Local experience on use of Colistin in ICU

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Introduction

- Colistin: Colistimethate Sodium (pro-drug), Polymyxin E
- Mechanism: A cyclic polypeptide
 Binds to lipopolysaccharides and phospholipids in the outer cell membrane of GNB
 - → Disruption of cell membrane
 - → Leakage of intracellular contents
 - → Bacterial death
- Available for clinical use since 1950s
- Had fallen out of favor due to its side effect and emerge of other antibiotics

Coly-mycin

Manufacturer: Parkdale Pharmaceuticals

Colistin base: in mg

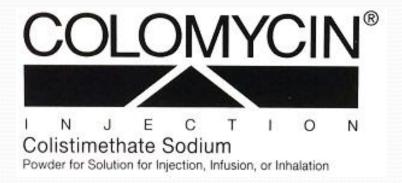
150mg 'colistin base' = 360mg colistimethate or 4,500,000units



Colomycin

Manufacturer: Axellia International units

imU = 8omg
colistimethate



Suggested dosage of Colomycin

Recommended dosage	Dosage	Interval
BW up to 6okg	0.05 – 0.075 mU/kg/day	Q8H
BW > 60kg	1 – 2 mU	Q8H

Suggested adjustment in renal impairment

Grade	CrCl (ml/min)	Over 6okg BW
Mild	20-50	1-2mU Q8H
Moderate	10-20	1mU Q12-18H
Severe	<10	1mU Q18-24H

Colistin

- Contraindications:
 - Hypersensitivity to colistin or polymyxin B
 - Myasthenia Gravis
- Drug interactions:
 - Suggested to avoid neurotoxic and nephrotoxic agents
 - May increase risk of nephrotoxicity with cephalosporin

Usage of Colistin in critically ill patients in Hong Kong

Local study

- Retrospective observational study
- Adult ICUs in HK, age ≥ 18
- Admitted from 1st Jan 2010 to 31st Dec 2012
- Received colistin during their ICU stay
- Objectives:
- 1. To review the bacteriology triggering colistin therapy
- 2. To review their LOS and mortality
- 3. To review their change of RFT

Acute	e Kidney Injury: RIFLE	classification
Class	Serum Cr or GFR criteria	Urine output criteri

353 umol/L

 $< 0.5 \text{ ml/kg/hr} \times 6 \text{ hrs}$

 $< 0.5 \text{ ml/kg/hr} \times 12 \text{ hrs}$

< 0.3 ml/kg/hr \times 24 hrs,

Hoste et al. Critical Care 2006

or anuria × 12 hrs

Serum creatinine \times 1.5

GFR decrease > 25%

Serum creatinine × 2

GFR decrease > 50%

Serum creatinine \times 3,

GFR decrease > 75%

Acute kidney injury should be both abrupt (within 1–7)

months

days) and sustained (more than 24 hours)

an acute rise > 0.5 mg/dl

kidney function > 4 weeks

End-stage kidney disease > 3

or serum creatinine ≥ 4 mg/dl with

Persistent ARF = complete loss of

Risk

Injury

Failure

Loss

End-stage

kidney

disease

Number of cases received colistin

- Hospital A: 150
- Hospital B: 57
- Hospital C: 44
- Hospital D: 20
- Hospital E: 19
- Hospital F: 12
- Hospital G: 11
- Hospital H: 10

