Colistin Use in MDROs

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Cases Discussion

Case One

- M/44
- Good past health
- Presented with neutrophilia + thrombocytopenia + multiple shotty LNs + renal impairment
- Confirmed to be castleman disease
- Progressive deterioration respiratory failure
- intubated and transferred to ICU
- Developed sepsis
- **Blood culture grew MDRAB**

Blood Culture grew	
organism 1: Acinetobacter baumannii (heavy growth)	
Amikacin	R
gentamicin	R
Levofloxacin	R
Ciprofloxacin	R
Unasyn	R
Cefoperazone-sulbactam	R
Ceftazidime	R
Piperacillin/tazobactam	R
Cefepime	R
Meropenem	R
Tienam	R
Colistin	S
Tigecycline	S

Question

a. Tigecycline

b. Colistin

c. High dose Meropenem

d. Colistin + Meropenem

Case Two

- M/81
- Left groin high grade pleomorphic sarcoma
- Elective wide excision
- Post-operative care at ICU
- Fever + CXR LUZ consolidation
- Started cefepime
- TA = multi-drug resistant *Acinetobacter baumannii*

Sensitive to tigecycline (MIC 1 ug/ml; Etest)

- Tigecycline started
- CXR – no improvement
- 2nd TA (collected after 4 days of tigecycline)
  - ★MDRAB intermediate to tigecycline (4 ug/ml; Etest)
  - ★*Pseudomona aeruginosa* (sensitive to all tested antibiotics)

Question

a. Step up the dose of Tigecycline

b. Colistin

c. High dose Meropenem

d. Colistin + Meropenem

Antimicrobial Therapy

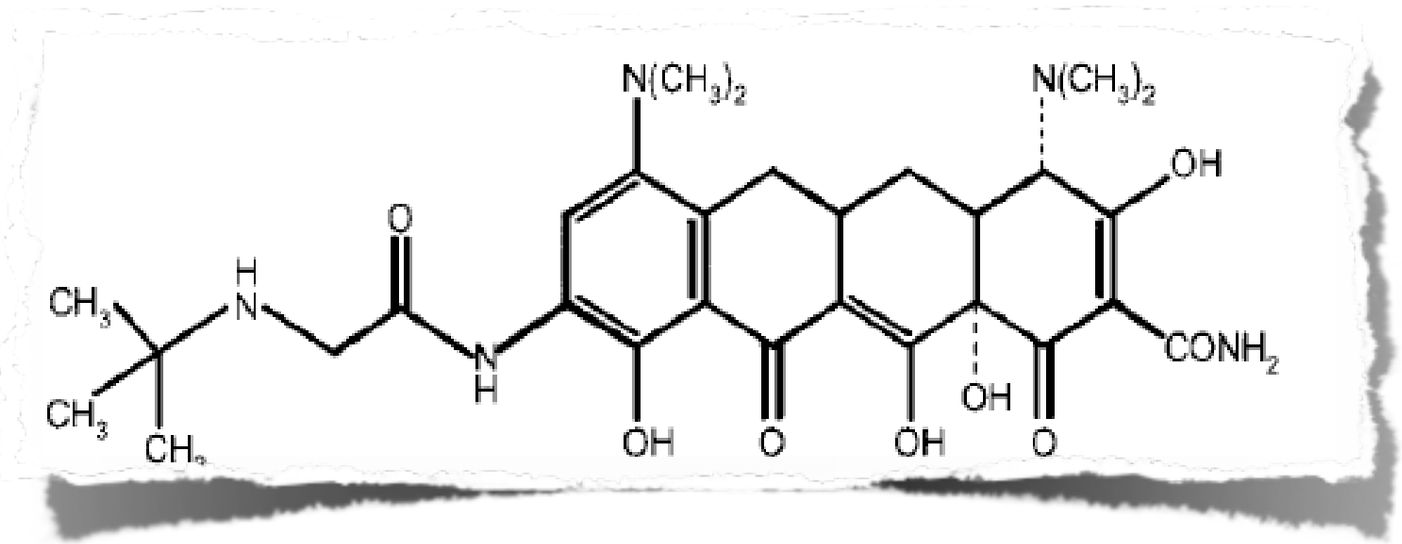
For Multiple Drug Resistant Gram Negative Bacillus

