UNIVERSITI PUTRA MALAYSIA

USE OF COLISTIN AMONG PATIENTS IN INTENSIVE CARE UNIT IN HOSPITAL SERDANG AND HOSPITAL SUNGAI BULOH AND ITS ASSOCIATION WITH NEPHROTOXICITY FROM 2010 UNTIL 2012

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A SECOND YEAR PROJECT (PACKAGE 11) DISSERTATION SUBMITTED TO

FACULTY OF MEDICINE AND HEALTH SCIENCES

UNIVERSITI PUTRA MALAYSIA

IN FULFILMENT FOR THE DEGREE OF

DOCTOR OF MEDICINE (MD)

USE OF COLISTIN AMONG PATIENTS IN INTENSIVE CARE UNIT IN HOSPITAL SERDANG AND HOSPITAL SUNGAI BULOH AND ITS ASSOCIATION WITH NEPHROTOXICITY FROM 2010 UNTIL 2012

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ABSTRACT

BACKGROUND: Colistin was originally used to treat Gram-negative infection particularly in critically ill patients (Reina, Estenssoro, Saenz, 2005) but early administration of this antibiotic was associated with reports of adverse effects in large number of patients (Brown, Dorman, Roy, 2005; Weser et al., 2005). Due to re-emergence of Gram-negative bacteria to all antibiotics except colistin has led to reused of colistin (Falagas et al., 2005). A lot of research has been done to make colistin as a life saving antibiotic over the world but however there is lack of local studies about the uses of colistin in Malaysia.

OBJECTIVES: This study was designed to study the uses of colistin in intensive care unit in Hospital Serdang and Hospital Sungai Buloh and its association with nephrotoxicity.

METHODS: One hundred (100) patients in intensive care unit who were administered with colistin between 2010 until 2012 in Hospital Serdang and Hospital Sungai Buloh were recruited and the collected data then were entered into SPSS.

RESULTS: Colistin was mainly used in male (71%) and malay (63%) patients. Most of the colistin was administered through intravenous route (82%). The daily dose and duration were within recommended range. Colistin was mainly used in treating pneumonia (47%) and sepsis (36%). There was increase trend of colistin use. Bacteria that was isolated most from patients with indication of colistin was *Acinetobacter baumanni* (71%). 70% of the sensitivity result showed colistin is sensitive against the bacteria isolated from patient. There was low rate of nephrotoxicity (23%). There is no significant association between daily dose (95% Cl; p=.802) and duration of treatment (95% C; p=.562) and nephrotoxicity.

CONCLUSION: In Malaysian Hospitals, most of the colistin is administered through intravenous route. The daily dose and duration is within the recommended range. There is low rate of nephrotoxicity after colistin administration. There is no significant association between daily dose and duration of treatment and nephrotoxicity.

Keywords: *Colistin, Nephrotoxicity*

USE OF COLISTIN AMONG PATIENTS IN INTENSIVE CARE UNIT IN HOSPITAL SERDANG AND HOSPITAL SG.BULOH AND ITS ASSOCIATION WITH NEPHROTOXICITY FROM 2010 UNTIL 2012

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ABSTRAK

PENGENALAN: Pada mulanya, kolistin digunakan untuk merawat jangkitan bakteria jenis gram negatif terutamanya dalam kalangan pesakit di unit rawatan rapi tetapi penggunaan awal antibiotik ini telah mengakibatkan beberapa kesan sampingan terhadap sejumlah besar pesakit. Walaubagaimanapun, kemunculan semula bakteria jenis gram negatif yang kebal terhadap semua antibiotik kecuali terhadap antibiotik kolistin telah menyebabkan antibiotik ini digunakan kembali. Banyak kajian telah dijalankan untuk menjadikan kolistin sebagai antibiotik yang mampu menyelamatkan nyawa. Walaubagaimanapun, di Malaysia, masih kurang kajian tentang kolistin ini dijalankan.

OBJEKTIF: Kajian ini bertujuan untuk mengkaji kegunaan kolistin dalam kalangan pesakit di unit rawatan rapi di Hospital Sungai Buloh dan Hospital Serdang serta kaitannya dengan nefrotoksik dari tahun 2010 sehingga 2012.

KAEDAH: Satu ratus (100) pesakit di unit rawatan rapi yang diberi kolistin antara tahun 2010 sehingga 2012 di Hospital Sungai Buloh dan Hospital Serdang telah dipilih secara rawak untuk kajian ini. Data klinikal mereka akan diambil melalui rekod perubatan dan dimasukkan ke dalam SPSS.

HASIL: Kebanyakkan pesakit diberikan kolistin melalui kaedah intravena (82%). Dos harian dan jangka masa kolistin diberikan kepada pesakit adalah dalam julat yang disyorkan. Kolistin banyak digunakan untuk merawat pneumonia (47%) dan sepsis (36%). Trend penggunaan kolistin telah menunjukkan peningkatan. Kolistin digunakan untuk membunuh *Acinetobacter baumanni* (71%). 70% daripada keputusan sensitiviti menunjukkan bakteria adalah sensitif terhadap kolistin. Kadar nefrotoksik adalah rendah (23%). Tiada perkaitan yang ketara antara dos harian (95% Cl; P=.082) dan jangka masa rawatan kolistin (95% Cl; p=.562)

KESIMPULAN: Di hospital di Malaysia, kebanyakan kolistin adalah diberi secara intravena. Dos harian dan jangka masa terapi kolistin adalah dalam julat yang disyorkan. Kadar nefrotoksik selepas kolistin diberikan kepada pesakit juga rendah. Tiada perkaitan yang ketara antara dos harian dan jangka masa rawatan kolistin.

Kata kunci: *Kolistin, Nefrotoksik*

ACKNOWLEDGEMENT

First and foremost, we would like to thank God for giving us the opportunity to carry out this research project, and strength and courage to overcome all the obstacles and problems we have encountered during research project.

We would like to thank our main supervisor, Dr. Syafinaz bt Amin Nordin for helping and guiding us throughout the research. Not forgetting our co-supervisor Dr. Aidalina bt Mahmud that was so kind and helpful in providing guidance whenever we needed her. We also want to express our gratitude towards Pharmacist Chong Li Yin from Hospital Serdang and Pharmacist Irmawati from Hospital Sungai Buloh, who assisted us along the data collection period. Without them, this research project would not be successfully accomplished. We are also grateful to our module coordinator, Dr. Hayati and other lecturers for facilitating and assisting us in our research. We also like to thank Clinical Research Centre (CRC) for helping us in ethical approval.

We are also very grateful to the Dean of Faculty of Medicine and Health Sciences, Prof. Dr. *Norlijah Othman*, Director Hospital of Hospital Serdang and Director Hospital of Hospital Sungai Buloh, for giving us the permission to conduct our research.

Lastly, we want to express our gratitude to those who were involved, whether intentionally or unintentionally. Their help and cooperation are warmly esteemed.

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LIST OF ABBREVIATION

IM	Intramuscular
IV	Intravenous
CMS	Colistimethane sodium
LPS	Lipopolysaccaride
MDR	Multidrug resistance
IU	International unit
ICU	Intensive care unit
IDSA	Infectious Disease Society America
NDM	New Delhi metallo b-lactamase
UK	United Kingdom
VAP	Ventilator associated pneumonia
HAP	Hospital associated pneumonia
CAP	Community Acquired Pneumonia
HCAP	Health Care Associated Pneumonia
SPSS	Social Package for Social Sciences
USA	United States of America
UPM	Universiti Putra Malaysia

1.0: INTRODUCTION

1.1 Introduction

Rapidly increasing antibiotic resistance and lack of new antibiotics in the development presented a major global medical challenge. This unmet medical need was highlighted by the Infectious Diseases Society of America (IDSA) in the 'Bad Bugs, No Drugs' report (IDSA Report, 2004). Due to 'superbugs' bacteria that resistant to almost all available antibiotics (IDSA, 2004, 2010), the World Health Organization has identified antibiotic resistance as one of the 3 greatest threats to human health (IDSA, 2010). Multidrug-resistant (MDR) Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* are against with all antibiotics except polymyxins. IDSA has placed these 3 problematic pathogens on a hit-list of top-priority dangerous pathogens.

Without novel antibiotics in the development pipeline, polymyxin was increasingly used as the only therapeutic option. The polymyxin actually was a polypeptide antibiotics discovered from different species of Bacillus polymyxa in 1940, was among the first antibiotics with significant activity against Gram-negative bacteria (Falagas & Kasiakou, 2005). This class of antibiotic consisted of five chemically different compound, polymyxin A, B, C, D, and E. However only polymyxins B and E has been used clinically (Yavac, Farbman, Leibovici, Paul, 2011). Although the effectiveness of polymyxins has not been questioned, early administration of this class of antibiotics was associated with reports of adverse effects in large number of patients (Brown et al., 2005; Weser et al., 2005). Thus, compounds of this class of antibiotics were gradually withdrawn from clinical practice as newer antibiotics with the same or broader antibacterial and reportedly lower toxicity were introduced, except for patients with

cystic fibrosis who suffer from recurrent pulmonary infection due to multidrug resistance bacteria (Falagas et al., 2005). However, due to re-emergence of Gram-negative bacteria to all antibiotics except polymyxins has led to the re-use of polymyxins group especially colistin (polymyxin E) (Falagas et al., 2005). The current reviews focus on colistin rather than polymyxin B because of its wider use in the current clinical practice. Since it was first introduced in 1952, colistin has been mainly used to treat Gram-negative infection especially pseudomonal infections (Reina et al., 2005). After used it back, the result was different for what has been reported in old literature. The data from the recent literatures suggest that the incidence of toxicity resulting from the use of colistin is less frequent and severe compared to what has been previously reported. This situation undoubtedly deserved an explanation (Falagas et al., 2005).

Many research has be done to find the reason and the most possible explanation is the fact that the available formulation of colistimethane sodium (CMS) for intramuscular administration was used intravenously in the old studies until a new formulation was prepared. In addition, the intramuscular formulation also contained dibucaine hydrochloride which could potentiate the neurotoxic effect. It should be highlighted that the dosages of colistin used in most of the studies published in the old literature were considerably higher compared to the recommended dosages nowadays. In fact, several reported cases of colistin-induces toxicity were associated with overdose and lack of dosage adjustment according to the condition of patient ecspecially for who have renal failure (Falagas et al., 2005). Besides, co-administration of potential toxicity agents with polymyxins also explained the different. Thus, this may account for the different in the incidence of colistin-induced toxicity noted between the old (Flanagan, 1971: Randall, Bridi, Setter, Brackett, 1970) and recently published studies (Pogue et al., 2011). We can conclude that even though previously there are several reports during the early years of use

of the medication, mainly in the decade 1960-1969 left medical community with the impression that the medication was very toxic but recent experience of several clinicians worldwide with the use of of the medication has not verified the old reports about the serious or common toxicity of colistin as there were reasons behind it which we could adjust to minimize its adverse effect or toxicity, maximize its efficacy and make it as a live saving antibiotic.

1.2 Problem Statement

In 1960s, colistin was originally used, but because of the concern of nephrotoxicity, it was abandoned as other less toxic antibiotics became available (Pogue et al., 2011). Recently, colistin has been reused as last therapeutic agent for the treatment of multidrug-resistant gram negative bacteria such as *Pseudomonas aeroginosa* and *Acinebacter baumannii* (Falagas et al., 2005). However, the old report about the serious or common toxicity of colistin has not been verified by the recent experience of clinician worldwide (Michalopoulos, Tsiodras, Rellos, Mentzelopoulos, & Falagas, 2005; Pogue et al., 2011). So, in order to avoid harm to the patient, it is important to study on factors associating colistin use with nephrotoxicity. Factors that potentially could lead to the nephrotoxicity such as dosage and duration of colistin administration should be highlighted in a particular medical research. Besides, considering on how important colistin is in treating critically ill patient, it is important to know the indication of colistin use, what type of bacteria react to this drug and its sensitivity towards colistin and also the outcome of the patients after using this drug. That is why a lot of research has been done to make colistin as a life saving antibiotic over the world but however there is lack of local study about the uses of colistin in Malaysian. So, our focus is on studying use of colistin specifically in Malaysian Public Hospitals.

