بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

Efficacy and Safety of Colistin Based Antibiotic Therapy for Multidrug Resistance Gram Negative Infections in Pediatric Intensive Care Unit

A Thesis

Submitted for the Fulfillment of the Requirements of the

Master Degree

In Pharmaceutical Sciences
(Clinical Pharmacy)

By

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Bachelor of Pharmaceutical sciences, 2014
Teaching assistant, Clinical Pharmacy
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2022

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List of Abbreviations

Abbreviation	Full Word
ABSSSI	Acute bacterial skin and skin structure infections
ABW	Actual Body Weight
AIDS	Acquired immune deficiency syndrome
AMEs	Aminoglycoside-modifying enzymes
AUC	Area under the curve
AUP	Acute uncomplicated pyelonephritis
BAL	Bronchoalveolar Lavage
BSI	Bloodstream infections
CDC	Centers for Disease Control and Prevention
cIAI	Complicated intra-abdominal infection
Cmax	Maximum plasma concentrations
CrCl	Creatinine clearance
CR-KP	Carbapenem-resistant *Klebsiella pneumonia*

cUTI	Complicated urinary tract infection
CVC	Central venous catheters
DBO	Diazabicyclo octane
E. coli	*Escherichia coli*
eGFR	Estimated glomerular filtration rate
ESBLs	Extended-spectrum β-lactamases
ELF	Epithelial lining fluid
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
gen.sp.	Genomic species
GNB	Gram-Negative Bacilli
HAP	Hospital acquired pneumonia
HCAP	Healthcare-associated pneumonia
HR	Heart Rate
ICUs	Intensive care units
KPC	*K. pneumoniae carbapenemase*

MAP	Mean Arterial Pressure
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MOA	Mechanism of action
MRSA	Methicillin-resistant *S. aureus*
NACHRI	National Association of Children's Hospitals and Related Institutions
NICUs	Neonatal intensive care units
NNIS	National Nosocomial Infections Surveillance
PBP	Penicillin binding proteins
PDR	Pandrug-resistant
PD/PK	Pharmacodynamics/pharmacokinetics
PICUs	Pediatric intensive care units
PPN	Pediatric Prevention Network
PRISM	Score Pediatric Risk of Mortality Score
RR	Respiratory Rate
S. aureus	*Staphelococcus aureus*

SSTI	Skin and soft tissue infections
TB	Tuberculosis
TDM	Therapeutic drug monitoring
TPN	Total parenteral nutrition
US	United States
VAP	Ventilator associated pneumonia
VRE	Vancomycin-resistant Enterococci
XDR	Extensively drug-resistant

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Abstract

Background and Aim:

Multidrug-resistant gram-negative bacterial infections are difficult to treat, especially in the pediatric ICU setting. Intravenous (IV) Colistin in combination with carbapenems is commonly used to eradicate MDRs. This study aimed to evaluate the safety and efficacy of IV Colistin combination in critically ill pediatrics suffering multidrug-resistant gram-negative infections.

Patients and Methods:

A prospective, interventional randomized study was conducted on sixty patients suffering from MDR bacterial infections. Who received either Imipenem/Cilastatin (Monotherapy group) or Imipenem/cilastatin in addition to IV Colistin (Combination group). Patients' hemodynamic parameters, vital signs and sepsis markers were monitored and patients were followed up for ICU mortality in Al-Demerdash hospital PICU, Ain Shams University, Cairo, Egypt.

Results:

Thirty patients received IV Colistin Imipenem/Cilastatin combination; their median age was 8.5 months (range: 3-36 months). Isolated microorganisms were *Acinetobacter baumannii, Klebsiella pneumonie, Pseudomonas aeruginosa* and *E. coli. Klebsiella pneumonia* was the most common isolate (51.7%) of the overall examined 60 patients. Combination therapy was correlated with improved vital signs, hemodynamic parameters and general improvement. No patients experienced renal impairment due to Colistin therapy.

