Incidence and Risk Factors of Acute Kidney Failure in Patients Receiving Colistin in a Provincial Hospital

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Abstract

The objectives of this study were to determine incidence and risk factors associated with acute kidney failure in patients receiving colistin. This study was a retrospective cohort study from medical records of patients who received colistin at Nakornping Hospital, Chiang Mai, during January 1, 2011 to December 31, 2013. The statistical analyses include descriptive statistic, multivariate analysis and Kaplan-Meier method. The results showed that most patients were male (65.7%) with the median age of 67 years (range of 19-95 years). The median value of serum creatinine was 0.9 mg/dl (range of 0.3-6.7 mg/dl). Approximately half of the patients (50.7%) received loading doses and 46% (171 pateints) of them received colistin more than 5 mg/kg/day. The study observed 262 patients (70.8%) developed nephrotoxicity with the median onset of 7 days (95% CI 6-7). Among the patients who experienced nephrotoxicity, the severity of acute kidney failure of 101 cases (27.3 %) were classified as "failure", 95 cases (25.7%) were classified as "risk" and 66 cases (17.8%) were classified as "injury". Multivariable analysis revealed the risk factors associated with acute kidney failure as follows: (1) age older than 70 years old (OR = 4.0; p = 0.001), (2) having diseases that may decrease renal blood flow (OR. = 2.1; p = 0.008), (3) receiving colistin more than 5 mg/kg/day (OR = 2.1; p = 0.007), and (4) co-administration of nephrotoxic drugs or drug affecting the glomuerulus filtration rate (OR = 1.8; p = 0.023). However, the patients with baseline serum creatinine more than 1.2 mg/dl appeared to have lower risk of acute kidney failure than the patients with the values of serum creatinine less than or equal to 1.2 mg/dl. This study showed high incidence (70.8%) of acute kidney failure in patients receiving colistin. Thus, renal functions should be closely monitored, especially in elderly patients, patients with diseases that may decrease renal blood flow, patients concurrently received nephrotoxic drugs or drug affecting the glomerular filtration rate. Besides, the patients' weight should be used to determine the appropriate colistin dose and adjusting dose should be performed based on the pateints' renal functions or avoiding the use of colistin doses greater than 5 mg/kg/day.

Keywords: colistin, acute kidney failure, nephrotoxicity

Introduction

Acute kidney failure is a serious complication that can be found in 7% of hospitalized patients (Nash, Hafeez, & Hou, 2002) and found more among critically ill patients (6-23%). It is also found that mortal rates among patients with acute kidney failure have gone up by 35 to 80%. (Pruchnicki & Dasta, 2002) The causes of acute kidney failure include a decrease in renal blood flow, infection, and exposure to nephrotoxic agent. Some examples of nephrotoxic agent are Contrast Media, NSAIDs (Non-Steroidal Anti-inflammatory Drugs), amphotericin B, aminoglycosides, cisplatin and colistin. (Dipiro et al., 2005)

Colistin is one of the polymyxin antibiotics produced from *Bacillus polymyxa* (Storm, Rosenthal, & Swanson, 1977) that has been used since 1949. However, because of its nephrotoxicity and the availability

of other more efficient and safer antibiotics, the use of colistin has decreased. Nevertheless, since currently more and more Gram-negative bacteria are resistant to many antibiotics, especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii* that are resistant to carbapenem (Thamlikitkul, 2008), colistin is being used again.

Colistin causes acute tubular necrosis renal failure (Falagas & Kasiakou, 2006) by increasing tubular epithelial cell membrane permeability causing an increased influx of cations, anions, and water. This change leads to leakage of cell contents and subsequent cell lysis. (Ko et al., 2010) Patients with this type of renal failure are reported to have an increase in serum creatinine (S_{cr}) and BUN while their urine output decreases. (Barlett, Auwaerter, & Pham, 2012) Recent studies have shown that colistin can lead to acute kidney failure in as many as 31.9 to 54.6% of the patients (DeRyke, Crawford, Uddin, & Wallace, 2010; Hartzell et al., 2009; Kim, Lee, Yoo, & Pai, 2009; Ko et al., 2010; Kwon et al., 2010; Pogue et al., 2011), and its nephrotoxic effects depend on the doses received. However, it is also found that the patients' renal function has recovered within one week to five months of discontinuation of colistin (Hartzell et al., 2009; Kim et al., 2009; Kwon et al., 2010) although some patients may need kidney replacement therapy. (Kim et al., 2009; Ko et al., 2010; Kwon et al., 2010) Nevertheless, there are still 4% of the patients whose kidney failure is irreversible. (Doshi, Mount, & Murphy, 2011) In most of the studies, acute kidney failure is evaluated according to Risk-Injury-Failure- Loss-End stage kidney disease criteria (RIFLE) to ensure that patients receive early and consistent diagnoses by using increased serum creatinine levels or decreased glomerular filtration rate. (Lopes & Jorge, 2013)