Examples: MDRA, CRA, MDRPA, NDM strains

Antimicrobial Options

- Colistin
- Tigecycline
- Combination therapy

Tigecycline



Glycylcyclines-a new class

Glycylcyclines-a new class

- **Glycylcyclines** (a new class of modified tetracycline)
- Inhibits the **30S ribosomal subunit** with higher affinity than tetracycline
- Ability to **evade the major determinants of tetracycline resistance** i.e., the tet(A) to tet(E) and tet(K) **efflux pumps** and the tet(M) and tet(O) determinants that provide **ribosomal protection**

Good for both GN and GP organisms

- **Broad spectrum activity** against both gram positive and negative bacteria **EXCEPT PSEUDOMONAS SPP.**
- Established clinical use in staphylococci, beta-hemolytic streptococci, enterococci, E.coli
- **Good tissue distribution** in bile, gallbladder, colon, lung
- **FDA approved for**
  - complicated skin and skin structure infection
  - complicated intra-abdominal infection

Can we use Tigecycline in MDRAB infections?

Controversies in Tigecycline Breakpoints!

Breakpoints!!

- Unusually high MIC when using **Etest** as compared with **broth microdilution (BMD)**
- Thamlikitkul et al (Thailand)
  - 148 MDRA isolates tested for MIC90
  - **1 mg/L** by **broth microdilution**
  - **4 mg/L** by **Etest**

Lack of universally accepted MIC interpretative breakpoints

- **BSAC** adopted the ***enterobacteriaceae*** **MIC breakpoints** for application to *acinetobacter* spp. (disc diffusion)

S: ≤ 1 mg/L
I: 2 mg/L
R: > 2 mg/L

Table 2
In vitro activity of tigecycline and comparators against Gram-negative organisms collected from the Asia-Pacific Rim between 2004 and 2007.

Organism/antimicrobial agent	MIC (mg/L)		%S	%I	%R
	MIC_{90}	Range			
Acinetobacter spp. (n = 447)					
Amikacin	≥128	≤0.5 to ≥128	67.1	3.1	29.8
Cefepime	≥64	≤0.5 to ≥64	54.2	6.0	39.8
Ceftazidime	≥64	≤8 to ≥64	50.4	4.9	44.7
Ceftriaxone	≥128	≤0.06 to ≥128	33.3	22.1	44.6
Imipenem[a]	≥32	0.12 to ≥32	66.2	4.4	29.4
Levofloxacin	≥16	≤0.008 to ≥16	60.4	15.0	24.6
Minocycline	4	≤0.5 to ≥32	90.8	6.7	2.5
Piperacillin/tazobactam	≥256	≤0.06 to ≥256	55.3	9.6	35.1
Tigecycline	1	0.03–8	–	–	–

Table 3
In vitro activity of tigecycline and comparators against resistant Gram-positive and Gram-negative organisms collected from the Asia-Pacific Rim between 2004 and 2007.

Organism/antimicrobial agent	MIC (mg/L)		%S	%I	%R
	MIC_{90}	Range			
MDR *Acinetobacter* spp. (n = 153)					
Amikacin	≥128	1 to ≥128	22.9	4.6	72.5
Cefepime	≥64	4 to ≥64	3.3	6.5	90.2
Ceftazidime	≥64	≤8 to ≥64	0.7	1.3	98.0
Ceftriaxone	≥128	8 to ≥128	0.7	2.0	97.3
Imipenem[a]	≥32	0.25 to ≥32	20.2	9.2	70.6
Levofloxacin	≥16	0.25 to ≥16	15.0	27.5	57.5
Minocycline	8	≤0.5 to ≥32	75.8	17.0	7.2
Piperacillin/tazobactam	≥256	0.12 to ≥256	4.6	3.9	91.5
Tigecycline	2	0.12–8	–	–	–

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Blood Stream infection

Be very cautious
when treating serious infections!