Conclusion:

Combination therapy was associated with superior clinical and survival outcomes of PICU patients and participated in the eradication of the multidrug-resistant gram-negative bacteria without noticeable nephrotoxicity.

Keywords:

Imipenem/Cilastatin; Colistin; *Acinetobacter baumannii; Klebsiella pneumoniae*; nosocomial infection; *Pseudomonas aeruginosa; E. coli*; MDR.

Introduction

Gram-negative bacteria of the *Enterobacteriaceae* are major cause of bloodstream infections, urinary tract infections, various intra-abdominal infections, and hospital-associated pneumonia. *Escherichia coli* is a frequent cause of urinary tract infections, *Klebsiella spp.* and *Enterobacter spp.* are important causes of respiratory tract disorders like pneumonia, and all of the *Enterobacteriaceae* have been participated in bloodstream infections and in cholangitis, peritonitis, and other intra-abdominal infections et **(Cerceo et al., 2016)**. Additionally, organisms such as *Salmonella* produce gastroenteritis and subsequently, in some patients, invasive infection. Emerging resistance in *Enterobacteriaceae* is a problem that needs immediate attention. Resistance related to production of extended-spectrum beta-lactamases is a particular problem in the dealing with *Enterobacteriaceae* infections, but other mechanisms of resistance are emerging, leading to multidrug resistance microorganisms **(Vlieghe, 2014)**.

Importance of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobials available for infections caused by these bacteria. Gram-negative and Gram-positive bacteria are both affected by the emergence and rise of resistance **(Ventola, 2015)**. As this problem propagated, harmonized definitions established to describe and segregate bacteria that are resistant to multiple antimicrobial agents are required, so that epidemiological surveillance data can be reliably collected and compared across healthcare settings and countries. In the strictest sense, multidrug-resistant organisms are labeled as such because of their *in*

vitro resistance to more than one antimicrobial agent. Infections with multidrug-resistant organisms can lead to inappropriate or delayed antimicrobial therapy, and are associated with poorer patient outcomes represented by improving of signs and symptoms **(da Ponte, 2016)**.

Pediatric intensive care units (PICUs) differ from adult intensive care units (ICUs) in different manner, apart from the age of their patients. First, they are usually multidisciplinary sectors which is mean we have a few number of patients to interpret the findings **(Alabdullah, 2020)**. Second, lack of the physical barriers between patients now commonly present as in adult (ICUs). Third, fewer children than adults in (ICUs) have chronic or degenerative organ system disorders **(Özdemir et al., 2010)** and probably the majority of children in (PICUs) will, successfully treated, return to a normal productive life. Nosocomial infections represent crucial cause of morbidity and mortality in this population **(Wattal and Oberoi, 2012)**.

Infection is a major cause of morbidity and mortality in intensive care units (ICUs) among different countries. However, little information is available about the global epidemiology of such infections **(Vincent et al., 2009)**. In fact, strongly recommended to initiate antibiotic therapy within the first hour of recognition of severe sepsis by the surviving sepsis campaign, after culture proven for further interpretation and examination **(Dellinger, 2004)**.

Many investigators demonstrated an observational study, the protective effect on mortality of adequate initial therapy in critically ill septic patients after adjusting for confounding variables **(Jose Garnacho-Montero et al., 2003)**.

According to different methodological issues (i.e. definition of inappropriate antibiotic treatment, analysis of confounding variables, such as degree of illness and underlying disorders, and statistical power) should be

considered to analyze the association between efficacy of antibiotic therapy and survival outcome in septic patients **(Harbarth et al., 2007; McGregor et al., 2007)**.

Multidrug-resistant (MDR) bacteria that are commonly associated with health care cause a health threat. Updated health care workers and society regarding to this group of pathogens are needed to inform public health actions and steps to control the spreading of infections **(Jernigan et al., 2020)**.