Recent studies show that high doses of colistin increase the risk of acute kidney failure. (DeRyke et al., 2010; Pogue et al., 2011; Rattanaumpawan, Ungprasert, & Thamlikitkul, 2011) Hence, suitable adjustment of doses according to patients' renal function will decrease this risk. (Kwon et al., 2010; Rattanaumpawan et al., 2011) Patients with chronic renal failure who have to take colistin are adviced to take suitable doses of colistin along with close monitoring of kidney function to avoid adverse drug reactions. (Kwon et al., 2010; Rattanaumpawan et al., 2011) Other factors include elderly (Rattanaumpawan et al., 2011) and concomitant of nephrotoxic drugs such as NSAIDs (Kim et al., 2009), diuretics (DeRyke et al., 2010), vancomycin (Rattanaumpawan et al., 2011), vasopressor (DeRyke et al., 2010), and rifampicin (Pogue et al., 2011).

High incident of nephrotoxicity using colistin results in longer period of hospitalisation and higher cost. However, currently colistin is the only drug effective for *Acinetobacter baumannii* (MDR) and there is still no other new drug substitutes for colistin. Although some studies reveal that there are several factors related to acute kidney failure from colistin, others show conflicting results such as doses, comorbidity disease. However, most of these studies were conducted abroad. Thus, this study intends to investigate the incident of and factors causing nephrotoxicity in patients using colistin at Nakornping hospital as well as changes in their serum creatinine levels in order to mornitor their drug use effectively.

Method

This retrospective cohort study collected data from medical records of 370 patients who had received colistin at Nakornping hospital, Chiang Mai from January 2011 to December 2013. Patients were $\geq$ 18 years old who had been receiving colistin for at least 24 hours for the first time. Patients whose weights and serum

creatinine had not been recorded in their medical records within 3 days before and after receiving the drug, as well as patients who received renal replacement therapy such as hemodialysis, peritoneal dialysis, and kidney transplant were excluded from the study.

After the data was collected, it was analyzed with G*Power software, version 3.1.9.2. The sampling parameters are medium effect size index (f^2) = 0.15, alpha = 0.05, power = 0.90 and variables = 6 (age, comorbidity disease, colistin dosing, concomitant nephrotoxic drugs, baseline serum creatinine and baseline albumin). The sample size was 123 patients

This study was approved by Nakornping hospital ethic committee: ที่ ว.0032.202/077, 26 june 2017

Statistical analysis

The data was analyzed with (1) Median and interquartile range (IQR) or N%, (2) logistic regression analysis which was used to explore risk factors of acte renal failure with p-value < 0.05, (3) Kaplan-Meier curves were used to assess the probability of acute kidney failure risk according to the duration of colistin treatmemt.

Acute kidney failure was defined by the RIFLE criteria according to serum creatinine or urine output (Lopes & Jorge, 2013) (Table 1)

Table 1 Definition of RIFLE criteria (Lopes & Jorge, 2013)

Class	GFR criteria	Urine output criteria
Risk	Serum Cr x 1.5 or GFR decrease >25%	<0.5 ml/kg/hour x 6 hours
Injury	Serum Cr x 2 or GFR decrease >50%	<0.5 ml/kg/hour x 12 hours
Failure	Serum Cr x 3, GFR decrease >75% or serum Cr >4 mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg/hour x 24 hours or anuria x 12 hours
Loss	Complete loss of kidney function >4 weeks	
ESKD	Complete loss of kidney function >3 months	

Results

From January 2011 to December 2013, 370 patients were included in the study. They were male 243 patients (65.7%). The median age of the patients was 67 years old (range 19-95 years). The median baseline serum creatinine was 0.9 mg/dl (range 0.3-6.7 mg/dl). The median dose of colistin was 5 mg/kg/day (range 0.5-10 mg/kg/day) and received a dose of colistin > 5 mg/kg/day 171 (46.2%) (Table 2)