1.3 Objective

1.3.1 General Objective:

To study the uses of colistin in intensive care unit in Hospital Serdang and Hospital Sungai Buloh and its association with nephrotoxicity.

1.3.2 Specific Objectives:

a) To describe the demographic of patients treated with colistin.

b) To describe the administration of colistin (route of administration, dose and duration) in patients, clinical outcome and microbiological profile of bacteria isolated from patients treated with colistin.

c) To determine the indications of colistin use among patients in intensive care unit.

d) To describe trend of colistin use from the aspect of patients population and nephrotoxicity.

e) To determine the association between duration of colistin and its nephrotoxicity.

f) To determine the association between dose of colistin being administered and its nephrotoxicity.

1.4 RESEARCH HYPOTHESIS

Alternative hypothesis

There is **association** between between dose of colistin and its nephrotoxicity.

There is **association** between duration of colistin being administered and its nephrotoxicity.

Null hypothesis

There is **no association** between between dose of colistin and its nephrotoxicity.

There is **no association** between duration of colistin being administered and its nephrotoxicity.

2.0: LITERATURE REVIEW

2.1 Overview of colistin

Colistin (also called polymyxin E) belongs to the polymyxins group of antibiotics. Colistin has a selective activity against Gram-negative rods. Colistin consists of D-leucine, L-threonine and L-αγ-diaminobutyric acid. The cationic molecule of colistin displaced Ca^{2+} and Mg^{2+} ions which normally stabilize the lipopolysaccharide (LPS) molecule of outer membrane of Gram-negative bacteria (Hale & Hancock, 2007; Brogden, 2005). This causes local disturbance of cell membrane, increase cell permeability, leakage of cell content, cell lysis and death (Hale et al., 2007; Brogden, 2005). However, some authors argue that the interaction with membranes is indeed a part of the action of colistin but it was not actual lethal mechanism for gram negative rods (Zhang, Dhillon, Yan, Farmer, Hancock, 2000). The true mechanism of colistin induces bacterial killing is still unknown. Colistin binds to LPS and in animal studies, block many of the biological effects of endotoxin (Hale et al., 2007; Mogi et al., 2009; Brogden, 2005).

2.2 Spectrum of activity and resistance

Spectrum of colistin activity included Gram-negative aerobic bacilli such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa, Klebsiella species, Enterobacter species, Salmonella species, Shigella species, Escherichia coli,* and *Stenotrophomas maltophilia* strain. However, *Proteus species, Serratia species, Burkholderia species, Providencia species,* and *Edwardsiella species* are resistance to colistin. It causes rapid bacterial killing in a concentration manner (Li, Turnidge, Milne, Nation, Coulthard, 2001). Colistin has no activity against Gram-positive bacteria, all cocci and anaerobes (Li et al., 2001). It has also been reported to be potentially active against several mycobacterial species including *Mycobacterium tuberculosis* (Falagas et al., 2005).

Colistin resistance has been relatively low because of its infrequent use. Nevertheless, resistance has recently been identified in several Gram-negative bacteria species (Ko et al., 2007). The study identified a high rate of colistin resistance in *A. baumannii* strains. Recently, colistin resistance mediated by complete loss of LPS production has been described in *A. baumannii* strains. Heteroresistance to colistin has also been recently detected in other species, including *K. pneumoniae* and *P. aeruginosa*. Resistance of *P. aeruginosa* to colistin has been described most commonly in patients with cystic fibrosis (CF) who have received aerosolized colistin therapy (Sun, Fujitani, Quintiliani, Yu, 2011; Johansen, Moskowitz, Ciofu, Pressler, Hoiby, 2008). The most common mechanism of colistin resistance is the modification of the LPS. Paenibacillus polymyxa subspecies colistinus, the organism that produces colistin, also produces colistinase, which inactivates colistin. Nevertheless, enzymatic resistance of bacteria to colistin has not been reported in clinical practice (Falagas et al., 2005).

2.3 Clinical indication

Colistin is mainly used in clinical practice to treat patient suffering from urinary tract infections, sepsis, cellulitis,osteomyelitis, mediastinitis, intraabdominal abscess, pneumonia, diabetic foot, and ischemic enchephalopathy (Yavac et al., 2011; Nasnas, Saliba, Hallak, 2009).

2.4 Formulation and dosage

There are two forms of colistin available clinically that are colistin sulphate and commercially available colistimethane sodium (CMS). CMS is an inactive form of colistin which will undergo spontaneous hydrolysis to an active form of colistin (Li, Nation, Turnidge et al., 2006). The recommended dosage of CMS by United States for adult and children with normal renal function is 2.5-5 mg/kg/day, administered as two or divided doses (Li et al., 2006). Dosage adjustments are recommended for patients with mild to moderate renal dysfunction. When the

serum creatinine level is 1.3-1.5 mg/dl,1.6-2.5 mg/dl or more than 2.6 mg/dl, the recommended dosage of intravenous colistin is 2 million IU every 12 hours, 24 hours or 36 hours respectively (Monarch Pharmaceuticals, Inc, 2002.). Meanwhile In United Kingdom, a dosing regimen of 4-6 mg/kg (50000-75000 IU/kg) of CMS per day in divided doses is recommended for adults and children with normal renal function and body weight less than 60kg and 240-480 mg (3-6 IU) per day in 3 divided doses for those with body weight more than 60kg (Forest laboratories, UK Limited, 2002). To avoid confusion regarding dosing system, it is preferable to use a dosing system based on International Unit (IU). The dosage of aerosolizes CMS recommended in the United Kingdom is 40 mg (50,000 IU) every 12 hours for patients with a body weight less than 40kg and 80 mg (1 IU) every 12 hours for patients with a body weight more than 40 kg. In recurrent pulmonary infections, the dosage can be increased to 160 mg (2 million IU) every 8 hours (Falagas, Kasiakou, Tsiorios Michalopolous, 2006).

2.5 Route of administration

CMS is either administered parenterally, intravenously or intramuscularly, intrathecally or intraventricular routes as it less toxic than colistin sulphate. Intramuscular injection is rarely used in clinical practice as it causes severe local pain and absorption is variable. Colistin sulphate is administered either orally or topically (for treatment of bacterial skin infection). Both CMS and colistin sulphate can be given via inhalation but colistin sulphate may result in a higher frequency of bronchoconstriction than CMS (Falagas et al., 2009; Ghannam, Rodriguez, Raad, Safdar, 2009).

2.5.1 Intrathecal / Intraventricular administration

There were a study on a case series reviewing 24 patients with *A. baumannii* CNS infections and result demonstrated 83% of clinical cure and 17% mortality rates

(Khawcharoenporn, Apisarnthanarak, Mundy, 2009). Early treatment (within 2 days) was associated with survival as compared with late-onset treatment. It was used as monotherapy in 11 patients, with high clinical cure rates (91%). Adverse events have been observed in four patients. Long-term survival and neurological outcomes of these patients were not described. Several case reports evaluating this type of administration for the treatment *P. aeruginosa* CNS infections and they showed favorable results.

2.5.2 Intravenous administration

Both CMS and colistin sulphate have been administered via IV route for the treatment of pneumonia, bacteremia, urinary tract infection as well as central nervous system infection. Frequency of clinical cure via this administration has been promising as reported by several published studies. CMS and polymyxin B also has been administered with other antimicrobial agents due to severity of the infection in ICU patients. Thus, definite statement regarding intravenous CMS as monotherapy cannot be made (Kasiakou et al., 2005; Ouderkirk, Nord, Turett, Kislak, 2003; Sobieszczyk et al., 2004).

2.5.3 Aerosolized administration

One small retrospective report and one case control study claimed success for aerosolized CMS, without intravenous antibiotics for the treatment of pneumonia (Falagas et al., 2009). Several small retrospective studies regarding aerosolized CMS with concomitant IV therapy for the treatment of MDR Gram-negative pneumonia demonstrated clinical success rates between 57% (Kwa, Loh, Low, Kurup, Tam, 2005; Lin, Liu, Kuo, Liu, Lee, 2010) and 87.5% (Michalopoulos et al., 2005) with aerosolized CMS (in addition to IV colistin).

Another prospective study also showed the bacteriological and clinical response is 83.3% with adjunctive aerosolized CMS (Michalopoulos et al, 2008). Two retrospective comparative

studies evaluated aerosolized plus IV CMS with IV CMS alone for the treatment of ventilator associate pneumonia (VAP). These studies demonstrated significantly higher clinical cure rates with dual therapy (54.5% vs. 32%) (Kofteridis et al., 2010) and 79.5% vs. 60.5% (Korbila et al., 2010).

2.6 Adverse Effects

2.6.1 Nephrotoxicity

According to Falagas, the prevalence of nephrotoxicity in critically ill patients with administration of intravenous colistimethate sodium (CMS) is 7% (Spapen, Jacobs, Gorp, Troubleyn, Honore, 2011). Other study found that there was no association between total cumulative colistin and toxicity (Pogue et al., 2011). However, according to an observational study of retrospective cohort that has been conducted, there was an association between total cumulative colistin and toxicity. Recent report also showed patients were developed nephrotoxicity within the first five days of colistin therapy (Deryke, Crawford, Uddin, Wallace, 2010). Differences in reporting toxicity between old and recent studies is due to the formulation of currently used colistin may be more purified and fluid treatment and supportive treatment of severely ill patient has been improved nowadays (Falagas et al., 2005).

Acute kidney injury is the common complication of intravenous colistin and as the cumulative colistin increases, the incidence of kidney injury increased (Kwon et al., 2010). Renal toxicity associated with the use of polymyxin is considered to be dose-dependent (Falagas, Kasiakou, 2006). Prescription of polymyxin is based on individual body weight in patient population. Falagas concluded that the use of polymyxin is relatively safe provided that recommended dosage is used, renal function is closely monitored and other potential nephrotoxic agent are avoided based on cases series (Falagas et al., 2006).

Nephrotoxicity is theorized related to increased in membrane permeability within the convoluted tubule epithelial cell in the kidney, that results in influx of cation, anion and water causes the edema and lysis of renal tubule epithelial cell (Falagas et al., 2005). Besides, most cases of nephrotoxicity were mild and reversible. The frequency and severity of nephrotoxicity in critically ill patiens were consistent with that found in non-critically ill patient (Doshi, Mount, Murphy, 2011). Recent studies used the RIFLE (Risk-Injury-Failure-Loss-End stage renal disease) classification to determine CMS-associated nephrotoxicity.

