV1	:	Forced expiratory volume in 1st second
GNB	:	Gram negative bacteria
GRV	:	Gastric residual volume
HAP	:	Hospital acquired pneumonia
ICP	:	Intracranial pressure
ICU	:	Intensive care unit
IDSA	:	Infectious diseases society of America IL-1β: Interleukin-1β
IL-8	:	Interleukin-8
IV	:	Intravenous

List of Abbreviations (Cont.)

IVAC	:	Infectious Ventilator associated condition
LPS	:	Lipopolysaccharide
MDR	:	Multi-drug resistant
MIC	:	Minimal inhibitory concentration
MMP	:	Matrix metalloproteinase
MRSA	:	Methicillin-resistant Staphylococcus aureus
MSSA	:	Methicillin-sensitive Staphylococcus aureus
MV	:	Mechanical ventilation
NIPPV	:	Noninvasive positive pressure ventilation
NNISN	:	National nosocomial infections surveillance
ORSA	:	Oxacillin resistant S. aureus
P a	:	Pseudomonas aeruginosa
PCT	:	Procalcitonin
PDDS	:	Pulmonary Drug Delivery System
PEEP	:	Positive end expiratory pressure
PMNLs	:	Polymorphonuclear lymphocytes
PMV	:	Prolonged mechanical ventilation
PSB	:	Protected specimen brush
PVC	:	Polyvinylchloride
RCT	:	Randomized clinical trial
TOBI	:	Tobramycin inhalation
VAC	:	Ventilator associated condition
VAE	:	Ventilator associated events
VAP	:	Ventilator associated pneumonia
VAT	:	Ventilator associated tracheobronchitis
WBC	:	White blood count

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Introduction

The traditional approach of the treatment of pneumonia in critically ill patients is to administer antibiotics via the systemic circulation. Because the airways provide a direct pathway to the lung cells and tissues, aerosolized delivery offers an alternative route, with antibiotic delivery directly to the air/liquid interface in the lung. New and improved delivery devices have made it possible to administer precise doses of inhaled drugs, with pulmonary delivery of 50 - 70 %of the nominal dose. Compared to systemic routes of administration (both enteral and parenteral), inhalational routes achieves higher pulmonary concentrations of antibiotics with the potential to reduce systemic toxicity **(Dhand and Mercier, 2007).**

Ventilator-associated pneumonia frequently complicates the clinical course of patients admitted to intensive care units for multiorgan failure. Its incidence may be as high as 28% in patients on mechanical ventilation for more than 48 hours and 70% in patients with acute lung injury or acute respiratory distress syndrome. It prolongs the duration of stay in the intensive care unit, increases costs, and represents the main reason for the prescription of antibiotics in critically ill patients **(Rouby et al., 2012).**

In fact, sputum and lung tissue antibiotic levels achieved after inhalation exceed the minimum inhibitory concentration required for treatment of infection with most common organisms that cause tracheobronchitis or pneumonia. The emergence of multiple-drug-resistant Gram-negative infections due to Pseudomonas aeruginosa or

Acinetobacter baumanniihas provided further impetus to the use of inhaled antimicrobial therapy as an adjunct to systemic treatment. The publication of several comprehensive reviews within the past few years reflects the renewed interest in inhaled antimicrobial therapy for treatment of pneumonia in critically ill patients **(Geller et al., 2002).**

Achieving adequate antimicrobial concentrations for sufficient duration is a prerequisite for successful treatment of pneumonia. Although effective antibiotic levels are achieved in the lung parenchyma after systemic administration, antibiotic penetration into the airway lumen and intraluminal secretions is limited. Moreover, inhibitory factors could prevent eradication of organisms within intraluminal secretions .A lingering infection /colonization propagates an inflammatory response within the airways that could damage the airway wall and lead to airway obstruction. Bacteria within the airway lumen also serve as a source for subsequent development of pneumonia and bacteremia. Thus, patients with cystic fibrosis (CF) (or bronchiectasis) have persistent colonization of the airways with Gram-negative organisms such as P. aeruginosa **(Orriolset al., 2001).**

Long-term treatment of patients with CF with aerosolized tobramycin improves lung function, decreases density of P. aeruginosa in sputum, and reduces hospitalizations.Despite an increase in the rate of resistant organisms with antibiotics inhalation, no significant clinical problems were observed in patients with CF **(Orriols et al., 2001).**

