Effect of nebulized colistin in multidrug-resistant Gram-negative ventilator associated pneumonia

Dr. Mohiuddin Ahmed
Assistant professor of medicine
Consultant, ICU
Enam Medical College, Savar

Introduction

- Ventilator associated pneumonia (VAP) due to multidrug-resistant Gram-negative bacteria, such as certain *Pseudomonas aeruginosa, Klebsiella spp and Acinetobacter baumannii strains, is among the most serious* complications that occur in the intensive care unit (ICU) setting.

Introduction

- Colistin (colistimethate sodium) is an antibiotic of the polymyxin family first used in 1960.
- Due to its nephrotoxicity and neurotoxicity, it has not been the drug of choice since 1980.
- However, intravenous colistin has made a recent comeback for the treatment of MDR Gram negative bacterial pneumonia.

Introduction

- Administration of inhaled antibiotics (including colistin) as an adjunctive to intravenous antimicrobials for the prevention and treatment of nosocomial pneumonia, has been supported on the basis of comprehensive systematic reviews.

Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. Crit Care 2006;10:R123.

Introduction

- ‘‘Aerosolized antibiotics may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy’’.

The American Thoracic Society and the Infectious Diseases Society of America Guideline Committee. Guidelines for the management of adults with hospital-acquired, ventilator associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388e416.

Introduction

- Administration of inhaled anti-infective without concurrent intravenous antimicrobials is primarily indicated for cystic fibrosis patients with Pseudomonas aeruginosa infection.

Klepser ME. Role of nebulized antibiotics for the treatment of respiratory infections. Curr Opin Infect Dis 2004;17:109e12.

Introduction

- Administration of inhaled colistin without its concurrent intravenous administration for nosocomial pneumonia has been reported, although very rarely, in the literature.

Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis. Crit Care 2005;9:R53e9.

Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. Clin Infect Dis 2005;41:754e7.

Introduction

- In clinical practice, physicians not rarely face conditions, which discourage the systemic administration of colistin (i.e. due to systemic toxicity), while the implicated pathogen is a colistin-only susceptible one.

Introduction

- Herein, I present my experience with patients with MDR Gram-negative VAP treated with inhaled (without concurrent intravenous) colistin.

Methods

- *Design: A retrospective study.*
- *Setting: Intensive Care Unit of a Tertiary hospital.*
- *Patients: Hospitalized patients* during the period 01/08/2012 to 31/01/2013 *on invasive mechanical ventilation* in the ICU *with positive MAB cultures of* the airway.

Methods

- *Interventions:*
  - All received treatment with colistin (CL).
  - One million IU colistin was diluted in 5 mL sterile normal saline and then delivered to the patients via the same route through which they inhaled β2-agonists.
  - *Ventilator associated pneumonia (VAP)* was determined according to routine criteria.

Methods

- Data collection and entry
  - demographics,
  - comorbidities
  - and Acute physiological and Chronic Health Evaluation II (APACHE II) scores on ICU admission and on the first day of colistin treatment,
  - the responsible pathogens

Methods

- Data collection and entry
  - Results of laboratory and radiological data were collected from medical records.

Methods

- Microbiological test:
  - An automated broth microdilution method (Vitek 2, bio-Merieux, Hazelwood, MO, USA) was used for routine laboratory susceptibility testing to commonly used antibiotics.

Definitions of pneumonia

- Pneumonia was considered to be VAP when it occurred 48 hours after the initiation of mechanical ventilation.

Definitions of pneumonia

- Diagnosis of VAP was based on
  - radiological (new or progressive infiltrate),
  - clinical (body temperature > 38°C or < 36°C)
  - and laboratory findings (abnormal white blood cell count, C-reactive protein and gas exchange).
- The diagnosis of VAP *should be* microbiologically confirmed by positive cultures *from either bronchial secretions or bronchoalveolar* lavage samples of each patient.