Two hundred and sixty two patients (70.8%) developed nephrotoxicity. 197 patients (75.2%) had an occurrence of acute kidney failure within 7 days. Univariate analysis showed that characteristics or factors that increased the risk of acute kidney failure were (1) age 41-70 years old (OR=2.6; p=0.011) and > 70 years old (OR=3.4; p=0.001), (2) patients who had baseline serum creatinine > 1.2 mg/dl (OR=0.6; p=0.019), (3) decrease renal blood flow disease(OR=2.3; p=0.001), (4) patients who received colistin more than 5 mg/kg/day (OR=1.5; p=0.092), (5) patients concurrently received nephrotoxic drugs or drug affecting the glomerular filtration rate (OR=1.9; p=0.008), and (6) patients who had baseline serum albumin < 3.5 g/dl (OR=3.7; p=0.012) (Table 2)

Table2 Univariate analysis of risk factors for colistin-associated nephrotoxicicty (n=370)

characteristics	All patients [n(%)] (n=370)	Nephrotoxicity [n(%)] (n=262)	Non nephrotoxicity [n(%)] (n=108)	Crude OR (95% CI)	p-value
gender					
male	243 (65.7)	174 (66.4)	69 (63.9)	1.1 (0.7-1.8)	0.642
female	127 (34.3)	88 (33.6)	39 (36.1)	1.0	
age (years)					
≤ 40	37 (10.0)	18 (6.9)	19 (17.6)	1.0	
41-70	178 (48.1)	126 (48.1)	52 (48.2)	2.6 (1.2-5.3)	0.011
> 70	155 (41.9)	118 (45.0)	37 (34.26)	3.4 (1.6-7.1)	0.001
Median (min-max)	67.0 (19.0-95.0)	69.0 (20.0-94.0)	63.0 (19.0-95.0)		0.011[a]
Baseline serum creatinine					
≤1.2 mg/dl	268 (72.4)	199 (76.0)	69 (63.9)	1.0	
>1.2 mg/dl	102 (27.6)	63 (24.0)	39 (36.1)	0.6 (0.3-0.9)	0.019
Median (min-max)	0.9 (0.3-6.7)	0.8 (0.3-3.3)	1.0 (0.4-6.7)		0.065[a]
Comorbidity disease					
Decrease renal blood flow disease[b]	136 (36.8)	110 (42.0)	26 (24.1)	2.3 (1.4-3.8)	0.001
CRF and DM or CRF and HT	39 (10.5)	24 (9.2)	15 (13.9)	0.6 (0.3-1.2)	0.181
Dose of colistin (mg/kg/day)					
< 2.50	41 (11.1)	15 (5.7)	26 (24.1)	0.2 (0.1-0.5)	<0.001
2.5-5.0	158 (42.7)	112 (42.7)	46 (42.6)	1.0	
> 5.0	171 (46.2)	135 (51.5)	36 (33.3)	1.5 (0.9-2.5)	0.092
Median (min-max)	5.0 (0.5-10.0)	5.2 (0.5-10.0)	4.3 (1.3-8.6)		<0.001[a]
loading dose	186 (50.27)	130 (49.62)	56 (51.85)	0.9 (0.6-1.4)	0.696
Concomitant 8 nephrotoxic drugs[c]	256 (69.2)	192(73.3)	64(59.3)	1.9 (1.2-3.0)	0.008
Baseline serum albumin (n= 154)					
<3.5 g/dl	136 (88.3)	112 (91.8)	24 (75.0)	3.7 (1.3-10.4)	0.012
≥3.5 g/dl	18 (11.7)	10(8.2)	8 (25.0)	1.0	
Baseline serum total bilirubin (n = 85)					
<1.2 mg/dl	55 (64.7)	48 (69.6)	7 (43.8)	1.0	
≥1.2 mg/dl	30 (35.3)	21 (30.4)	9 (56.3)	0.3 (0.1-1.0)	0.058

CRF, chronic renal failure; DM, diabetes mellitus; HT, hypertension

[a] Mann-Whitney U test

[b] septic shock or cirrhosis with acute kidney failure or congestive heart failure

[c] concomitant of 8 nephrotoxic drugs or drug affecting the glomuerulus filtration rate such as Aminoglycosides, Amphotericin B, Vancomycin, Contrast media, Nsaids, ACEIs/ARBs, Furosemide, Rifampicin