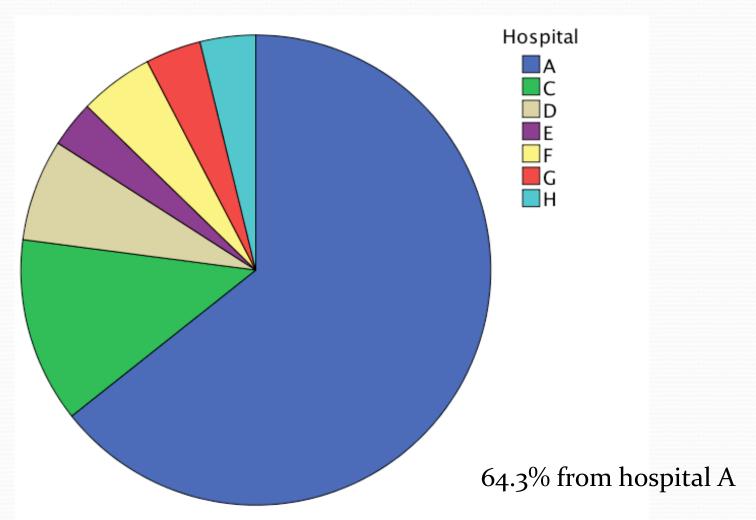
- Hospital I: 6
- Hospital J: 3
- Hospital K: 3
- Hospital L: 2
- Hospital M: 1
- Hospital N: 1
- Total: 14 ICUs
- 337 cases

Cases received colistin during ICU stay

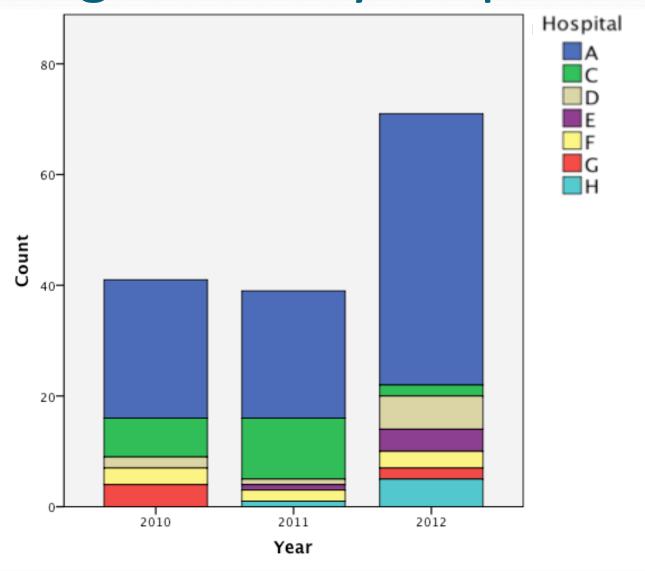
- Hospital A: 150 -> 101
- Hospital B: 57 -> ?
- Hospital C: 44 -> 20
- Hospital D: 20 -> 11
- Hospital E: 19 -> 5
- Hospital F: 12 -> 6
- Hospital G: 11 -> 8
- Hospital H: 10 -> 6

- Hospital I: 6 -> 3
- Hospital J: 3
- Hospital K: 3
- Hospital L: 2
- Hospital M: 1
- Hospital N: 1
- Total 14 ICUs -> 7 ICUs
- 337 cases -> 157 cases

Contribution of cases by different ICUs



Usage over 3-year period



Patient characteristics (Preliminary data)

- Gender M:F = 2.27:1
- Age: 18 89
 - Mean age = 60.7 + / 15.7
- Parent Specialty
 - Med: 44.6%
 - Surg: 46.6%
 - Including Gen Surg, Urology, CTS, NS, ENT
 - O&T: 6.4%
 - O&G: 0.6%
 - Oncology: 0.6%

Patient characteristics (Preliminary data)

- OAHR: 5.1% (8 cases)
- DM: 32.8%
- Chronic renal impairment: 15.8%
- Chronic renal failure on dialysis: 5.7%
- APACHE II: 24.6 +/- 9.1
- APACHE IV: 91.5 +/- 35.0

Microbiology results

Micro-organisms in related to colistin treatment

Micro-organisms	n	%
Acinetobacter 'Carbapenem resistant' 'Ampicllin/Sulbactam sensitive'	110 (106) (4)	70.1%
Pseudomonas	21	13.4%
Stenotrophomonas	3	1.9%
ESBL Klebseilla	4	2.5%
ESBL E coli	1	0.6%
Enterobacter	1	0.6%
No growth	9	5.7%
Other (eg., CNS, candida)	8	5.1%
Total	157	100

