The Effect of Administration of Fosfomycin in the Treatment of Ventilator Associated Pneumonia in Respiratory Intensive Care Unit and Poison Control Centre in Ain Shams University Hospitals

Thesis

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List of Abbreviations

Abb.	Full term
ALT:	Alanine aminotransferase
ARDS:	Acute respiratory distress syndrome
AST:	Aspartate aminotransferase
ATS:	American Thoracic Society
BAL:	Bronchoalveolar lavage
CDC:	Center of Disease Control
CFU:	Colony-Forming Units
CNS:	Coagulase negative staphylococcus
CPIS:	Clinical Pulmonary Infection Score
CRP:	C-reactive protien
CSSS:	Continuous suctioning of subglottic secretions
ESBL:	Extended-spectrum beta-lactamase producing bacteria
ETA:	Endotracheal tube aspirates
ETT:	Endotracheal tube
FIO_2:	Fraction of inspired oxygen
ICU:	Intensive care unit
IDSA:	Infectious Diseases Society of America
IHI:	Institute of Healthcare Improvement
IL:	Interleukin
IVAC:	Infection-related Ventilator-Associated Complication
LT:	Leukotriene
MDR:	Multidrug resistant
MRSA:	Methicillin- resistant Staphylococcus aureus
MSSA:	Methicillin- sensitive Staphylococcus aureus
NIPPV:	Non-invasive positive pressure ventilation
Pao_2:	Arterial oxygen tension
PCo_2:	Carbondioxide tension
PEEP:	Positive End Expiratory Pressure
PSB:	Protected specimen brush

PVAP:	Possible Ventilator associated pneumonia
PVC:	Polyvinyl chloride
ROI:	Reactive oxygen intermediate
Sao_2:	Arterial oxyhemoglobin saturation
SDD:	Selective digestive decontamination
TNF:	Tumor necrotizing factor
UTIs:	Urinary tract infection
VAC:	Ventilator-Associated Condition
VAE:	Ventilator-associated event
VAP:	Ventilator associated pneumonia

Abstract

In view of the above, the present study was undertaken to assess the effect of oral administration of Fosfomycin in the treatment of ventilator associated pneumonia.

The study included 25 males & 15 females ranging in age from 18 to 81 years with a mean age of 51.85 ± 17.07 years who were diagnosed with VAP. They were classified into two groups where oral fosfomycin was used as adjunctive treatment in comparison to empirical antibiotics alone.

Key words: Selective digestive decontamination - Tumor necrotizing factor - Urinary tract infection - Infectious Diseases Society of America

Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs 48-72 hours following endotracheal intubation, and is characterized by the presence of new progressive infiltrates, signs of systemic infection (fever, altered white blood cell count, changes in sputum characteristics), and detection of a causative agent ***(American Thoracic society, 2005)***.

VAP can be classified as early onset or late onset according to whether the infection began within the first 4 days of hospitalization or later (more than or equal 5 days). Approximately, one-half of all cases of VAP occur within the first 4 days of mechanical ventilation ***(American Thoracic Society, 2005)***.

VAP is estimated to occur in 9-27% of all mechanically ventilated patients. The crude mortality rate associated with VAP ranges from 24% to 50% among patients in the intensive care unit (ICU) and can reach 76% in some specific settings or when the infection is caused by some pathogens ***(Chastre et al., 2002).***

VAP is associated with increased hospital costs due to longer ICU stay, duration of mechanical ventilation and due to the costs associated with using the diagnostic methods and the antibiotic regimen to treat a patient with VAP ***(Safdar et al., 2005).*** Increasing rates of drug

resistance among these pathogens, coupled with an increased likelihood of the administration of inappropriate antimicrobial therapy in the hospital setting, have become a serious health care problem that affects not only patient outcomes but also the use of health care resources ***(Kollef, 2004).***