Definition of outcome

- Cured: resolution of presenting symptoms and signs of infection by the end of treatment.
- Improved: partial resolution of presenting symptoms and signs or infection.
- Failed: persistence or worsening of presenting symptoms and/or signs of infection during colistin administration.
- Indeterminate: clinical assessment was not possible.

Microbiologic outcomes

- Eradication: no growth of the responsible pathogen
- Persistence: persistent growth of the responsible pathogen, or
- Indeterminate: when microbiological assessment was not possible.

MDR

- Resistant to all but two antipseudomonal classes of antimicrobial agents (namely antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, and polymyxins).

Colistin-only susceptible

- Resistant to all antipseudomonal agents except colistin

Results

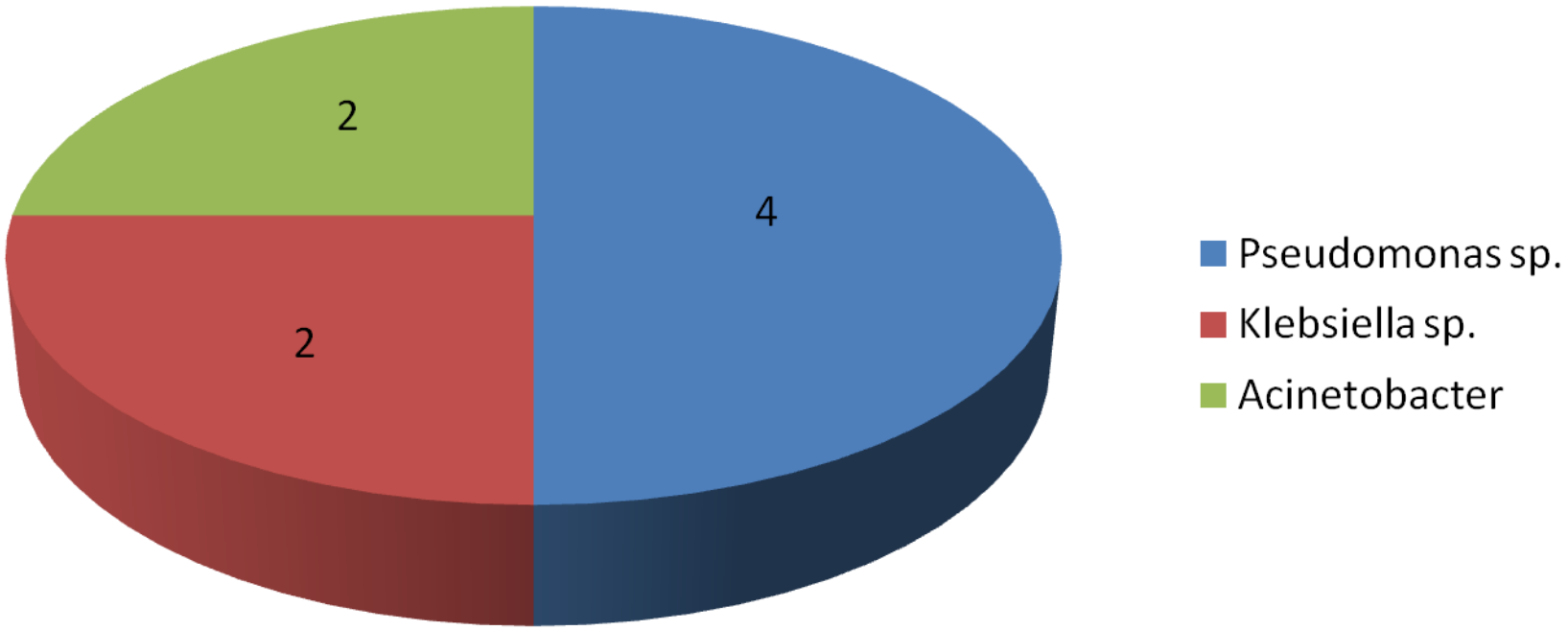
Results

- During the study period, in eight patients colistin was given through nebulization only (not systemically) for the treatment of Colistin only sensitive gram-negative infections.
- Six males and two female were included.