Table 1: RIFLE classification (serum creatinine and GFR criteria)

Category	**Criteria**
Risk **(R)**	Increased creatinine level x 1.5 or GFR decrease > 25%
Injury **(I)**	Increased creatinine level x 2 or GFR decrease > 50%
Failure **(F)**	Increased creatinine level x 3 or GFR decrease > 75% or creatinine level >4mg/Dl
Loss **(L)**	Persistent acute renal failure or complete loss of function for > 4 weeks
ESKD **(E)**	EKSD for > 3 months

GFR = glomerular filtration rate; EKSD= end-stage kidney disease

(Spapen et.al, 2011)

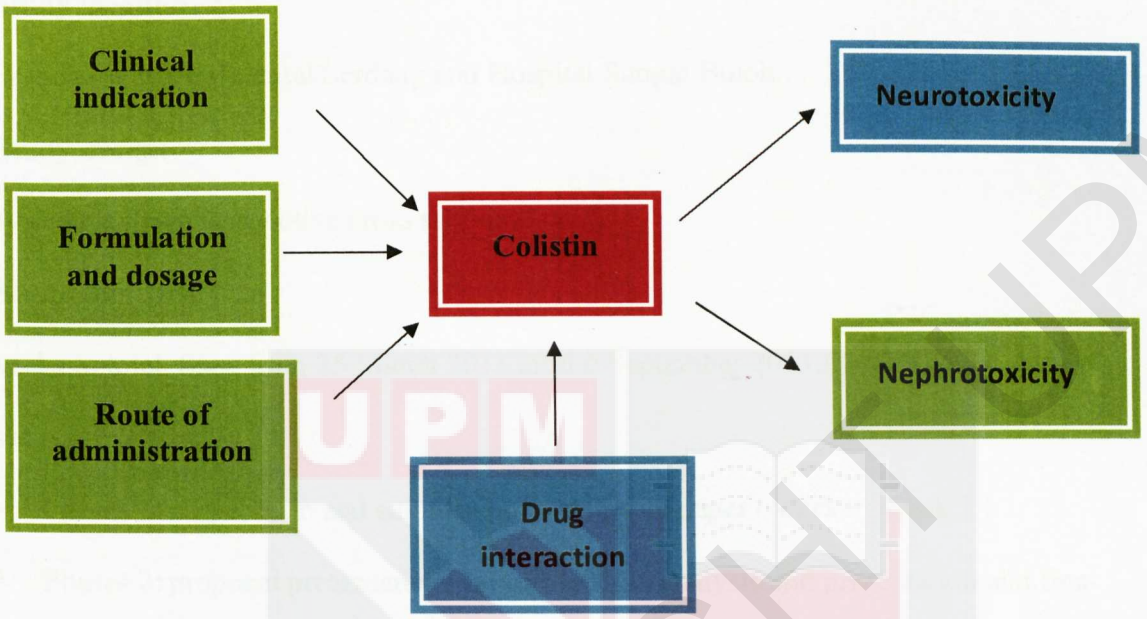
2.6.2 Neurotoxicity

In patients who received prolonged treatment with colistin, no neuromuscular toxicity was found (Falagas et al., 2005). In the literature over the past 15 years or more, there were no episodes of neuromuscular blockade or apnea induced by colistin. Neurotoxicity is dose dependent (Falagas et al., 2006). Neurotoxicity in CMS includes neuromuscular blockage and apnea, have been observed with high doses of CMS administered intravenously, it is more commonly presents in patients with renal dysfunction where the dosage is not adjusted (Falagas et al., 2006).

2.7 Drug interaction

Combination of colistin with an antipseudomonal agent (azlocillin, piperacillin, aztreonam, ceftazidime, imipenem, or ciprofloxacin) was more effective than colistin monotherapy (Falagas and kasiako, 2006). However, neurotoxicity will be enhanced with the co-administration of sodium cephalothin and polymyxin (Falagas et al., 2005). The concurrent use of polymyxin with curariform muscle relaxant and other neurotoxic drugs may trigger the development of neuromuscular blockade (Falagas et al., 2005). If aminoglycoside or colistin were to be given, especially if there are sign of renal impairment, it would seem wise to administer cephalothin with caution (Falagas et al., 2005).

2.8 Conceptual framework



3.0: METHODOLOGY

3.1 Study location

Study location were Hospital Serdang and Hospital Sungai Buloh..

3.2 Study design

Study design was retrospective cross sectional study.

3.3 Study duration

24 weeks in total. Start from 25 March 2013 until 6 September 2013.It was divided into two phases :

- Phases 1: preparation and submission of proposal paper (week 1- week 2)
- Phases 2: proposal presentation, data collection, analysis and presentation and final presentation/seminar.

3.4 Sampling

3.4.1. Study Population

Subjects were patients admitted to Hospital Serdang and Hospital Sungai Buloh between 2010 until 2012.

3.4.2. Sampling Population

3.4.2.1. Inclusion Criteria

I. Individual who was admitted to intensive care unit.

II. Individual who was administered with colistin.

3.4.2.2. Exclusion Criteria

I. Individual who had incomplete data or missing data.

3.4.3. Sampling Frame

A list of patients with administration of colistin during their stay in intensive care unit at Hospital Serdang and Hospital Sungai Buloh from 2010 until 2012.

3.4.4. Sampling Unit

A patient admitted to Hospital Serdang and Hospital Sungai Buloh who fulfilled the inclusion criteria.

3.4.5. Sampling Method

Simple random sampling.

3.4.6 Sample Size

The formula that was used to calculate sample size estimation is as below.

$$n = \frac{z^2 p(1-p)}{d^2}$$

n = Required sample size

z = confidence level at 95 % (standard value of 1.96)

p = Estimates prevalence of nephrotoxicity after administered by colistin (Spapen et al., 2011)

d = Precision (in proportion of 1)

α = level of significant

The sample size calculations:

$$n = \frac{1.96^2 \times p(1-p)}{d^2}$$

$$= \frac{1.96^2 \times 0.07(1-0.07)}{0.05^2}$$

$$= 100$$

Therefore, our final sample size was 100.

3.5 Intruments and data collection

3.5.1. Data collection technique

Clinical data were extracted from medical records and the data were entered into a proforma. Collected data then were entered into SPSS. Data were chosen based on inclusion and exclusion criteria.

3.5.2. Quality control

In this study, we as the researchers completed a set of pro-forma with the data that was obtained. To minimize error, one researcher would fill up the pro-forma while the other cross-checked the information collected.

3.6 Data analysis

Data were analyzed by using Statistical Package for Social Sciences Program (SPSS) version 21. Data also were analyzed by using descriptive analysis; association between variables was examined by using Chi square test. Confidence interval was set at 95% for estimation of the mean and all significant levels were set at standard p value of <0.05.

3.7 Study ethics

The ethical forms were submitted to the following individuals/institution.

- The Ethical Committee of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.
- Medical Research Ethical Committee, Ministry of Health (MOH), Malaysia.

Approval letter was written to the following institutions:

- Director of Hospital Serdang and Hospital Sungai Buloh.

3.8 Variables

3.8.1. Dependant Variable

The dependant variable for this study was the nephrotoxicity among patients in intensive care unit of Hospital Serdang and Hospital Sungai Buloh who was administered with colistin.

3.8.2. Independent Variable

The independent variables in this study were amount of dosage and duration of colistin administered to the patients.

3.9 Definition of terms

i) Nephrotoxicity

The nephrotoxicity was measured based on RIFLE criteria (Spapen et al., 2011). Based on RIFLE criteria, it futher classified patient who having either 'risk', 'injury', 'failure', 'loss' or 'ESKD' as having nephrotoxicity and 'no risk' as not having nephrotoxicity (Spapen et al., 2011). It was shown in table 2.**Table 2: RIFLE criteria and nephrotoxicity**

Category	**Risk**	**Injury**	**Failure**	**Loss**	**End Stage Kidney Disease (ESKD)**	**No risk**
Nephrotoxicity	Yes					No

ii) Prevalence

Prevalence of nephrotoxicity among patients administered with IV colistimethate sodium (CMS) in critically ill patients (Spapen et al., 2011).

iii) Critical ill patients

Patients who suffered from life-threatening condition such as burn, severe pneumonia, sepsis, surgery, stroke, heart attack and head trauma (Lewis, Gill, Bobek, Dasta, 2004). These patients required specialized treatment that other units in the hospital are unable to provide due to serious nature of illness (Lewis et al., 2004).

iv) Intensive care unit

Critical care or intensive therapy department was a section within a hospital that look after patients whose conditions were life threatening and needed constant close monitoring and support from the equipment and medication to keep normal body function going (Intensive care society, 2011).

v) Indication use of colistin

Diseases that were treated by administered colistin. They were classified into pneumonia and sepsis and others (Yavac et al., 2011; Nasnas et al., 2008). As for pneumonia, it includes all kind of pneumonia which are Hospital Acquired Pneumonia (HAP) or Nosocomial Pneumonia, Community Acquired Pneumonia (CAP), Aspiration Pneumonia, Atypical Pneumonia, and Health Care Associated Pneumonia (Yavac et al., 2011; Nasnas et al., 2008). Some patient might have both pneumonia and sepsis at the same time with indication of colistin (Yavac et al., 2011; Nasnas et al., 2008) so we put is as pneumonia and sepsis. Other than this we classified it as 'others'. 'Others' include intrabdominal abcess, kidney infection, diabetics and ischaemic encephalopathy (Yavac et al., 2011; Nasnas et al., 2008).

vi) Dose of colistin

It was measured in International Unit (IU) (Forest laboratories, UK Limited, 2002). It was measured from the first day colistin being administered to the patients in ICU until it is stopped (Spapen et al., 2011).

vii) Duration

It was measured in day (Falagas et al., 2005). From the day patients start being administered colistin in ICU until the last day he or she is on colistin therapy.

viii) Microbiological profile

Types of microorganisms that were isolated through culture with indication of colistin use. Also, look for its sensitivity towards colistin either sensitive, resistant (Li et al., 2001).

ix) Empirical

Patients were administered with colistin in ICU without waiting for culture results due to critical condition (Kasiakou, Argyris, Michalopoulos, Matthew, Falagas, 2005).

xi) Definitive

Patients were administered with colistin after getting result of culture (Kasiakou et al., 2005)

xii) Clinical outcome

Outcome of ICU patients after administration of colistin, either having nephrotoxicity or not (Kasiakou et al., 2005).

xiii) Demographic

Gender, race and age of patients in ICU with indication of colistin use (Falagas et al., 2005).

xiv) Serum creatinine baseline

Serum creatinine level on the day administration of colistin was started (Kasiakou et al., 2005).

xv) Peak serum creatinine

The highest level of serum creatinine during colistin therapy (Kasiakou et al., 2005).

3.10 Limitations

3.10.1. Bias

I. Nephrotoxicity was determined using serum creatinine level as opposed to 24 hour urine creatinine which is more accurate. This was a limitation of our study because serum creatinine is not as accurate as urinary creatinine.

4.0: RESULTS

The data analysis for the study comprises of descriptive data and analytical data. The total number of patients who fulfilled the inclusion criteria was 100. The data were collected and entered into proforma. For the analytical data, Chi square test and Fisher exact test were used.

Descriptive data

4.1 Patients demography

We had altogether recruited 100 patients. Demographic of patients treated with colistin in Hospital Serdang are shown in Figure 1 and 2. In Hospital Serdang, majority of patients were male (74%) and Malay (62%). Since the data were normally distributed, the mean age of patients was 47.14 ± (19.57) years old. The range of the age was (9-83) years old.