Blood Stream infection

Treatment Failure in Bacteremia

- Steady-state **peak serum concentration** of tigecycline after IV tigecycline 50mg doses was **0.62 – 0.72 mg/L**
- **MIC90 for MDRA = 2 mg/L**

Raised MIC90 associated with worse prognosis

Table 1. *(Continued.)*

Causative organism	Resistance mechanism	Initial TIG MIC, μg/mL	Therapy duration, days	Coadministered antibiotics	Response		Final disposition[b]
					Clinical	Microbiological	
…	…	3.00 (I)	7	FEP[c]	Negative	ND	Died (related)
…	…	1.00 (S)	15	VAN[d]	Positive	Positive	Alive
…	…	3.00 (I)	28	AMK, COL	Negative	Negative	Died (related)
…	…	3.00 (I)	10	COL (inhaled)	Negative	ND	Died (related)
…	…	2.00 (S)	49	None	Positive	Positive	Alive
…	…	ND	8	TOB (inhaled)	Positive	ND	Alive
…	…	3.00 (I)/ 2.00 (S)	8	TOB	Negative	ND	Died (related)
…	…	1.00 (S)	17	None	Positive	Positive	Alive
…	…	3.00 (I)	17	LEV[e]	Positive	ND	Alive
…	…	2.00 (S)	42	None	Uncertain	ND	Alive

Anthony KB, Fishman NO, Linkin DR et al. Clinical and microbiological outcomes of serious infections with multidrug-resistant Gram-negative organisms treated with tigecycline. Clin Infect Dis 2008; 46: 567–70.

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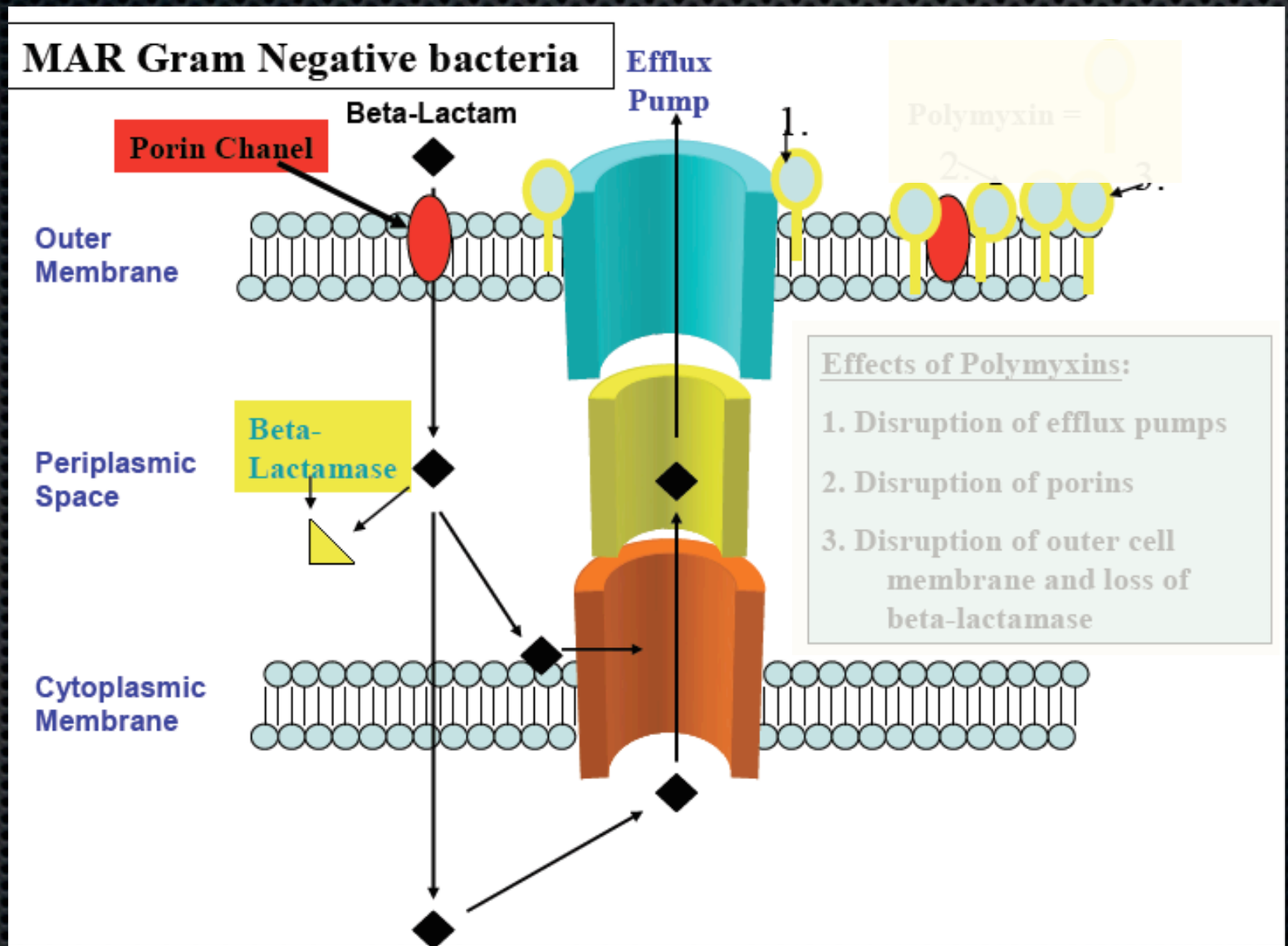
Case reports of **Resistance development** during tigecycline therapy in *A.baumannii* infections