Results

- The median age was (24+63)/2=43.5 years.
- Mean Acute Physiological and Chronic Health Evaluation (APCHE) II scores on the day of ICU admission and on day 1 of nebulized colistin administration were 16 and 13.1, respectively.
- All patients had ventilator-associated pneumonia.
- Mean Clinical Pulmonary Infection Score (CPIS) was 8.3.

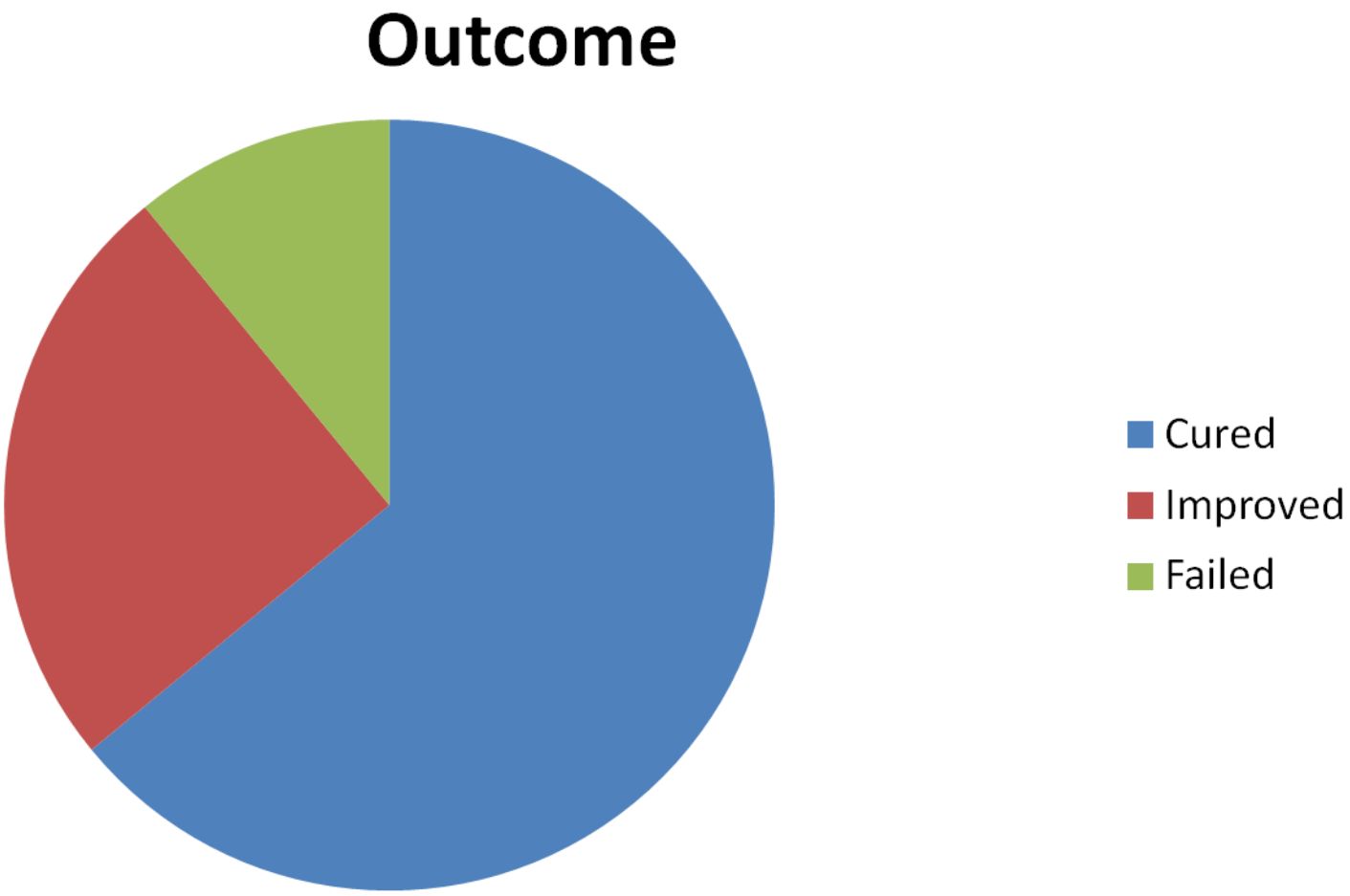
Implicated Pathogens



Clinical characteristic in patients receiving aerosolized colistin therapy for VAP

Patient	Reason for admission	Discharge diagnosis
1	Traumatic brain injury (SAH, ICH, DAI) , Acute Respiratory Failure	Traumatic brain injury (SAH, ICH, DAI) Hospital acquired infections(UTI, RTI, ASOM, Lip ulcer), SIADH
2	PTB, NSTEMI,ALVF	VAP, PTB, NSTEMI,ALVF
3	Type II respiratory failure, OHS, RTI	VAP, Type II respiratory failure, OHS, RTI
4	Acute on CKD, Pulmonary Edema	VAP, Acute on CKD, Pul Edema, DM, HTN
5	Respiratory failure due to Intermediate Syndrome (OP Poisoning)	VAP, Respiratory failure due to Intermediate Syndrome (OP poisoning)
6	Sedative poisoning	VAP, Sedative poisoning
7	GBM posterior fossa, Obstructive hydrocephalus, S/P VP shunt	VAP, GBM, DM, Septic shock with MOF
8	Stoke, DM, CKD	VAP, Stroke, DM, CKD, UTI

Clinical characteristic in patients receiving aerosolized colistin therapy for VAP								
Patient	1	2	3	4	5	6	7	8
Duration of mechanical ventilation (days)	10	5	11	8	8	4	9	10
Duration of nebulized Colistin	8	10	13	12	8	12	8	8
Duration of hospitalization (days)	32	14	15	17	16	16	14	14
Duration of ICU stay (days)	26	8	12	10	8	5	10	11


Outcome
Cured
Improved
Failed

Tolerance and safety of inhaled colistin

- No patient experienced adverse events from inhalation of colistin, such as bronchoconstriction, chest tightness or apnoea.