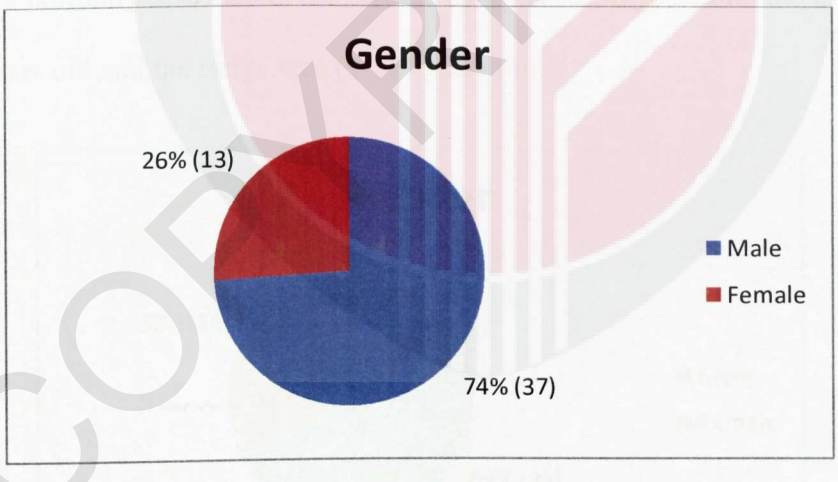


Figure 1: Gender of the patient treated with colistin in Hospital Serdang. (n=50)

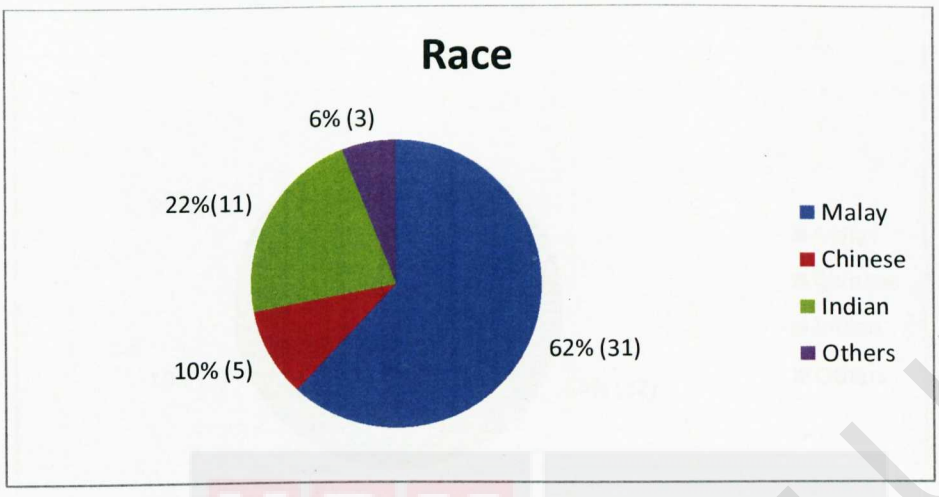


Figure 2: Race of patient treated with colistin in Hospital Serdang. (n=50)

Demographic of patients treated with colistin in Hospital Sungai Buloh are shown in Figure 3 and 4. In Hospital Sungai Buloh, majority of patients were male (68%) and Malay (64%). Since the data were not normally distributed, the median age was 42.50 years old, the interquartile range was 36 years old and the range was (6-76) years old.

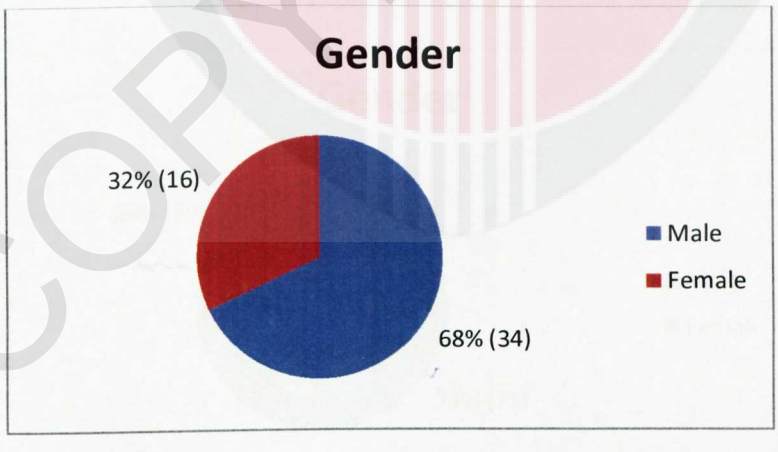


Figure 3: Gender of the patients treated with colistin in Hospital Sungai Buloh (n=50)

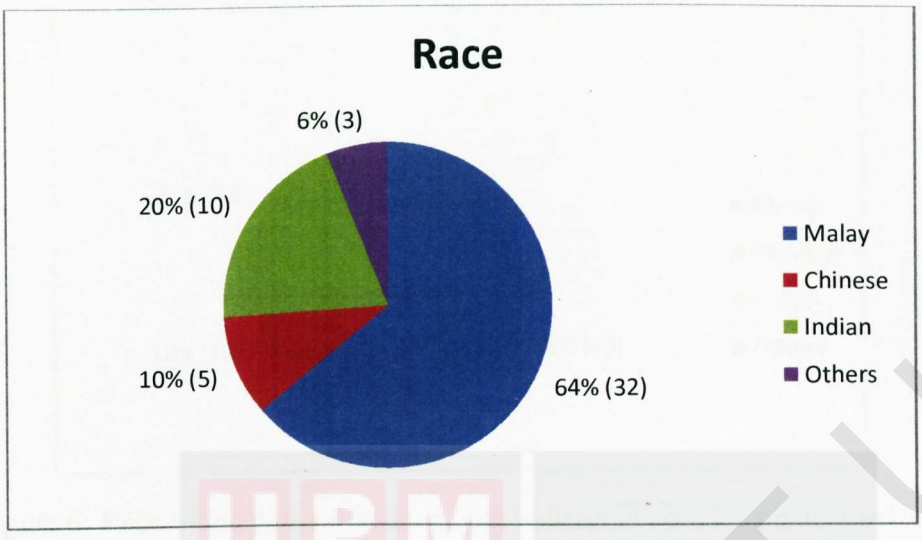


Figure 4: Race of the patients treated with colistin in Hospital Sungai Buloh (n=50)

Demographic of patients treated with colistin in both hospitals are shown in Figure 5 and 6. In both hospitals, since the data were normally distributed, the mean age of patients was 45.49±19.56 years old and the range was (6-83) years old. Majority of patients were male (71%) and Malay (63%).

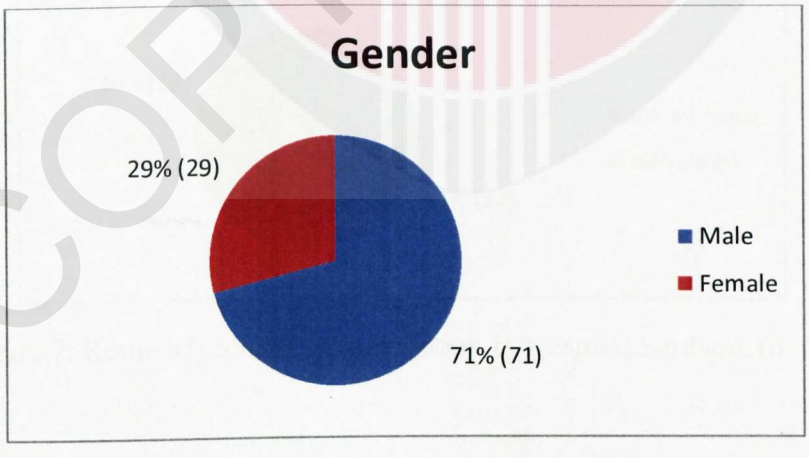


Figure 5: Gender of the patients treated with colistin in both hospitals. (n=100)

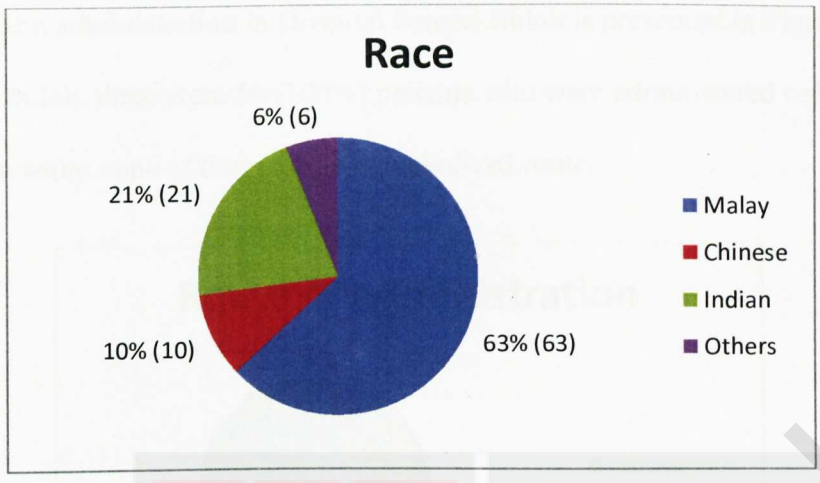


Figure 6: Race of the patients treated with colistin in both hospitals. (n=100)

4.2: Colistin administration

The route of colistin administration in Hospital Serdang is presented in Figure 7. In Hospital Serdang, there were 32 (64%) patients who were administered colistin by intravenous route while only 18 (36%) by nebulized route.

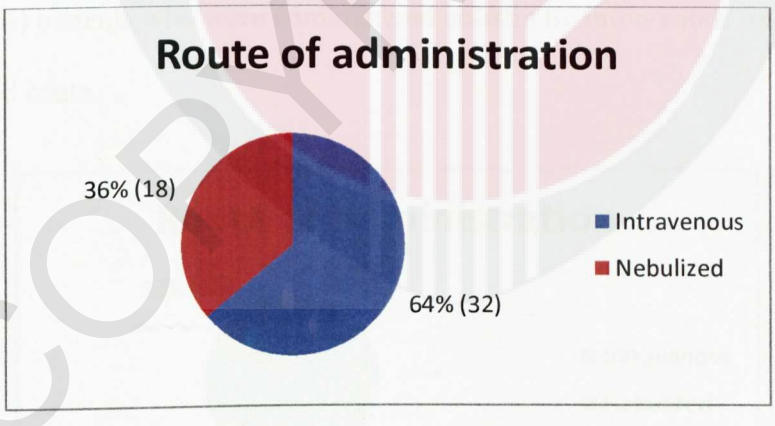


Figure 7: Route of colistin administration in Hospital Serdang. (n=50)

The route of colistin administration in Hospital Sungai Buloh is presented in Figure 8. In Hospital Sungai Buloh, there were 50 (100%) patients who were administered colistin by intravenous route while none of the patients by nebulized route.

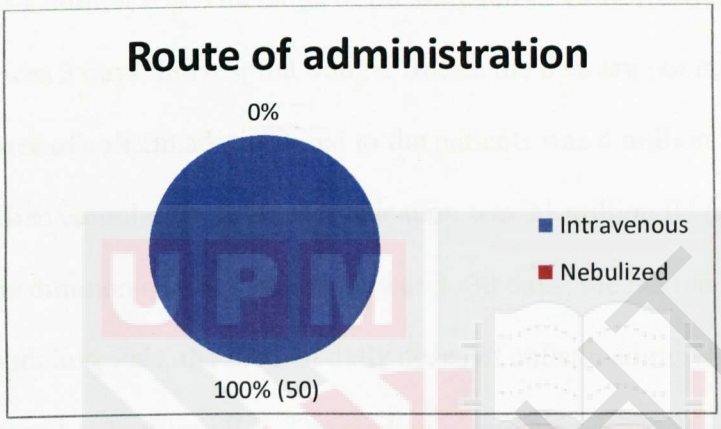


Figure 8: Route of colistin administration in Hospital Sungai Buloh (n=50)

The route of colistin administration in both hospitals is presented in Figure 9. In both hospitals there were 82 (82%) patients who were administered colistin by intravenous route while only 18 (18%) by nebulized route.