- Schafer JJ et al.. Pharmacotherapy 2007; 27: 980–7
- Anthony KB et al. Clin Infect Dis 2008; 46: 567–70.
- Associated with clinical failure

Multi-drug efflux pump-AdeABC



Polymyxin

What was old is new again!

In the old days....

- Used in **1960s** for gram negative infections
- polymyxin B & polymyxin E
- **Abandoned** during 1970s because of **toxicity** (neuro and nephro) and when better tolerated anti-pseudomonal agents were available

How does Colistin act?

- Targets **the anionic LPS molecules** in **the outer membranes** of gram negative bacteria, leading to membrane disturbance and osmotic instability
- **Bactericidal**
- **Anti-endotoxin** (neutralise bacterial lipopolysaccharides)
- Active against **most aerobic gram negative bacilli**

Polymxin E = Colistin

2 salt forms

✳**Colistin sulphate**

➡used in MIC testing

➡oral / topical

✳**Colistin methanesulphonate (CMS)**

➡also known as colistimethate sodium

➡non-active prodrug of colistin

- not used in MIC testing
- **IV / inhalation**

Formation of Colistin from CMS

CMS
Non-active
pro-drug

Aqueous
solution

Colistin
Active
Bactericidal

Occurs in:
- Water
- Buffer
- Infusion solutions
- Growth media
- Blood/ Plasma/ Urine

(Require specific assays for PK/PD studies)

Occurs *in vitro* and *in vivo*
Colistin (sulfate) should be used in MIC tests

Colistin Breakpoint

	Susceptible	Resistant
CLSI (2007)	≤ 2 mg/L	≥ 4 mg/L
EUCAST (2008)	≤ 2 mg/L	> 2 mg/L

Disk diffusion methods are unreliable for susceptibility testing because polymixin diffuse poorly in agar

Good Activities

SENTRY antimicrobial surveillance programme 2001-04

	MIC_{90}	Range	% R
Acinetobacter spp.	2	≤1 - >8	2.1
Pseudomonas spp.	<1	≤1 - >8	1.3