Currently, antimicrobial resistance rates are increasing among Acinetobacter species, extended-spectrum b-lactamase producing Enterobacteriaceae (ESBL) and pseudomonas aeruginosa, all of which are gram-negative pathogens associated with nosocomial infections in the ICU ***(Gaynes et al., 2005).***

The shortage of new antimicrobial agents has made the scientific community reconsider the potential value of old antibiotics. Fosfomycin, a phosphonic acid derivative was initially described and isolated in 1969. Today, Fosfomycin tromethaine, a soluble salt with improved bioavilability over Fosfomycin, is being synthetically prepared and is approved for the treatment of uncomplicated in urinary tract infections (UTIs). It has activity against a range of Gram-positive and Gram-negative bacteria including some strains of Pseudomonas aeruginosa ***(Hutzler et al., 1977).*** It has synergistic antimicrobial effects with aminoglycosides and beta-lactams ***(Afshari et al., 2012).***

Fosfomycin also exerts immunomodulatory effects, mainly on lymphocyte and neutrophil function ***(Roussos et al., 2009)***.

Fosfomycin is available in two oral formulations – Fosfomycin tromethamine and Fosfomycin calcium approved for the treatment of urinary tract infections. There is also an intravenous formulation – Fosfomycin disodium that has been used successfully to treat adult patients with serious infections ***(Mirakhur et al., 2003)***. Nebulized fosfomycin sodium was also used effectively in the treatment for chronic sinusitis ***(Astushi et al., 2001).***

Aim of the Work

This study was conducted to assess the effect of oral administration of fosfomycin in the treatment of ventilator associated pneumonia, in combination with empirical therapy, in Respiratory Intensive Care Unit and poison Center in Ain Shams University Hospitals.

Ventilator Associated Pneumonia

Definition

Ventilator-associated pneumonia (VAP) is defined as a pneumonia that occurs in patients mechanically ventilated for at least 48 hours and characterized by the presence of new or progressive infiltrates, signs of systemic infection (temperature, blood cell count), changes in sputum characteristics, and detection a causative agent ***(American Thoracic Society, 2005).*** Pneumonia that occurs within 4 days of intubation is defined as *early onset* VAP and its usually caused by antibiotic sensitive pathogens whereas *late onset* VAP emerges after 4 days of intubation and is more likely to be caused by multidrug resistant (MDR) bacteria ***(Hunter, 2012).***

The precise definition of VAP is still a matter of debate, due to the lack of criteria to distinguish it from other pulmonary conditions that are very likely to occur in critically ill patients. Each of the VAP findings is non-specific and could be consistent with other diseases ***(Cristina et al., 2013).***

In addition, the current definitions are subjective and have low specificity as most of the involved criteria are linked to the observer's opinion (secretions characteristics

and amount, clinical examination) and most radiographic findings are prone to inter-observer variability and unreliability ***(Wunderink, 1992).***

The Centers of Disease Control (CDC) recently proposed a surveillance definition based upon objective and recordable data in an effort to limit definition inaccuracy and improve reproducibility of the diagnosis. The CDC proposed the term ventilator-associated event (VAE) an algorithm that includes:

1. Ventilator Associated Condition (VAC);
2. Infection-related Ventilator-Associated Complication (IVAC); and
3. Possible VAP (PVAP). IVAC is divided into possible and probable, based upon different implications of qualitative and quantitative microbiological culture ***(CDC, 2013).***

Precise time limits are set to detect only new events directly as a consequence of mechanical ventilation. A 48-hour time lapse of stability or improvement of the respiratory function has been fixed to differentiate any new condition from the evolution of the underlying disease.