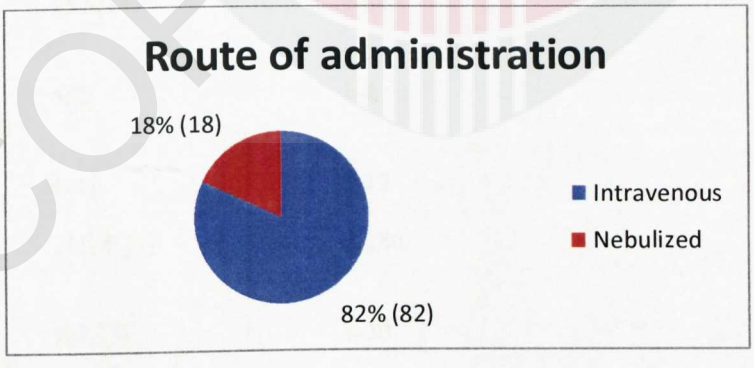


Figure 9: Route of colistin administration in both hospitals. (n=100)

The administration of colistin in patients is presented in Table 3. In Hospital Serdang, the data are not normally distributed. The median daily doses of colistin administered to the patients was 3 million IU (range 1–16 million IU). The median cumulative doses of medication was 15.5 million IU (range 2–84 million IU). The range of the duration of CSM treatment was 1–14 days; the median duration was 5 days. In Hospital Sungai Buloh, the data are not normally distributed. The median daily doses of colistin administered to the patients was 4 million IU (range 1–12 million IU). The median cumulative doses of medication was 21 million IU (range 2–180 million IU). The range for the duration of CSM treatment was 1–30 days; the median durations were 7 days. In overall, in both hospitals, the median daily doses of colistin administered to the patients was 3 million IU (range 1–12 million IU). The median cumulative doses of medication was 17.8 million IU (range 2–180 million IU). The range of the duration of CSM treatment was 1–30 days; the median durations were 7 days.

Table 3: Administration of colistin (n=100)

Administration	Median (IQR)	Range
Hospital Serdang (n=50)		
Daily Dose (Million International Unit)	3(2)	1-6
Cumulative Dose (Million International Unit)	15.5(14)	2-84
Duration (Days)	5(2)	1-4
Hospital Sungai Buloh (n=50)		
Daily Dose (Million International Unit)	4(4)	1-12
Cumulative Dose (Million International Unit)	21(34.25)	2-180
Duration (Days)	7(4.25)	1-30
Both Hospitals (n=100)		
Daily Dose (Million International Unit)	3(4)	1-12
Cumulative Dose (Million International Unit)	17.8(31.5)	2-180
Duration (Days)	7(4)	1-30

4.3 Indication for colistin use

Figure 10 shows indication of colistin use among patients in ICU in Hospital Serdang. In Hospital Serdang, patients with pneumonia had highest percentage (58%) of indication of colistin use in ICU.

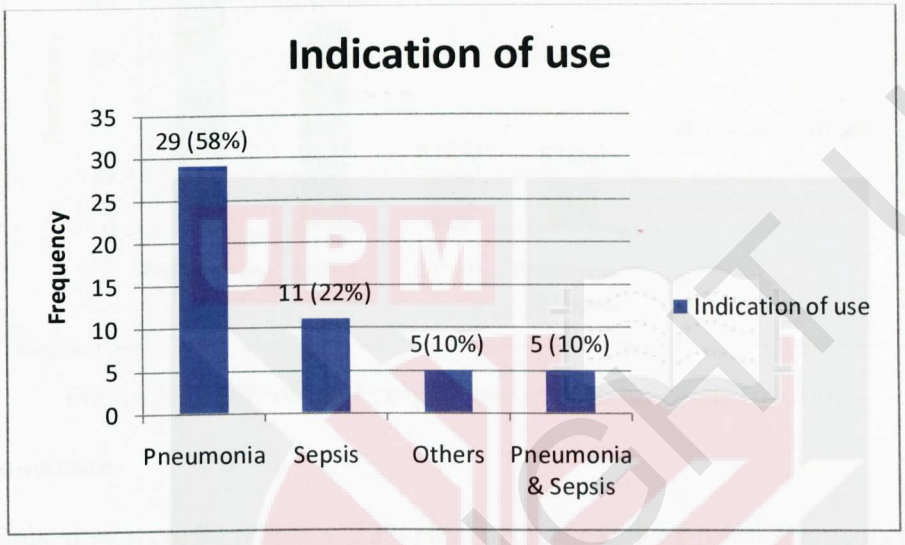


Figure 10: Indication of colistin use in Hospital Serdang (n=50)

Figure 11 shows indication of colistin use among patients in ICU in Hospital Sungai Buloh. In Hospital Sungai Buloh, patients with sepsis had highest percentage (50%) of indication of colistin use in ICU.

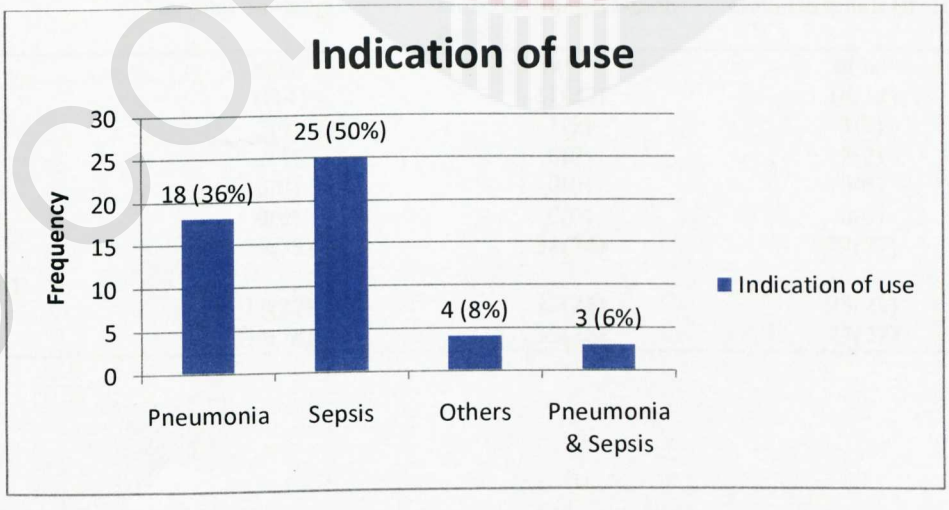


Figure 11: Indication of colistin use in Hospital Sungai Buloh (n=50)

Figure 12 shows indication of colistin use among patients in ICU in both hospitals. In both hospitals, colistin was widely used in patient with pneumonia (47%).

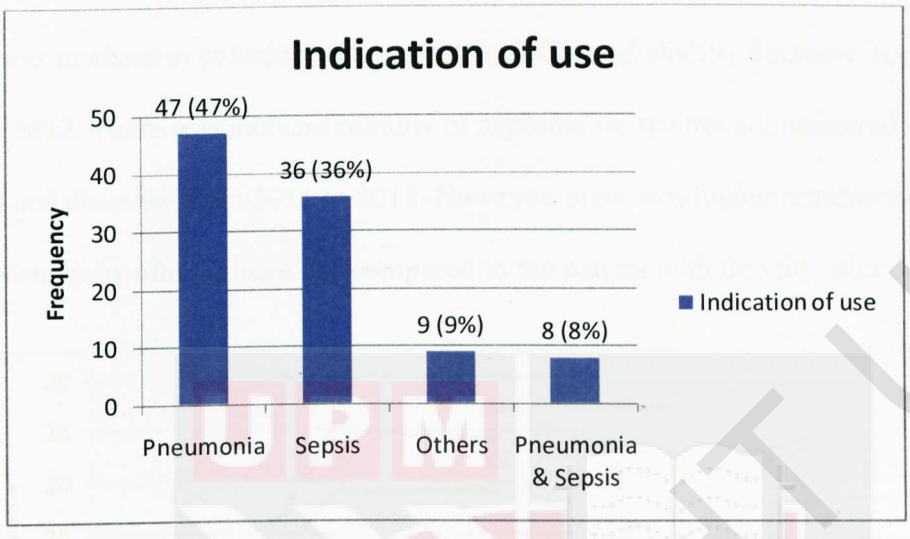


Figure 12: Indication of colistin use in both hospitals (n=100)

4.4 Clinical outcome

In both hospitals, they were 23 patients (23%) had nephrotoxicity while 77 patients (77%) had not. It was shown in Table 4. There were 18 patients (18%) at 'risk', 3 patients (3%) at 'injury', 2 patients (2%) at 'failure' and 77 patients (77%) had no nephrotoxicity.

Table 4: Number of patients and percentages according to its nephrotoxicity and RIFLE criteria.

	Hospital Serdang(n=50)	Hospital Sungai Buloh (n=50)	Both Hospitals (n=100)
Category	n(%)	n(%)	n(%)
Risk	7(14)	11(22)	18(18)
Injury	2(4)	1(2)	3(3)
Failure	2(4)	0(0)	2(2)
Lost	0(0)	0(0)	0(0)
ESKD	0(0)	0(0)	0(0)
No risk	39(78)	38(76)	77(77)
Nephrotoxicity			
Yes	11(22)	12(24)	23(23)
No	39(78)	38(76)	77(77)

4.5 Trend of colistin use and nephrotoxicity

Figure 13 shows the trend of colistin use and nephrotoxicity in Hospital Serdang from 2010 to 2012. There was increase in colistin use from 2010 to 2011 and slightly decrease in colistin use from 2011 to 2012. There was increase number of nephrotoxicity after administered colistin from 2010 to 2011 and decrease from 2011 to 2012. However, there was higher number of patient without nephrotoxicity after colistin use compared to the patient with toxicity after colistin use.

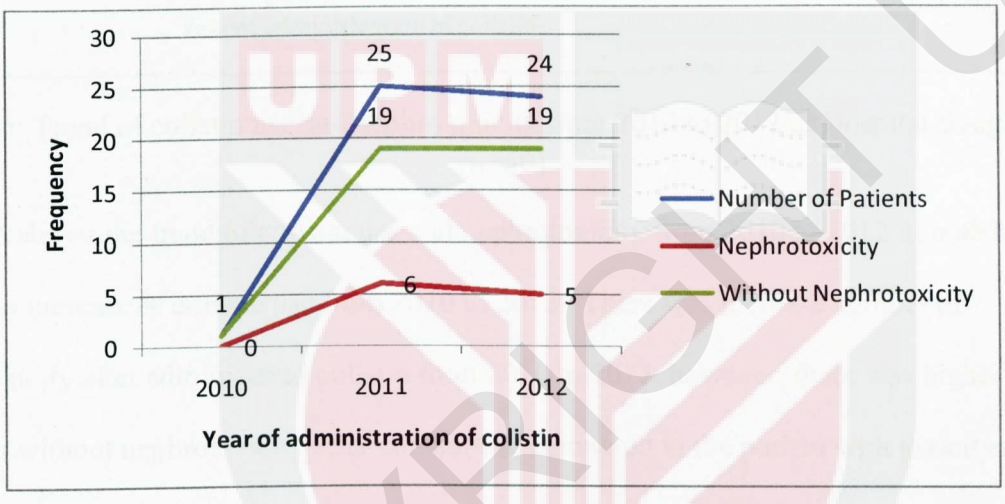


Figure 13: Trend of colistin use and nephrotoxicity from 2010 to 2012 in Hospital Serdang (n=50)

Figure 14 shows the trend of colistin use and nephrotoxicity from 2010 to 2012 in Hospital Sungai Buloh. There was great increase of colistin use from 2011 to 2012. There was increase number of nephrotoxicity after administered colistin from 2010 to 2012, however, there was higher number of patient without nephrotoxicity after colistin use compared to the patient with toxicity after colistin use.