Multivariate logistic regression analysis revealed the risk factors associated with acute kidney failure as follows: (1) age more than 70 years (OR=4.0; p=0.001), (2) having diseases that may decrease renal blood flow (OR. = 2.1; p = 0.008), (3) receiving colistin more than 5 mg/kg/day (OR = 2.1; p = 0.007), (4) co-administration of nephrotoxic drugs or drug affecting the glomuerulus filtration rate (OR = 1.8; p = 0.023), and (5) baseline serum creatinine lower than 1.2 mg/dl (OR=0.5; p=0.037) (Table 3)

Table 3 Multivariate analysis of risk factors for colistin-associated nephrotoxicicty (n= 370)

characteristics	Adjust OR	95% CI	p-value
Age - 41-70 years	2.5	1.2-5.4	0.017
- > 70 years	4.0	1.8-8.8	0.001
Baseline serum creatinine > 1.2 mg/dl	0.5	0.3-0.9	0.037
Decrease renal blood flow disease[a]	2.1	1.2-3.7	0.008
Dose of colistin > 5 มก./กก./วัน	2.1	1.2-3.7	0.007
Concomitant 8 nephrotoxic drugs[b]	1.8	1.1-3.1	0.023

[a] septic shock or cirrhosis with acute kidney failure or congestive heart failure

[b] concomitant of 8 nephrotoxic drugs or drug affecting the glomuerulus filtration rate such as Aminoglycosides, Amphotericin B, Vancomycin, Contrast media, Nsaids, ACEIs/ARBs, Furosemide, Rifampicin

The incidence of acute kidney failure associated with colistin was determined using RIFLE criteria by serum creatinine found that "Failure" 27.3%, "Risk" 25.7% and "Injury" 17.8%. (Table 4)

Table 4 the severity of acute kidney failure by RIFLE criteria (n=370)

severity	**N (%)**
Non nephrotoxicity	108 (29.2)
Risk	95 (25.7)
Injury	66 (17.8)
Failure	101 (27.3)
Loss	0 (0.0)
End stage	0 (0.0)

The patients developed acute kidney failure within 48 hours after colistin use 10.7% and survival time of acute kidney failure 7 days (95%: CI 6-7) (Figure 1)

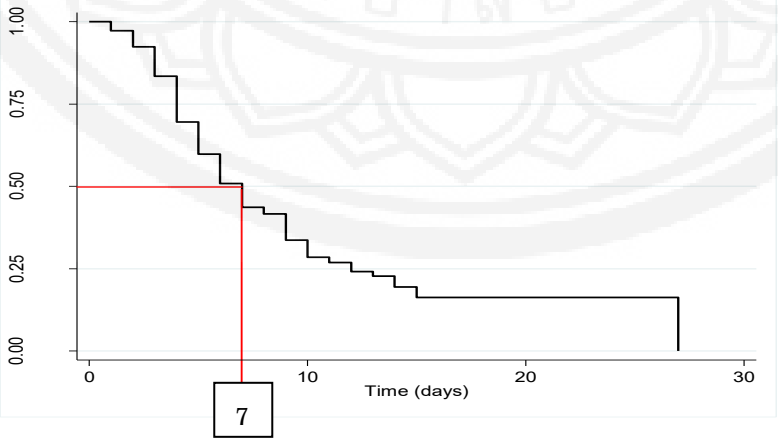

Figure 1 Probability of acute kidney failure based on duration of colistin use

Dicussion

The total number of patients in this study was 370. 243 of them were male (65.7%). The median age of the patients was 67 years old (range 19-95 years). The median baseline serum creatinine was 0.9 mg/dl (range 0.3-6.7 mg/dl). 50.27% received a loading dose and 171 patients (46.2%) received a dose of colistin more than 5 mg/kg/day. It was found that 262 patients exhibited acute kidney failure with an onset of 7 days (95%CI 6-7). These patients were in the Risk (25.7%), Injury (17.8%) and Failure (27.3%). The multivariate analysis of risk factors for colistin nephrotoxicity showed that the age of more than 70 years old (OR = 4.0; p = 0.001), decrease renal blood flow disease (OR = 2.1; p = 0.008), receiving more than 5 mg/kg/day of colistin (OR = 2.1; p = 0.007) and co-administration of nephrotoxic drugs or drug affecting the glomuerulus filtration rate (OR = 1.8; p =0.023) increased the risk of acute kidney failure in patients who received colistin. However, the study revealed that patients with more than 1.2 mg/dl of serum creatinine had lower risk of acute kidney failure than patients with less than or equal to 1.2 mg/dl of serum creatinine.