Type of specimens

Respiratory

Blood

tissue

Urine

Skin ulcer

IV catheter

(Sputum, TA, BAL)

Surgical wound, drain or

Other (bile, pleural fluid,

CSF, aspirate of cyst, etc)

. 7 5 5 . 5 5				
Specimen	n	% of patient	Acinetobcter (MDR)	Pseudomonas

102

27

26

4

2

3

7

+ve culture in > 1 site in 18.5% (29) of patients

65.0

17.2

16.6

2.5

1.3

1.9

4.5

79

17

16

3

2

2

4

16

3

1

0

1

1

Respiratory C	ulture :-			
	: Acinetobacter : Proteus speci	baumannii (heavy) es (scanty)		
	ANTIBIOTICS	23.6% cases had mo		n M
Different hospitals report different antibiotic panels	Amikacin Amoxicillin + Ampicillin Ampicillin + s Cefoperazone + Ceftazidime	ulbactam	R R R	S M R
	Ceftriaxone Cefuroxime(iv) Cephalothin Ciprofloxacin		R	S M R
	Co-trimoxazole Gentamicin Imipenem Levofloxacin		R R R	R R S
	Piperacillin Piperacillin + Ticarcillin + Tobramycin		R R R	

红: ICU重症监护室床号: 1202 病历号: 0051342 行: 气短 采集部位: 合格 备注: 样本类型:痰

3结果: 鲍氏不动杆菌

20. 9.4	抗生素	敏感性	MIC (ug/ml)	成人剂量(建议)	血药浓度 (ug/ml)	尿药浓度 (ug/ml)
М	氨苄西林+舒巴坦	中介 I	16	IV3000(2000mg 氨苄)	109-150	1000mg 舒巴坦
C.	替卡西林+棒酸	耐药 R	>16	IV 3.1-3.2gms >30分钟	330替卡西林 8-16棒酸	
7	哌拉西林+他唑巴坦	耐药 R	>16	IV 3.375gm.	240	
ίΙ	亚胺培南	耐药 R	>8	IV 500mg	40	100
1Z	头孢他啶	耐药 R	>16	IV 1000mg	60	4000-6000
EN	庆大霉素	耐药 R	>8	IM 1.25mg/kg.	5-7	>=100
IP	环丙沙星	耐药 R	>2	PO 500mg.	2. 0	300
EV	左旋氧氟沙星	耐药 R		*		
F.	舒普深	敏感 S	*			
SU	复方新诺明	耐药 R	>38	PO 80mgT/400mgS IV 160mgT800mgS	1-3T/20-50S 3-9T/45-100S	58-761/975
80	头孢曲松	耐药 R		IV 1000mg	150	995
L	多粘菌素 E	敏感 S	≤2			
	妥布霉素	耐药 R	>8	IV 2. Omg/kg.	3. 1-14	322
Я	阿米卡星	耐药 R	>32	IV 7.5mg/kg.	38	
RO .	美洛培南	耐药 R	>8			
•	头孢吡肟	耐药 R	>16	IV 2mg	193	
C	哌拉西林	耐药 R	>16			保? 0耐药
						MIC: >16 用量1: IV 4000mg>30分 用
С.	替卡西林	耐药 R	>16	IV 3000mg>2小时	140	#92000