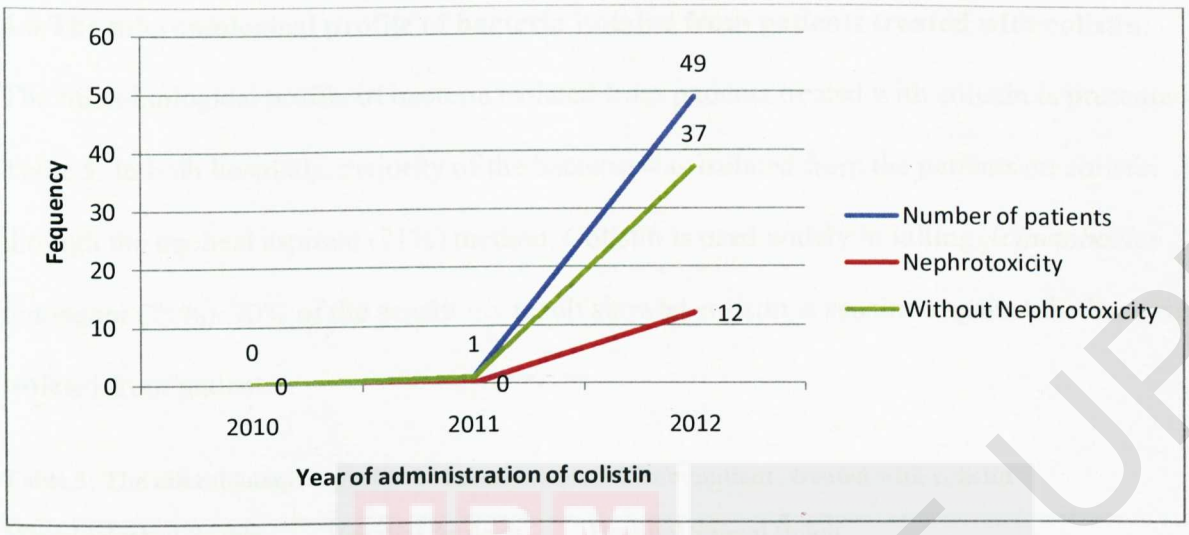


Figure 14: Trend of colistin use and nephrotoxicity from 2010 to 2012 in Hospital Sungai Buloh (n=50)

Figure 15 shows the trend of colistin use and nephrotoxicity from 2010 to 2012 in both hospitals. There was increase of colistin use from 2010 to 2012. There was increase number of nephrotoxicity after administered colistin from 2010 to 2012, however, there was higher number of patient without nephrotoxicity after colistin use compared to the patient with toxicity after colistin use.

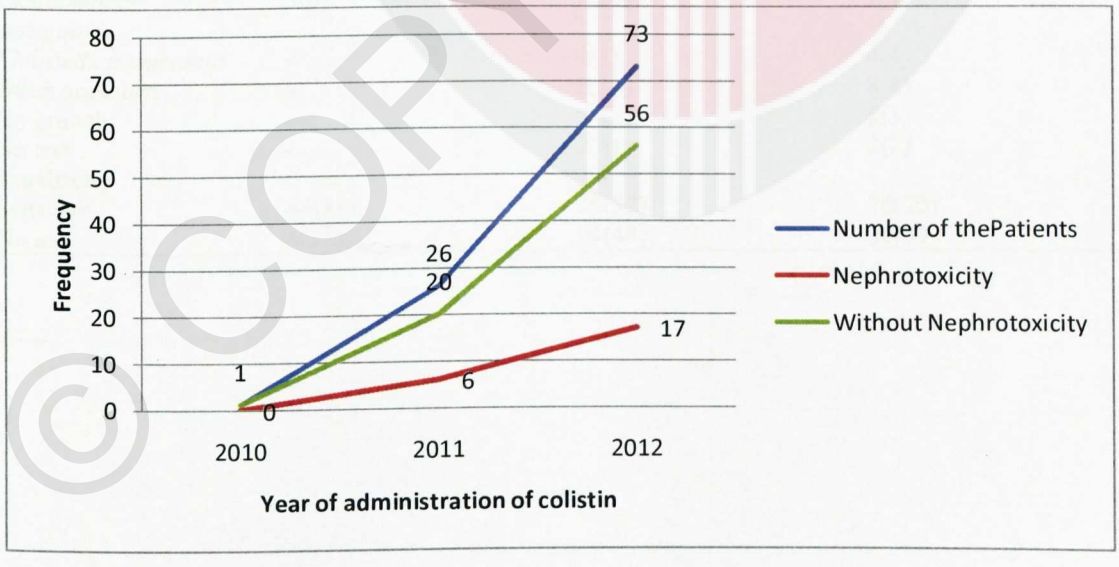


Figure 15: Trend of colistin use and nephrotoxicity from 2010 to 2012 in both hospitals (n=100)

4.6 The microbiological profile of bacteria isolated from patients treated with colistin.

The microbiological profile of bacteria isolated from patients treated with colistin is presented in Table 5. In both hospitals, majority of the bacteria was isolated from the patients on colistin through the tracheal aspirate (71%) method. Colistin is used widely in killing *Acinetobacter baumanni* (71%). 70% of the sensitivity result showed colistin is sensitive against the bacteria isolated from patient.

Table 5: The microbiological profile of bacteria isolated from patients treated with colistin

Microbiological Profile	Hospital Serdang (n=50)	Hospital Sungai Buloh (n=50)	Both Hospitals (n=100)
Method	n(%)	n(%)	n(%)
Tracheal aspirate	39(78)	32(64)	71(71)
Bronchoalveolar lavage	7(14)	-	7(7)
Blood culture	1(2)	4(8)	5(5)
Gram stain	-	2(4)	2(2)
Urine culture	1(2)	-	1(1)
IVDU	-	1(2)	1(1)
Wound swab	2(4)	-	2(2)
Tissue culture	-	2(4)	2(2)
Pus culture	-	5(10)	5(5)
Peritoneal fluid culture	-	1(2)	1(1)
No test	-	3(6)	3(3)
Microorganism			
Acinetobacter baumanni	47(94)	24(48)	71(71)
Pseudomonas aeroginosa	3(6)	7(14)	10(10)
Klebsiella pneumonia	-	4(8)	4(4)
Other organism	-	8(16)	8(8)
No growth	-	5(10)	5(5)
No test	-	2(4)	2(2)
Sensitivity			
Sensitive	44(88)	26(52)	70(70)
No test	6(12)	24(48)	30(30)

4.8 Duration and nephrotoxicity

The association between duration and nephrotoxicity is presented in Table 6 through Fisher exact test. As the data was not normally distributed, we chose the median duration (7 days) as our cut of point. Less than 7 days or equal to 7 days is the short duration while more than 7 days as the long duration. The prevalence of nephrotoxicity in less than or equal to 7 days is 21.5%. The prevalence of nephrotoxicity in more than 7 days is 28.6%. The prevalence of nephrotoxicity after administered colistin is 23%. Since the p value > 0.05, it is not significant and the null hypothesis is not rejected. Therefore, it can be concluded that there is no significant association between duration and nephrotoxicity.

Table 6 Association between duration and nephrotoxicity

	Nephrotoxicity					
	Yes n(%)	**No n(%)**	**Total n(%)**	**df**	**x^2**	**P value**
Duration						
Less than or equal to 7 days	17(21.5)	62(78.4)	79(100)	-	-	0.562
More than 7 days	6(28.6)	15(71.4)	21(100)			
Total	23(23)	77(77)	100(100)			

4.9 Dose and nephrotoxicity

Chi square test was used to determine the association of dose and nephrotoxicity. We chose 3MU as the median daily dose in our study is 3MUand the data was not normally distributed. Less than 3 MU or equal to 3 MU we had classified them as the low dose while more than 3 MU as the high dose. The prevalence of nephrotoxicity in the dose that less than or equal to 3 MU is 21.6%. The prevalence of nephrotoxicity in the dose that more than 3 MU is 23.8%. The p-value is 0.763. Since the p-value> 0.05, the null hypothesis is not rejected. It is statistically not

significant. Therefore, there is no association between dose and nephrotoxicity. This was shown on table 7.

Table 7: Association between daily dose and nephrotoxicity

	Nephrotoxicity					
	Yes n(%)	**No n(%)**	**Total n(%)**	**df**	**x^2**	**P value**
Daily Dose Less than or equal to 3MU	8(21.6)	29(78.4)	37(100)	1	0.063	0.802
More than 3MU	15(23.8)	48(76.2)	63(100)			
Total	23(23)	77(77)	100(100)			

5.0: DISCUSSION

5.1: Discussion

5.1.1 Trend of colistin use

There was increase of colistin use from 2010 to 2012 because colistin is the only antibiotics available to kill multi-drug resistant bacteria. In United States, colistin cases rose every year from 524 in 2005 to 1156 in 2011, while total all cause admission only increased by 9% (Sameer et al., 2013). Meanwhile in Indian Hospital, colistin is saving thousands of lives of patients every day (Abdul Ghafur, 2012). This trend also being proven by Bergen et.al (2012), that colistin will continue as last line option to kill multidrug resistant bacteria as there are no new antibiotics available. Besides, there was increase incidence of infection caused by highly resistant gram negative bacteria, therefore there was increased use of colistin (Yahav, Farbman, Leibovici, Paul, 2012). Furthermore, colistin is mostly used when the bacteria is resistant to all available antibiotics, failure of the treatment by other available antibiotics or even empirically in ICU (Falagas & Rafailidis, 2012). Based on the evidence from hospital studies in several countries, colistin is effective and safe in treating infection caused MDR bacteria (Michalopoulos et al., 2005; Falagas et al., 2005). Therefore, colistin is increasingly used in Malaysia hospitals in recent years.

5.1.2 Indication of colistin use and microbiological profile of bacteria isolated from patient on colistin

Based on our result, colistin was widely used in patients with pneumonia because pneumonia is mostly caused by multi-drug resistant *Acinetobacter baumanni.* In our study, most

of isolated bacteria from patients with indication of colistin were *Acinetobacter baumanni.* 80.5% of the *Acinetobacter baumanni* which were isolated from VAP was determined to be multidrug resistant. (Falagas et al., 2005). It is supported by the Ferrara (2006) and Garnacho, Sole-Violan, Sa-Borges, Diaz and Rello, (2003) that stated that *Acinetobacter baumanni* is one of the important pathogens in pneumonia and cause high mortality in VAP. This is also because *Acinetobacter baumanni* is sensitive to colistin. Based on our result, 70% of the sensitivity result showed colistin was sensitive to kill the bacteria. Colistin is the best option to kill multi-drug resistant *Acinetobacter baumanni* because as mentioned by Dizbay, Altuncekic, Sezer, Ozdemir and Arman (2008), *Acinetobacter baumanni* is resistant to drugs such as ciprofloxacin, cefepime, imipenem, meropenem and sulbactam except colistin. In addition, according to Timurkaynak et al. (2006), susceptibility to colistin was reported as 97.9-100%. However, resistance of *Klebsiella sp.* to colistin had been increased, but resistance rates of colistin had been remain stable from 2006 to 2009 (Gales, Jones, Sader, 2011). Based on Florescu et al. (2012), it showed 72% favorable clinical response rate and 34% in-hospital mortality rate with colistin therapy. In our study, colistin is also used in sepsis because of the capability of the colistin to bind and neutralize lipopolysaccharide endotoxin (Davies & Cohen, 2011). Therefore, colistin is a good alternative in treating pneumonia with multidrug resistant bacteria and sepsis since it is highly sensitive to it.