The incidence of acute kidney failure in this study was 70.8%, which was a lot higher than other studies. In other countries, the incidence was between 31.9 and 54.6% (DeRyke et al., 2010; Hartzell et al., 2009; Kim et al., 2009; Ko et al., 2010; Kwon et al., 2010; Pogue et al., 2011). In Thailand, the incidence was between 30.8 and 52.5% (Koomanachai, Tiengrim, Kiratisin, & Thamlikitkul, 2007; Rattanaumpawan et al., 2011). This might be due to the difference in how each study defined acute kidney failure. The studies that had high incidence of acute kidney failure (43.0 - 54.6%) tend to define acute kidney failure according to RIFLE criteria (Hartzell et al., 2009; Ko et al., 2010; Pogue et al., 2011). Moreover, this study collected the data from patients who had been receiving colistin for at least 24 hours while some studies collected the data from patients who had been receiving colistin for more 72 hours (Gauthier et al., 2012; Hartzell et al., 2009; Kwon et al., 2010) and other studies excluded patients who exhibited acute kidney failure within 2 days after administration of colistin (Kwon et al., 2010). Due to this study had high incidence than other study.

The data analysis using the Kaplan-Meier method showed that the median onset of acute kidney failure was 7 days (95% CI: 6-7). There were 197 patients (75.2%) who had acute kidney failure within 7 days and 65 patients (24.8%) had acute kidney failure after 7 days, which was in accordance with other studies, where most patients exhibited acute kidney failure within the first week (58.9-78.0%) of colistin administration more than the second week (22.0-30.1%) (Ko et al., 2010; Pogue et al., 2011; Rattanaumpawan et al., 2011).

The multivariate analysis of factors that might increase the risk of acute kidney failure from colistin showed that age, decrease renal blood flow disease, and baseline serum creatinine, dose, and concomitant nephrotoxic drugs were factors that associated with colistin acute kidney failure. It was found that older age increased the risk of acute kidney failure. For example, the patients who were 41-70 years old were 2.5 times as risky as those who were 40 years old or younger (p = 0.017), and patients who were more than 70 years old were 4 times as risky as those who were 40 years old or younger (p = 0.001). This was because of the decrease of renal function according to the increase of age, which was in accordance to previous studies, which found that patients who were more than 70 years old were at risk of renal failure from receiving colistin (Kim et al., 2009) and Deryke's study which found that patients who exhibited acute kidney failure were averagely older

than patients who did not exhibit acute kidney failure (57±15.5 years and 43.3±16.5 years; p=0.033) (DeRyke et al., 2010).

As for comorbidity disease, it was found that decrease renal blood flow disease, such as septic shock, cirrhosis with acute kidney failure and congestive heart failure, were 2.1 times as risky of having acute kidney failure as those who did not have these diseases (p = 0.008). This might cause prerenal acute kidney failure because of decrease renal blood flow disease, For example; septic shock, congestive heart failure, cirrhosis and hepato-renal syndrome (Garcia-Tsao, Parikh, & Viola, 2008; Handin et al., 2005; Plataki et al., 2011). Therefore, patients with various conditions were an increased risk of acute kidney failure.

Patients whose serum creatinine levels were more than 1.2 mg/dl were found to be twice less likely to have acute kidney failure than patients with creatinine levels were less than or equal to 1.2 mg/dl (p = 0.037). This might be due to the adjustment of dose according to their kidney function and closely monitoring, which might have reduced the risk of acute kidney failure. Moreover, patients with serum creatinine levels were more than 1.2 mg/dl would receive a smaller daily dose per kg of body weight than patients with serum creatinine levels were less than or equal to 1.2 mg/dl. This was in accordance with the results of this study that a larger dose per kg of body weight resulted in a higher risk of acute kidney failure. This study found that among patients whose serum creatinine levels were more than 1.2 mg/dl had monitoring serum creatinine 5-7 times/week more than patients with serum creatinine levels were less than or equal to 1.2 mg/dl (43.1% and 16.4%). Whereas Koomanachai's study found that kidney function deficiency was the risk factor of acute kidney failure (Koomanachai et al., 2007).