		CU重症监护室床号	: 1202	病历号	: 0051342		合格	羊本类型:痰
	F: ⁴ 3结!	_	ir.			备注:		
	2207				;			
		抗生素	etobacte 敏	er baun 感性			血药浓度	尿药浓度
Unasyn		3/0-12/19		((ug/ml)		(ug/ml)	
	М	氨苄西林+舒巴坦	中介	I 16	IV	3000(2000mg 氨苄)	109-150	1000mg 舒巴坦
Timentin	:C	替卡西林+棒酸	耐药	R >1		3.1-3.2gms O分钟	330替卡西林 8-16棒酸	
Tazocin	7	哌拉西林+他唑巴坦	耐药	R >1		3. 375gm.	240	
Imipenem	íI.	亚胺培南	耐药	R >8	B IV	500mg	40	100
Ceftazidime	4Z	头孢他啶	耐药	R >1	.6 IV	1000mg	60	4000-6000
Gentamicin	EN	庆大霉素	耐药	R >8	. IM	1.25mg/kg.	5-7	>=100
Ciprofloxacin	IP	环丙沙星	耐药	R >2	PO	500mg.	2. 0	300
Levofloxacin	EV	左旋氧氟沙星	耐药	R				
Sulperazon	(CF	舒普深 _	敏感	s	•			
Septrin	SU	复方新诺明	耐药	R >3		80mgT/400mgS 160mgT800mgS	1-3T/20-50S 3-9T/45-100S	58-761/975
Ceftriazxone	RO	头孢曲松	耐药	R	IV	1000mg	150	995
Colistin	OL	多粘菌素 E	敏感	S ≤2		,		
Tobramycin		妥布霉素	耐药	R >8	IA	2. Omg/kg.	3. 1-14	322
Amikacin	Κ.	阿米卡星	耐药	R >3	2 IV	7.5mg/kg.	38	
Meropenem	"ERO	美洛培南	耐药	R >8				
Cefepime	PEP	头孢吡肟	耐药	R >1	6 IV	2mg	193	
Pipercilline	PIC	哌拉西林	耐药	R >1	6			No and the
-								髁? e耐药 MIC:>16 用量1:IV 4000mg>30分 用
Ticarcilline	TIC	替卡西林	耐药	R >1	6 IV	3000mg>2小时	140	#92000

Various definitions o Does not exit in this column

Multi-drug resistant (MDR)

Definitions

Resist to at lease 3 classes of drugs:

- 1. All cephalosporins and inhibitor combination
- 2. Fluroquinolones
- 3. Aminoglycosides

Therapeutic options

Carbapenems **Polymyxins**

Sensitive to Carbapenems

J Glob Infect Dis. 2010

Various definitions of 'MDR' Acinetobacter

Multi-drug resistant (MDR)

Sensitive to at least one class

classes of drugs:

- All cephalosporins and inhibitor combination
- 2. Fluroquinolones
- 3. Aminoglycosides

Therapeutic options

Definitions

Carbapenems Polymyxins Extensively-drug resistant (XDR)

MDR Acinetobacter

+

Resistant to \ Carbapenems

Polymyxims

Tigecycline

Pan-drug resistant (PDR)

XDR Acinetobacter

+

Resistant to Polymyxins

??Combination

J Glob Infect Dis. 2010

Carbapenem-Resistant Acinetobacter baumannii

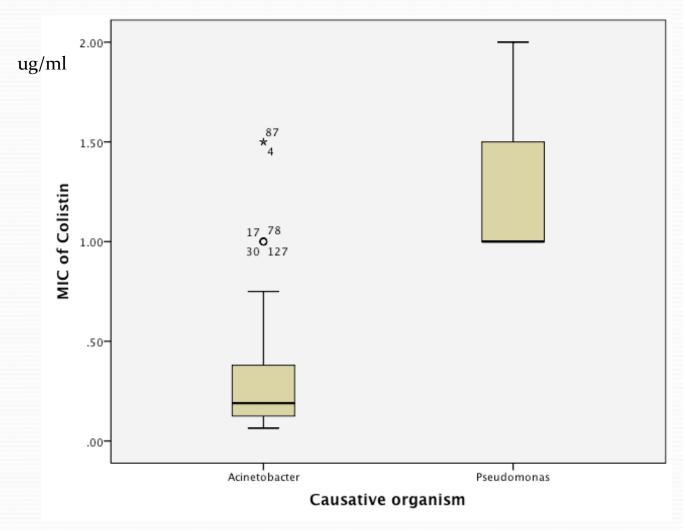
Sensitivity			
Antibiotics	Sensitive	Intermediate	Resistant
Gentamicin	13.7%	1.1%	85.7%
Amikacin	32.3%		67.7%
Cefoperazon/Sul bactam	6.5%	40.9%	52.7%
Fluoroquinolone	4.2%	2.1%	93.7%