5.1.3 Route of administration of colistin

Based on our results, most of the colistin was administered through intravenous route in hospitals, while only a few through nebulized routes. This shows that intravenous route is a preferable route for the colistin administration compared to nebulized route in these two tertiary Malaysian hospitals. It may due to intravenous route cause fewer side effects than nebulized

route. This is supported by Berlana et al. (2005) and Falagas et.al (2006) that colistin administration by nebulized route cause bronchoconstriction, cough, sore throat and chest tightness and the risk of bronchoconstriction is even greater in patient with the history of asthma or atopy. Bronchoconstriction though aerosolization of colistin is believed to be caused by chemical stimulation, allergy in the airway, the liberation of histamine, irritation form the chemicals or from the foam that is produced during nebulization and hyperosmolariy in the airways. A report of desensitization to colistin through nebulized route was also found, but there was no report of rapid intravenous desensitization (Dominguez-Ortega et al., 2007). Besides, it is easier to adjust the dose through intravenous route compared to the nebulized route, because some of the colistin is lost during inhalation. It is complemented with the recent study that there were approximately 7% colistin sulphomethate lost during inhalation because nebulized performance in treatment of colistin was influenced by individual breathing pattern, physic-chemical properties of inhalation liquids and nebulizer performance (Westerman et al., 2007). Moreover, intravenous route is a safer and more preferable route because the colistin concentration decreases at the end of treatment. According to Sarker, DeSanti and Kuper (2007), intravenous administration of colistin results in higher peak serum concentrations but a more rapid decline in serum drug concentrations occurs.

However, aerosolized colistin is still be used in some of the patients because some of the adverse effects of the nebulized colistin can be overcomed. This is supported by Falagas (2006) mentioned that bronchoconstriction can be treated by the administration of bronchodilator and supplemental oxygen. According to study conducted by Westerman et al. (2007), it also stated that adverse effect is lessening by dry powder inhalation of colistin compared to liquid inhalation. Recent study by Nakwan et al. (2011) stated that aerosolized colistin maybe a useful

adjunctive therapy in VAP as there were no clinical or laboratory adverse events related to aerosolized colistin administration. Therefore, aerosolized colistin can also be used in patients. Besides, aerosolized colistin is used in some patients because it has advantages in time gain and is more localized compared to intravenous route. Nebulized colistin also has a high drug concentration in the airway with minimal absorption. Used as adjunctive or monotherapy, nebulized colistin (65.3 mg/day) was determined 100% effective in treating *A. baumanii* pulmonary infections and 57% for *P. aeruginosa* based on follow-up cultures (Berlana et al., 2005). This result is supported by Michalopoulos et al. (2008) that aerosolized colistin was effective in treating 83% of VAP. Aerosolized colistin (1MU every 8 h) sometimes was given in conjunction with the intravenous form in some cases of pneumonia, depending on the severity of pneumonia. Therefore, colistin can be administered through intravenous and nebulized route, but nebulized route is only used when necessary in some of the cases due to its disadvantages.

5.1.4 Daily dose and duration

The median daily dose was 3MU in our study. It is quite similar to the recent studies. Azzopardi et al. (2013) stated that the recommended dose of the manufacturer is 31,250-65,500 IU /kg per day, divided into 2-4 equal doses. According to Nasnas, et al. (2009), average daily dose of colistin was 2.5 MU with a maximum daily dose of 4 MU. Besides, in the study conducted by Garonzik et al. (2011) median daily dose across the 105 patients was 2.5–13.7 (IU). Pavles (2006) in his study also stated that the dosage was 2.5–5.0 mg/kg per day, divided into three doses. Pogue (2011) also found that, common colistin doses was ranged with the majority in the 3–6 million IU, and from 1 to 9 million international units (IU) daily. In our study, median duration is 7 days (Range 1-30 days). As for the range, it is quite similar in other studies. For example, a study conducted by Andrea, Loh, Jenny, Kurup, Vincent, (2005) found

that with the median duration of nebulized colistin therapy study 13.5 days (range 4–24 days),and it showed 61% of clinical response (Peter et al., 2003). Besides, study conducted by Nikolaos et al. (2003) found that with the median duration 13.5 days (range 4–24 days), the clinical response was (73%). They also found that the survival rate was 57.7% at 30 days. Compared with other recent studies, it is undeniable that the daily dose prescribed by both hospitals was within the recommended range. However, the daily dose of the colistin and combination of colistin with other drugs should be prescribed with caution because of the presence of the colistin resistance recently. In 2007, presence of the colistin resistance subpopulation before therapy and amplication of colistin-resistant subpopulation through colistin monotherapy had been suspected (Li et al., 2007)

5.1.5 Nephrotoxicity

In our studies, we had used RIFLE criteria to access nephrotoxicity. Nephrotoxicity is manifested as decreased creatinine clearance and increased serum urea and creatinine levels (Tamma & Lee, 2009). According to Falagas et al. (2006), major adverse effects of the colistin are manifested by renal insuffiency, which is defined by increase in serum creatinine and decrease in creatinine clearance. As in our study, there is a low rate of nephrotoxicity which by only 23% of patients developed nephrotoxicity after administered with colistin. It is complemented by the recent studies that suggest that colistin has less toxicity than previously reported (Tamma et al., 2009). According to Falagas et al. (2006), previous studies reported there was higher rate of nephrotoxicity may be due to total daily dose used in previous studies is higher than currently recommended dose. Colistin causes low rate of renal dysfunction, a rate that did not change significantly when we adjusted for age or for the route of administration (Florescu et al., 2012). However, 23 of our patients were still having nephrotoxicity with

indication of colistin and this situation undoubtedly deserved the explanations. There are several reports on risk factors for increased colistin-associated nephrotoxicity. The incidence of nephrotoxicity increased with age, and no serious nephrotoxicity was observed in populations with mean ages below the seventh decade (Kim, Lee, Yoo, and Pai, 2009). In this study, the mean age of patients was 45.9 years. However, we could not prove old age as a risk factor for colistin-associated nephrotoxicity as we do not analyze that association. In our study, low rate of nephrotoxicity that was occurred could be caused by concomitant administration of nephrotoxic agents as we did not exclude those patients. This is supported by Kim et al.(2009), Nasnas(2009) and Azzopardi et.al.(2013) that colistin is often administered as last line therapeutic option on intensive care patients on multiple nephotoxic drugs, therefore risk factor of the nephrotoxicity could be due to other nephrotoxic drug. Besides, development of nephrotoxicity also can be due to the septic shock and and severity of patients condition in ICU (Monica and Rocco et al., 2013). As discussed above, there are several reports on risk factors that enhance colistin-induced renal toxicity however most of them were not evaluated statistically.

5.1.6 Association between daily dose and duration and nephrotoxicity

In our studies, there was no significant association between daily dose and duration and nephrotoxicity. These results are complement to the recent studies. According to Nasnas (2009), among the risk factors such as patients' age, daily and cumulative dose and treatment duration, only age and cumulative dose were identified to be risk factors of nephrotoxicity. Based on Dalfino et al. (2012), no correlation was found between variation in serum creatinine level and daily and cumulative doses of colistin, and between variation in serum creatinine level and duration of colistin treatment. Therefore, it is concluded that colistin doses, duration of treatment, or cumulative colistin doses did not influence renal damage. Besides, prolonging dosing interval

may have cause low rate and moderate severity of nephrotoxicity (Garonzik et al., 2011). Therefore, it is proven that there is no association between daily dose and duration and nephrotoxicity. However the result is different from the studies conducted by Pogue, J. M (2011). In his studies, there was a significant association between increasing colistin dose and increased risk for renal insufficiency within each strata of creatinine clearance. The result was different maybe due to the different parameter that used to access nephrotoxicity. Kim et al. (2009) found that incidence of nephrotoxicity was 31.9%, which is higher than the most recently reported incidence even though they applied relatively strict criteria for nephrotoxicity When they defined renal failure as an increase of more than 50% of the baseline creatinine level to a value higher than threshold, 19 patients (40.4%) developed nephrotoxicity. If an increase of creatinine level by 1 mg/dL was defined as renal toxicity, 15 patients (31.9%) developed renal failure (Kim et al., 2009). This clearly shows that different parameter used will influence the result of nephrotoxicity. Therefore, there was no significant association between daily dose and duration of treatment prescribed and nephrotoxicity in both hospitals and nephrotoxicity may be caused by others factors that are not evaluated statistically.

5.2: Conclusion

In two tertiary Malaysian Hospitals, there was increase trend of colistin use. Most of the colistin is administered through intravenous route. The daily dose prescribed is within the recommended range. There is low rate of nephrotoxicity after colistin administration. There is no significant association between daily dose and duration of treatment prescribed and nephrotoxicity.

5.3: Limitation

There were several limitations in this study. First, it has the inherent weakness of studies with a retrospective design, including the use of data from past medical records. Second, as it involves

critically ill patients from ICU, the possibility that renal toxicity was induced by causes other than CMS cannot be excluded. Third, we did not analyze the concomitant nephrotoxin and other drugs administred simultaneously with colistin. Forth, we do not analyze the association of duration and daily dose if they combine. What if the duration is short but the daily dose is high and vice versa. Next, there is no control group for the comparison of outcomes, including mortality, cure of infection, and nephrotoxicity. Finally, a great proportion 30% of the bacterias isolated was not tested for susceptibility to colistin.

5.4: Recommendation

The recommendation are additional studies are necessary to examine the efficacy and safety of combinations of colistin with other antibiotics and potential predictor and other risk factors of nephrotoxicity in Malaysian hospitals.

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APPENDIX 1

Table 8: Patients, duration, daily dose and nephrotoxicity

Patient ID	Daily Dose (MU)	Duration (Days)	Nephrotoxicity
1	3.00	7	Toxicity
2	4.00	5	Without toxicity
3	2.00	1	Without toxicity
4	3.00	7	Toxicity
5	2.00	1	Without toxicity
6	2.00	7	Without toxicity
7	6.00	7	Without toxicity
8	6.00	5	Without toxicity
9	6.00	7	Without toxicity
10	2.00	4	Without toxicity
11	2.00	1	Without toxicity
12	4.00	3	Toxicity
13	3.00	5	Without toxicity
14	3.00	5	Without toxicity
15	1.00	7	Without toxicity
16	4.00	1	Toxicity
17	3.00	9	Without toxicity
18	3.00	1	Toxicity
19	2.00	4	Without toxicity
20	1.00	10	Without toxicity
21	2.00	10	Without toxicity
22	3.00	7	Without toxicity
23	4.00	5	Without toxicity
24	2.00	3	Without toxicity
25	1.40	3	Without toxicity
26	1.60	11	Toxicity
27	3.00	7	Without toxicity
28	6.00	14	Without toxicity
29	1.50	12	Without toxicity
30	4.00	6	Without toxicity
31	2.00	9	Without toxicity
32	4.00	5	Toxicity
33	4.00	4	Without toxicity
34	3.00	10	Without toxicity
35	6.00	4	Without toxicity
36	2.00	6	Without toxicity
37	4.00	7	Without toxicity
38	6.00	7	Without toxicity
39	2.00	5	Without toxicity
40	2.00	4	Toxicity
41	1.00	5	Toxicity
42	2.00	5	Without toxicity
43	3.00	7	Without toxicity
44	3.00	4	Without toxicity
45	3.00	5	Toxicity
46	2.00	1	Without toxicity
47	1.50	3	Toxicity
48	4.00	7	Without toxicity
49	4.00	8	Without toxicity
50	2.00	3	Without toxicity

51	2.00	2	Without toxicity
52	2.00	1	Without toxicity
53	2.00	4	Without toxicity
54	4.00	7	Toxicity
55	9.00	1	Without toxicity
56	3.00	3	Without toxicity
57	4.00	1	Without toxicity
58	2.00	3	Toxicity
59	4.00	3	Toxicity
60	6.86	1	Without toxicity
61	2.00	1	Toxicity
62	3.00	4	Without toxicity
63	3.00	1	Without toxicity
64	3.00	1	Without toxicity
65	3.00	4	Without toxicity
66	6.00	7	Without toxicity
67	2.00	1	Without toxicity
68	2.00	10	Without toxicity
69	2.00	7	Without toxicity
70	2.00	10	Toxicity
71	3.00	5	Toxicity
72	2.00	11	Without toxicity
73	6.00	7	Without toxicity
74	4.00	2	Without toxicity
75	4.00	12	Without toxicity
76	6.00	7	Without toxicity
77	12.00	7	Without toxicity
78	2.00	3	Without toxicity
79	2.00	8	Without toxicity
80	3.00	14	Toxicity
81	6.00	7	Without toxicity
82	6.00	12	Toxicity
83	2.00	8	Without toxicity
84	6.00	13	Without toxicity
85	6.00	7	Without toxicity
86	6.00	17	Toxicity
87	6.00	7	Without toxicity
88	6.00	30	Without toxicity
89	6.00	7	Without toxicity
90	4.00	1	Without toxicity
91	6.00	7	Without toxicity
92	9.00	7	Without toxicity
93	6.00	5	Without toxicity
94	6.00	7	Without toxicity
95	6.00	7	Toxicity
96	2.00	14	Toxicity
97	9.00	7	Without toxicity
98	1.00	7	Without toxicity
99	9.00	7	Without toxicity
100	6.00	7	Toxicity

APPENDIX 2

GANTT CHART FOR RESEARCH ACTIVITIES

TITLE: USE OF COLISTIN IN INTENSIVE CARE UNIT IN HOSPITAL SERDANG AND HOSPITAL SG.BULOH AND ITS ASSOCIATION WITH NEPHROTOXICITY FROM 2010 UNTIL 2012.