Microorganisms that cause pneumonia in mechanically ventilated patients are often similar to those encountered in patients with CF or bronchiectasis (eg, Pseudomonas species, Acinetobacter species, and methicillin-resistant Staphylococcus aureus) and these may not be effectively treated with systemic antibiotic therapy alone .Several investigators have studied the efficacy of inhaled antimicrobial therapy for prevention of ventilator-associated pneumonia, and as an adjunct to systemic antibiotics for treatment of established ventilator-associated pneumonia. Although inhaled antibiotic therapy appears to be theoretically attractive and relatively straightforward, clinicians may not appreciate the many complexities of this form of therapy **(Richards et al., 2000).**

Aim of the Work

The aim of this work is to discuss and highlight the role of antibiotics that may be administered via inhalational or endotracheal routes in patients on mechanical ventilator requiring such therapies for prophylaxis or adjunctive and/or primary treatment of respiratory infections.

Chapter 1

Pathophysiology of ventilator associated pneumonia

Ventilator associated pneumonia (VAP) is a common condition between patients on mechanical ventilation, difficult to diagnose accurately, expensive to treat and hard to prevent because of controversies and uncertainties in the literature concerning accurate diagnosis, effective prevention measures, and appropriate empiric antibiotic treatment, also the emergence of multi-drug resistant (MDR) pathogens and resistance to commonly prescribed antibiotics magnifies the problems inherent in the management of these patients. VAP development prolongs a patient's stay in the intensive care unit (ICU) and also is associated with significant morbidity and mortality. Moreover VAP accounts for more than 50% of the antibiotics prescribed in ICU, making it a primary focus for risk-reduction strategies **(Mietto et al., 2013)**.

Patients treated in critical care units after recovering from catastrophic critical illness often require prolonged mechanical ventilation (PMV). Prolonged mechanical ventilation, defined as ventilator dependence for >21 days, is associated with increased hospital morbidity and mortality **(Verceles et al., 2013)**.

Definition:

Ventilator associated pneumonia (VAP) is defined as pneumonia that occurs 48–72 hours or thereafter following endotracheal intubation and mechanical ventilation, characterized by the presence of a new or progressive

infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent. VAP contributes to approximately half of all cases of hospital-acquired pneumonia **(Kalanuria et al., 2014)**.

Although the term 'ventilator associated' suggests that the ventilator itself is not really the cause; rather it is the endotracheal tube that bypasses the body's natural defense mechanisms against respiratory infection. The terms intubation-associated pneumonia for early onset and tube-associated pneumonia for late onset VAP would be more precise. On the other hand there is no minimum period of time that the ventilator must be in place in order for the pneumonia to be considered ventilator-associated **(Torres et al., 2009)**.

Types of VAP:

VAP is usually classified as either early onset, occurring within the first four days of MV or late onset, developing five or more days after initiation of MV **(Joseph et al., 2009)**.

When the concept of early and late onset pneumonia is applied, it is essential to rely on hospital admission (and not intubation) as day one. Otherwise, when intubation occurs after hospital admission, nosocomial colonization of the upper airways may have already occurred and consequently pneumonia may be caused by pathogens typically associated with late onset pneumonia **(Torres et al., 2009)**.

Emergency intubation and intravenous sedatives were the specific risk factors for development of early-onset VAP.

While tracheostomy and re-intubation were found to be the independent predictors of late-onset VAP **(Joseph et al., 2009)**.

Time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with hospital acquired pneumonia and VAP. Early-onset hospital acquired pneumonia and VAP, defined as occurring within the first 4 days of hospitalization, usually carry a better prognosis, and are more likely to be caused by antibiotic sensitive bacteria. Late-onset HAP and VAP (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity **(Torres et al., 2009)**.

However, patients with early-onset HAP who have received prior antibiotics or had prior hospitalization within the past 90 days are at greater risk for colonization and infection with MDR pathogens and should be treated similar to patients with late-onset HAP or VAP **(Torres et al., 2009)**.

Pathogenesis:

The conventionally understood mechanism of pathogenesis of bacterial pneumonia is a natural extension of the tenet that the lungs are sterile. When large inoculum of a pathogenic species enters the lower respiratory tract it overwhelms host defense, resulting in rapid and unrestrained growth of a bacterial species. Within this model, few factors should be all that is needed to predict the features of a given pneumonia: size of inoculum, virulence of the bacterial species, and strength of host defense **(Dickson et al., 2014)**.