Pseudomonas

Sensitivity, Pseudomonas (n=21)

Anitbiotics	Sensitive	Intermediate	Resistant
Carbapenems (n=21)	19%	4.8%	76.2%
Gentamicin (n=21)	85.7%	4.8%	9.5%
Amikacin (n=11)	81.8%		18.2%
Cefoperazon/Sulbacta m (n=17)		23.5%	76.5%
Fluoroquinolone (n=21)	52.4%	9.5%	38.1%

Different in MIC between Acinetobacter and Pseudomonas



Use of Colistin

Dosage, interval, route

- Dosage range: 0.5 2mU
 - Mostly 1mU (86.1% of cases)
- Interval range: every 8 48 hours
 - Q8H: 47.3%
 - Q12H: 42.0%
- All cases had received colistin intravenously
- 4 cases were given IV + inhalation

Duration of treatment

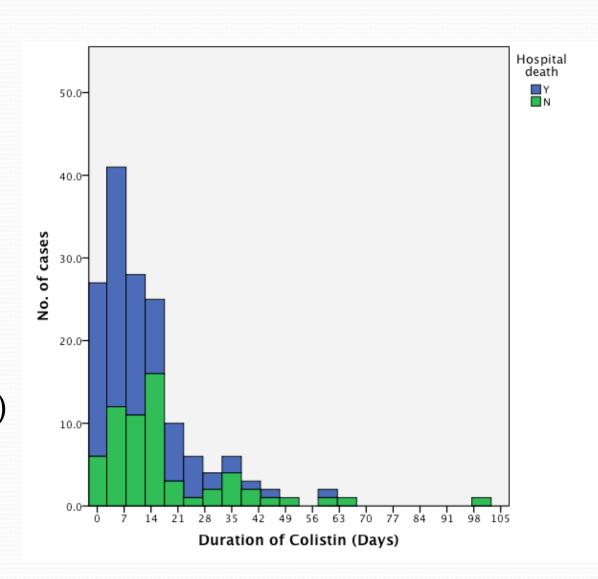
Range: 0-99 days

Mean: 13.4 +/- 14.4

70% cases < 2 weeks

80% cases < 3 weeks

Most common cause of termination: patient died (47.8%)



Recorded possible side effect, apart from nephrotoxicity

- 2 cases stopped because of skin rash
- 1 case stopped because of thrombocytopenia
 - Plt dropped to 85
 - Plt increased after change to tigecycline

Combination therapy

Combination therapy	38.9%

15.9%

Rifampicin 8.3%

Tigecycline 3.8%

Fluroquinolone 3.8%

Co-trimoxazole 0.6%

Cefoperazon/Sulbactam 0.6%

Other 5%

In-hospital mortality:

for combination therapy 60.4%

for monotherapy 39.6% (p=0.008)

Concurrent nephrotoxic agents

- Aminoglycosides
- Vancomycin
- IV contrast
- Amphotericin B
- ACEI / ARB
- NSAIDs
- Cyclosporin A

- 87.8% patients received at least one of these drugs, either before or during colistin treatment
- 93.9% if frusemide is also regarded as nephrotoxic

Patient outcome

Outcome: LOS and Mortality

ICU length of stay (mean) o - 349 days (26.5 + / - 37.8)

Hospital length of stay (mean) 3 - 410 days (57.1 + / - 51.5)