TASK	WEEK 1 25/3	WEEK 2 4/4	WEEK 3 15/4	WEEK 4 16/4	WEEK 5-16 22/4	WEEK 17-19 15/7	WEEK 20 5/8	WEEK 21 – 22 12/8	WEEK 22-23 21/8	WEEK 24-25 6/9
Start of module										
Proposal draft preparation										
Proposal submission										
Preparation for proposal presentation										
Proposal presentation										
Correction of proposal										
Preparation of letters										
Submission of letter										
Data collection and data analysis										
Submission of analyzed data report										
Preparation of report of analyzed data										

TASK	WEEK 1 25/3	WEEK 2 4/4	WEEK 3 15/4	WEEK 4 16/4	WEEK 2 4/4	WEEK 17-19 15/7	WEEK 20 5/8	WEEK 21 – 22 12/8	WEEK 22-23 21/8	WEEK 24-25 6/9
Presentation of analyzed data										
Correction of data analysis										
Report wrinting										
Submission of project report and scientific article										
Preparation of final presentation										
Rehersal for final presentation										
Final Presentation										
Correction for final report and scientific article										
Submission of log book and final report										
Result										

APPENDIX 3

PROFORMA

1) **Colistin**

- Date of starting administration :
- Date of stopping administration:
- Duration :
- Route of administration : Intravenous / Aerosol
- Dosage :
- Indication of use : Pneumonia / Sepsis / Both pneumonia and sepsis / Others : _____

2) **Patient**

a) Registration no.:

b) Age :

c) Gender : Male / Female

d) Race : Malay / Chinese / Indian / Others : _____

e) Outcome : Survived / Deceased

3) **Laboratory Data**

a) Date :

b) Sample : Tracheal Aspirates / Blood / Urine / Others : _____

c) Bacteria isolated : *Pseudomonas aeruginosa* / *Acinetobacter baumannii* /*Klebsiella pneumoniae* / Others : _____

d) Sensitivity result : Sensitive / Resistant / No test

e) Renal Profile :

	Before	First day colistin administration	Peak creatinine level during colistin administration	After
Serum creatinine				

APPENDIX 4

RESEARCH TEAM

Supervisor	Dr Syafinaz Binti Amin Nordin Dept. of Microbiology syafinaz@medic.upm.edu.my
Co-Supervisor	Dr.Aidalina Binti Mahmud Dept. of Comunity of Health Aidalaina@medic.upm.edu.my
Leader	Wan Mazuan bt Wan Mahmud ; 162640
Members	Ling Siew Mei : 163921

APPENDIX 5

BUDGET PLANNING

Item	**Quantity**	**Price**
Photostating	400	RM 100
Printing	50	RM 50
Stationery	-	RM 50
Transportation	-	RM 50
TOTAL		**RM250.00**

PUSAT PENYELIDIKAN KLINIKAL,
HOSPITAL SUNGAI BULOH,
JALAN HOSPITAL, SUNGAI BULOH,
47000 SELANGOR DARUL EHSAN.
Tel: 03-6145 4333 samb: 5231 Faks: 03-6145 4222

Rujukan Kami :Bil (16)HSB/CRC/770/21/01/05
Tarikh :03 Jun 2013

Wan Mazuan Bin Wan Mahmud
Fakulti Perubatan dan Sains Kesihatan,
Universiti Putra Malaysia,
43400 UPM Serdang, Selangor.

Tuan,

PERMOHONAN UNTUK MENJALANKAN PENYELIDIKAN

Dengan hormatnya perkara di atas adalah dirujuk.

2. Pihak Pusat Penyelidikan Klinikal (CRC) telah menerima satu kertas kerja kajian, borang IA-HOD-IA serta surat permohonan menjalankan penyelidikan untuk projek penyelidikan bertajuk **" Use Of Colistin Among Patients In Intensive Care Unit In Hospital Serdang And Hospital Sg.Buloh And Its Associated Factors Of Nephrotoxicity From 2010 Until 2012".**

3. Sehubungan dengan itu pihak kami tidak mempunyai sebarang halangan ke atas perlaksanaan kajian ini. Untuk makluman, kajian ini telah didaftarkan secara online di *National Medical Research Register* (www.nmrr.gov.my) bagi memenuhi garis panduan penyelidikan Kementerian Kesihatan Malaysia (KKM) berdasarkan surat pekeliling Ketua Pengarah Kesihatan Malaysia Bil.9/2007 bertarikh 5 Sept 2008 dengan rujukan (1) dlm KKM/NIHSEC/03/0301-01.

4. Walaubagaimanapun, setelah mendapat kelulusan dari Pengarah Hospital Sungai Buloh, borang IA-HOD-IA serta dokumen-dokumen tertentu perlu dimuat naik ke laman NMRR sehingga lengkap, seterusnya diikuti dengan mendapat kelulusan Jawatankuasa Etika & Penyelidikan Perubatan (MREC).

5. Salinan surat kebenaran menjalankan kajian dari Jawatankuasa Etika & Penyelidikan Perubatan harus dikemukakan ke Pusat Penyelidikan Klinikal (CRC) untuk simpanan dan rujukan sebelum tuan/puan boleh menjalankan penyelidikan di Hospital Sungai Buloh.

Attachment 2

JKEUPM Ref No. : FPSK_Mei (13)29(undergraduate)

Members of the JKEUPM who reviewed the documents:

Prof. Dr. Zamberi Sekawi

Date of approval: 28/5/2013

Endorsed at JKEUPM Meeting on **7/6/2013**, attended by:

NAME	DESIGNATION	GENDER	TICK IF PRESENT
Prof. Dr. Norlijah Othman	Paediatrics& Dean, Faculty of Medicine and Health Sciences	Female	√
Prof. DrZamberiSekawi	Medical Microbiologist & Deputy Dean of Research and Internationalization, Faculty of Medicine and Health Sciences	Male	
Prof. Dato' Dr. Lye Munn Sann	Medical Statistician, Dept of Community Health, Faculty of Medicine and Health Sciences	Male	√
Prof. Dr. TengkuAizanAbd Hamid	Gerontologist & Director, Institute of Gerontology	Female	
Prof. Dr. LekhrajRampal	Medical Statistician, Dept of Community Health, Faculty of Medicine and Health Sciences	Male	√
Prof. Dr. Elizabeth George	Pathologist, Dept of Pathology, Faculty of Medicine and Health Sciences	Female	
Prof. Dr. Lim ThiamAun	Anesthesiologist, Dept of Surgery, Faculty of Medicine and Health Sciences	Male	
Prof. Dr. Wan Omar Abdullah	Medical Parasitologist, Dept of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences	Male	√
Prof. Dr. Patimah Ismail	Professor of Biomedicine, Dept of Biomedical Sciences, Faculty of Medicine and Health Sciences	Female	√
Prof. Dr. Azali Mohamed	Professor of Macroeconomics, Dept of Economics, Faculty of Economics and Management	Female	
Assoc. Prof. Dr. Johnson Stanslas	Pharmacologist, Dept of Medicine, Faculty of Medicine and Health Sciences	Male	√
Assoc. Prof Dr. Mansor Abu Talib	Assoc. Professor of Guidance and Counselling, Dept of Human Development and Family Studies, Faculty of Human Ecology	Male	
Assoc. Prof. Dr. Noritah Omar (Lay Person)	Assoc. Professor of English Language, Dept of English Language, Faculty of Communication and Modern Languages	Female	√
Dr. RojanahKahar (Lay Person)	Lecturer of Dept of Human Development and Family Studies, Faculty of Human Ecology	Female	√
Tan Sri Dato' Napsiah Omar (Lay Person)	Chairman, National Population and Family Development Board	Female	√

UNIVERSITI PUTRA MALAYSIA
BERILMU BERBAKTI

FAKULTI PERUBATAN DAN SAINS KESIHATAN
FACULTY OF MEDICINE AND HEALTH SCIENCES

Rujukan Kami : UPM/FPSK/(TDAP)600-3/1/3-(SPP3621)
Tarikh : 18 APRIL 2013

Ketua Uresetia NIH
Kementerian Kesihatan Malaysia
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit
Bangsar
59000 Kuala Lumpur

Melalui:

Dr Hayati Bte Kadir @ Shahar
Penyelaras
Projek & Kaedah Penyelidikan SPP3621
Program Perubatan Tahun 2
Fakulti Perubatan dan Sains Kesihatan
43400 Serdang
Selangor.

Dr,

MEMOHON KELULUSAN JAWATANKUASA ETIKA PENYELIDIKAN PERUBATAN KEMENTERIAN KESIHATAN MALAYSIA

Berhubung dengan perkara di atas, sekumpulan pelajar perubatan Tahun 2 Fakulti Perubatan dan Sains Kesihatan, Universiti Putra Malaysia (UPM) ingin menjalankan kajian bertajuk "Use of Colistin among patients in Intensive Care Unit in Hospital and Hospital Sungai Buloh and its associated factors of nephrotoxicity from 2010 until 2012". Kajian ini adalah bagi memenuhi keperluan kursus SPP3621 Projek Dan Kaedah Penyelidikan dalam Program Perubatan di Universiti Putra Malaysia.

2. Nama-nama pelajar yang terlibat dalam kumpulan ini adalah seperti berikut:

Nama	No. Matrik
Wan Mazuan bt Wan Mahmud	162640
Ling Siew Mei	163921

3. Pelajar-pelajar ini akan diselia oleh pensyarah dari Fakulti Perubatan dan Sains Kesihatan, yang terdiri daripada Dr. Syafinaz bt Amin Nordin dan Dr Aidalina bt Mahmud.

✉ Fakulti Perubatan dan Sains Kesihatan, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor Darul Ehsan.
✆ 603-8947 2300 🖷 603-8947 2585 🌐 http://www.medic.upm.edu.my.
✉ Fakulti Perubatan dan Sains Kesihatan, Aras 9 & 10B, Grand Seasons Avenue, 72, Jalan Pahang, 53000 Kuala Lumpur.
✆ 603-2050 1000 🖷 603-2050 1001