The new algorithm (Figure 1) is a proposal to detect all the ventilator-associated complications, not only VAP, and the omission of radiological findings ***(CDC, 2013).***

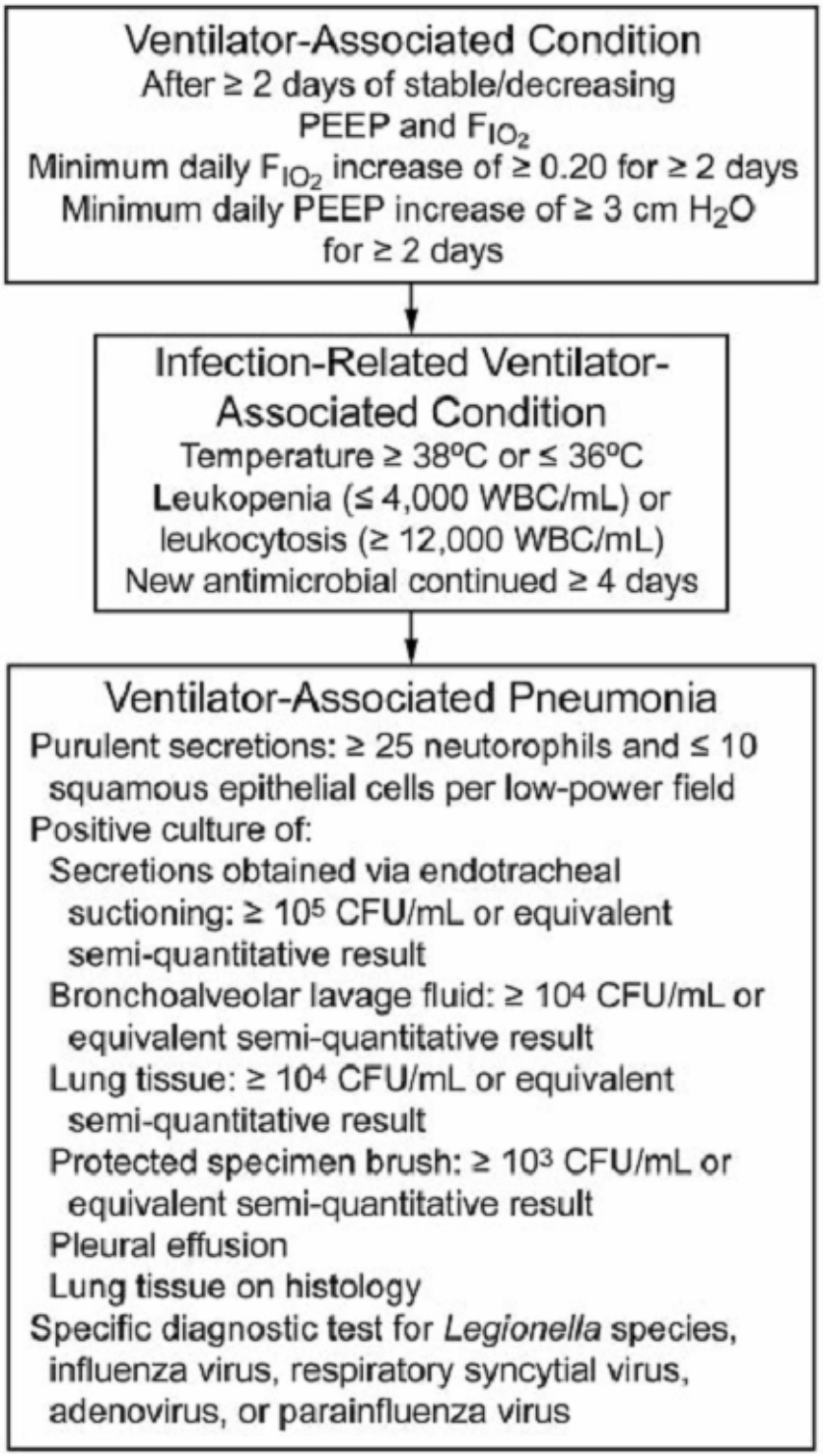

Figure (1): CDC algorithm for diagnosis of VAE ***(CDC, 2013).***