ICU mortality 40.1%

In-hospital mortality 59.1%

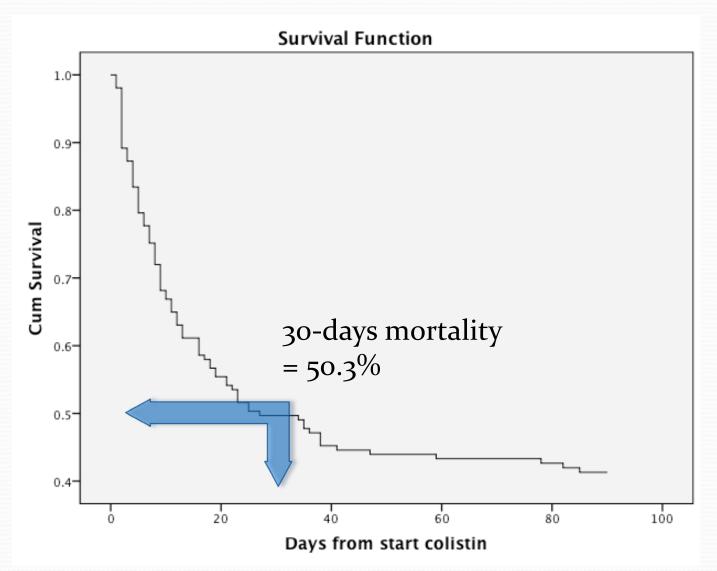
Carbapenam-resistant 58.5%

Acinetobacter

Pseudomonas 71.4%

Positive blood culture 74.1%

Survival



APACHE scores and mortality

		Alive on ICU discharge	
APACHE II	26.9 +/- 9.8	23.1 +/- 8.3	P = 0.024
APACHE IV	100.8 +/- 40.2	85.3 +/- 29.8	P = 0.021

	In-hospital death	Survivors	
APACHE II	26.3 +/- 9.0	21.8 +/- 8.6	P = 0.006
APACHE IV	98.4 +/- 35.9	80.3 +/- 30.9	P = 0.003
Age	61.8 +/- 14.9	59.9 +/- 16.2	P= 0.46

	Carbapenem- resistant Acinetobacter	Pseudomonas	Other Multi- drug Resistant Organism
Total cases	106	21	9
Survived > 14 days after stopped colistin	49 (46.2%)	6 (28.6%)	4
Among these survivors			
Clearance of organisms	25 (51.0%) N.B. 4 cases had recurrence	1 (6.3%)	2 (50%)
Failed to clear	20 (40.8%)	4	
No repeated culture	4	1	

No colistin resistance case was identified

after treatment

Change of renal function

Number of patients with possible AKI

157

• 22 patients: Died within 48H of start colistin

135

106

- 29 patients: Required RRT both before and after colistin
- 65 patients (61.3%): No lab evidence of AKI
 - Cr < 1.5 folds
- 41 patients (38.7%):
 - 7 patients: Required RRT after started colistin
 - 34 patients: Cr > 1.5 folds from baseline

For 41 patients with 'AKI' by predefined criteria

34 patients: Cr > 1.5 folds increase.

- 14: Cr 1.5 2 folds
- 17: Cr 2 3 folds
- 3: Cr > 3 folds

No RRT required

7 patients: Required RRT after commencement of colistin

- 6 hospital death
- 1 survivor:
 - Recovered in renal function
 - Not required RRT while still on colistin

Average days to peak Cr: 12.0 +/- 8.7

Baseline Serum Creatinine and age in related to AKI

	AKI group (n=41)	No AKI group (n=60)	P
Baseline Creatinine (umol/L)	111.4 +/- 91.9	130.7 +/- 133.0	0.441
Peak Creatinine while on colistin (umol/L)	218.6 +/- 180.1	137.6 +/- 134.6	0.019
	A TZT	NT ATZT	
	AKI group (n=41)	No AKI group (n=60)	p
Age	64.1 +/- 14.3	57.6 +/-16.1	0.033

Compared with other studies

Renal and neurological side effects of colistin in critically ill patients. Spapen et al. Annals of Intensive Care 2011, 1:143

Table 1 Dosage, duration, outcome, and toxicity of intravenous colistimethate sodium in critically ill patients