In addition, patients who received dose of colistin more than 5 mg/kg/day were 2.1 times more likely to have acute kidney failure (p = 0.007), which was in accordance with previous studies which confirmed that the dose of colistin was related to the incidence of acute kidney failure (DeRyke et al., 2010; Pogue et al., 2011; Rattanaumpawan et al., 2011). Especially the dose more than 5 mg/kg/day. It was found that the dose larger than those recommended by ABX Guide 2012 (Barlett et al, 2012) increased the risk of acute kidney failure 1.5 times (p = 0.156). On the other hand, the dose smaller than the recommended dose decreased the risk of acute kidney failure 0.5 times (p = 0.067) (not show data). This was in accordance with previous studies which found that patients with kidney function deficiency or chronic kidney disease could receive colistin without having acute kidney failure if suitable dose of colistin was used (Kwon et al., 2010; Rattanaumpawan et al., 2011). Although low dose of colistin could reduce the risk of acute kidney failure, some studies found that it resulted in higher death rate among patients (Gauthier et al., 2012). Similarly, this study found that 53.7% of patients died after they received less than 2.5 mg/kg/day, and 29.7 % and 38.0 % of patients died after they received 2.5-5 mg/kg/day and more than 5 mg/kg/day of colistin, respectively. This was because large dose of colistin increased the risk and severity of acute kidney failure, but small dose of colistin increased the risk of treatment failure as well as resistance of gram negative bacteria (Vicari, Bauer, Neuner, & Lam, 2013). Thus, both the suitable dose and the result of treatment must be taken in to consideration. Furthermore, this study found that there was no relation between loading dose and acute kidney failure (OR=0.9, p 0.694).

When the ideal body weight (IBW) was used to calculate the suitable dose, it was found that the dose more than 5 mg/kg (IBW)/day resulted in an increase of nephrotoxicity by 13.2 times (DeRyke et al., 2010) และ 23.4 times (Pogue et al., 2011). Thus, it was recommended that the patient's IBW should be

used to calculate the suitable dose for each patient. Since this study was a retrospective study and the heights of a lot of patients were missing, the IBW cannot be calculated. However, most of the patients in this study were not overweight. The male patients' average actual body weight was 55.85 ± 11.72 kg and the female patients' average actual body weight was 46.70 ± 11.38 kg.

Nevertheless, in some studies there was no increase in nephrotoxicity when the dose more than 5 mg/kg/day, but an increase in cumulative dose resulted in an increase of nephrotoxicity (Hartzell et al., 2009; Kwon et al., 2010) when the cumulative dose per the patient's body weight (mg/kg) (Kwon et al., 2010) including the total cumulative dose (g) (Hartzell et al., 2009). It was found that the patients who developed nephrotoxicity had received higher cumulative dose of colistin than those who did not, so patients who had received colistin for a long time would developed nephrotoxicity, contrast with onset of acute kidney failure. Most cases of acute kidney failure occur in the first week rather than the second week. (Ko et al., 2010; Pogue et al., 2011; Rattanaumpawan et al., 2011)

Moreover, co-administration of nephrotoxic drugs might increase the risk of acute kidney failure among the patients. 8 nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, ACEIs/ARBs, furosemide, amphotericin B, vancomycin, contrast media, rifampicin (Cramer et al., 1985; Hock & Anderson, 1995; Mingeot-Leclercq & Tulkens, 1999) were found to increase the risk of acute kidney failure by 1.8 times ($p = 0.023$)

Limitations of this study are that (1) there was no estimate glomerular filtration (eGFR) recorded in the patients records, so the severity of chronic and acute kidney failure could not be analyzed, (2) there was no duration to concomitant nephrotoxic drugs used because long time use nephrotoxic drugs will increase the risk of acute kidney failure, (3) patients who had baseline serum albumin were too small to be analyzed by multivariate and (4) there was no data urine output, therefore the severity of acute kidney failure could not be assessed by urine output.

It can be seen that the incidence of acute kidney failure was high, and occurred mostly within the first week. Furthermore, the factors that increased the risk of renal failure were the age of more than 70 years, the dose more than 5 mg/kg/day, decrease renal blood flow disease and co-administration of nephrotoxic drugs or drug affecting the glomuerulus filtration rate. Since colistin is usually the last choice for cure gram negative bacteria, but it is very likely to cause acute kidney failure, so there should be closely monitoring of kidney function, weighing every patient to calculate the suitable dose, and adjustment of dose according to the kidney function.

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