- Serum creatinine level was not deteriorated.

Discussion

- This is a case series of eight patients with MDR Gram negative ventilator associated pneumonia treated with inhaled (but not intravenous) colistin.
- The implicated pathogens were colistin-only susceptible in all cases.
- Six out of the eight patients were cured, survived and were discharged.

Discussion

- Concerns regarding nephrotoxicity and neurotoxicity associated with systematic administration of colistin discouraged physicians from prescribing it in potentially vulnerable patients.

Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006;10: R27.

Discussion

- It seems reasonable that the exact delivery of a medication directly to the suffering lung tissue may be beneficial.
- Pharmacokinetic studies have shown that a single inhalation of colistin leads to high sputum concentrations of the drug even 12 h after the administration.

Ratjen F, Rietschel E, Kasel D, Schwiertz R, Starke K, Beier H, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. J Antimicrob Chemother 2006;57:306e11.

Limitations

- The retrospective design,
- Sample number of patients,
- Absence of a control group
- And the patients of our report received concurrently intravenous antibiotics; however, the responsible pathogens were not susceptible to intravenous antibiotics

Key messages

- Aerosolized administration of colistin is a promising therapy for management of patients with pneumonia (whether ventilator associated or not) due to multidrug resistant Gram-negative bacteria.

- Aerosolized colistin was safe in this group of patients.

- There is an urgent need for randomized controlled trials examining the efficacy and safety of nebulized colistin for the management of patients with nosocomial pneumonia.

Thank You