Author	Patients (N)	APACHE II (mean ± SD)	CMS dose/duration [mean ± SD or median (range)]	Clinical cure N (%)	Nephrotoxicity N (%)	Neurotoxicity
26 stud		13.1 ± 7	152.8 mg ± 62.8 mg 12.6 ± 6.8 days	35 (58.3)	22 (37)	none
Markou Loc	infections)		3 MIUq8h 13.5 days (4-24 days)	17 (65.4)	3 (145)	none
Garnachd-2-2 Montero	_		2.5 mg-5 mg/kg/day 14.7 ± 4.1days	12 (57.1)	5 (24)	none
Michalopoulos	N=157	CANCEL DE L'ANDE	3 MIUq8h	32 (74)	8 (18.6)	none
Falagas	APAC 17 (19 infections)	14 history	an 8.3 days 25.8	14 (74)	1 (5.2)	1
Kasiakou	50 (54 infections)	APACE	HE II: 24.6 21.3 ± 16 days Clinical Cu	ıre: 32.5-8	0.8%)ª
Reina	55	21 ± 7	5 mg/kg (max 300 mg/day)	survival: 4	0 (0)	none
Petrosillo ^b	14	NA	2 MIUq8h 12 days (mean)	9 (64)	1 (7.1)	none
Kallel	75 (78 infections)	NA (SAPS II 37 ± 14)		Nephro MIU 93 ± 38 days	toxicity: o 'AKI' 3	
Koomanachai	78	21.9 (mean)	179.6 mg/day (mean) 11.9 days (mean)	63 (80.8)	24 (30.8)	none
Betrosian	15	14 ± 2	5.83 MIU ± 2.3 MIU duration NA	9 (60)	5 (33)	none
Bassetti ^b	29	17 ± 3.7	2 MIUq8h 17.7 ± 10.4 days	22 (76)	3 (10)	none
Kallel	60	NA (SAPS II 35 ± 12)	2 MIUq8h 95 ± 3.8 days	45 (75)	0 (0)	NA

com	pare wit	th recer	nt studie	es using	RIFLE
	Hartzell et	Kwon et al.	DeRyke et	Pogue et al.	Local

30

33%

3 (10%)

5 (17%)

2 (7%)

All received at least colistin for 48 or 72 hours

N.B. different in patient characteristics between studies

al. 2010

2011

126

43%

16 (13%)

22 (17%)

16 (13%)

106

38.6%

14 (13%)

17 (16%)

10 (9%)

Com	pare wit	th recer	nt studie	es using	RIFLE
	Hartzallat	Kwon et al	DoRyko ot	Pogua et al	Local

Com	pare wit	th recer	nt studie	es using	RIFLE
	Hartzell et	Kwon et al	DeRvke et	Pogue et al	Local

Com	pare wit	th recer	nt studie	es using	RIFLE
	Hartzell et	Kwon et al.	DeRvke et	Pogue et al.	Local

2010

53.5%

11 (15%)

10 (14%)

17 (24%)

71

al. 2009

13 (20%)

10 (15%)

7 (11%)

66

45%

n

% of AKI

Risk

Injury

Failure

Loss

ESKD

Limitations

- Wide difference in practices of different hospitals
 - Indication
 - Dosage
 - Route
 - Combination of therapy
- 64.3% (101/157) cases was contributed by one hospital

Limitations

- Difficult to identify the cases of AKI purely attributed by colistin
 - Overlapped with sepsis / critical illness
 - Used nephrotoxic agents in about 90%
 - AKI required RRT: 6.6%
- Not able to follow up the renal function in those patients who died early
 - Days to peak Cr level: 12 +/- 8.7
 - more AKI / higher peak if receive longer colistin

Summary

For critically ill patients treated with IV colistin in this cohort,

- High mortality: 59.2% in-hospital mortality
- Suboptimal clearance: <50% showed long term clearance
- Colistin-resistant micro-organism did not emerge
- Transient increase in serum creatinine is not uncommon (38.6%, but confounded by various factors)
- No cases had long term renal function loss due to colistin

Studies for optimal dosage and route is needed

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