Rapid Killing Action

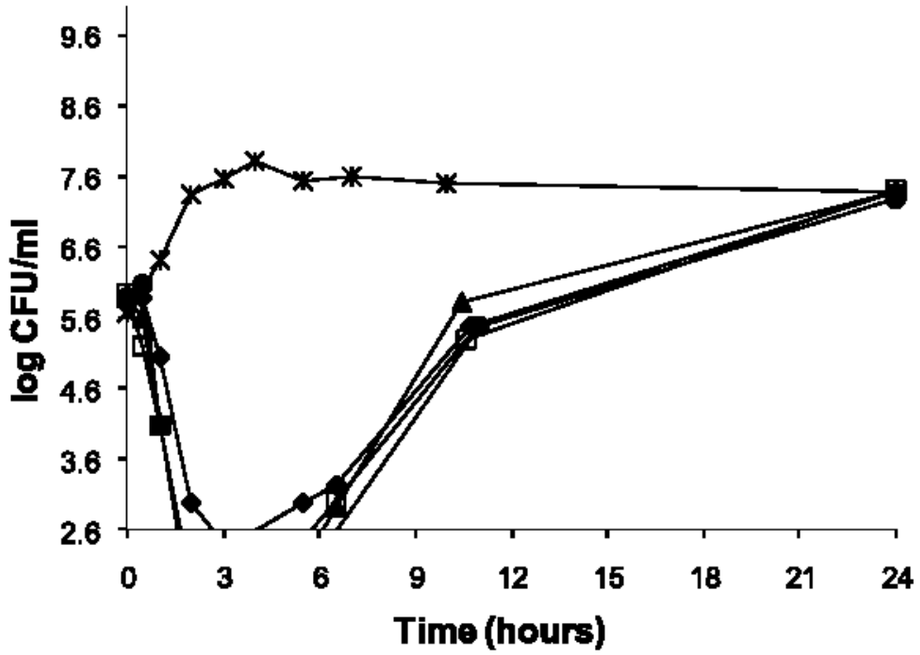
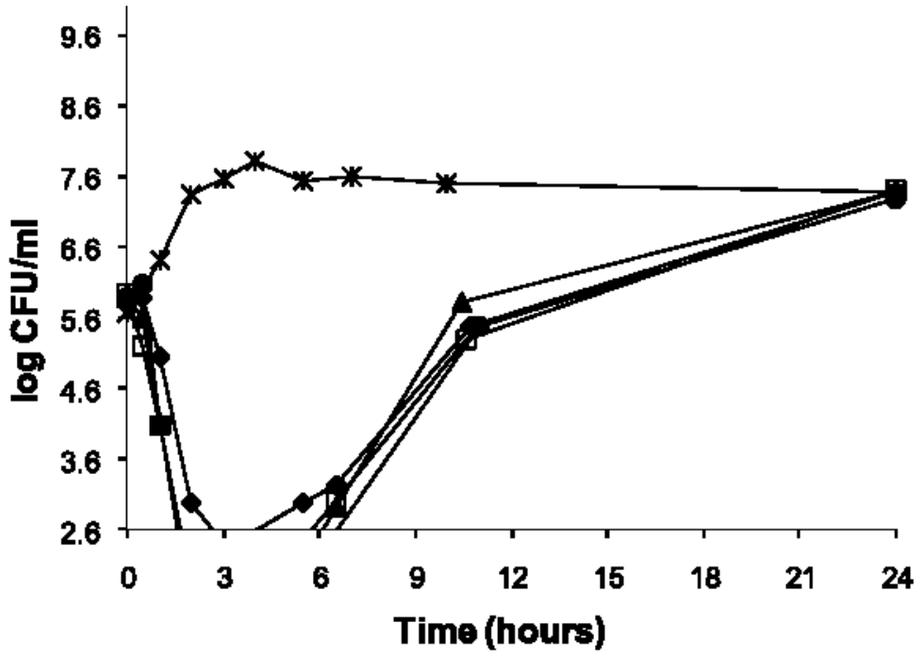


FIG. 1. Time-kill curves of CMS against *A. baumannii* at maximum serum drug concentrations of 3 μg/ml (◆), 6 μg/ml (●), 12 μg/ml (▲), and 24 μg/ml (□). The growth control (×) is also depicted.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2007, p. 3431–3433

Rapid Killing Action

≥ 3 log kill achieved within 30 – 90 minutes



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Good Clinical Efficacy

Across a range of infections

Efficacy and safety of colistin (CMS) for therapy of infections caused by MDR-PA and MDR-AB

- Prospective cohort
- pneumonia (69%), bacteremia (12%), intra-abd (6%), UTI (5%), skin/soft tissue (5%), sinus (1%)
- Colistin (n=78) vs other antibiotics of physician's choice (n=15)

Treatment outcomes

Outcome	Colistin group (n=78)	Non-Colistin (n=15)	p value
Good Clinical response	63 (80.8%)	4 (26.7%)	<0.001
All cause mortality <30 days	36 (46.2%)	12 (80%)	0.03
Microbiological response	74 (94.9%)	0	<0.001
Nephrotoxicity	24 (30.8%)	10 (66.7%)	0.02
Neruotoxicity	0	0	-

Pornpan et al. Int J Infect Dis (2007) 11, 402—406

Safety and efficacy of colistin in *Acinetobacter* and *Pseudomonas* infections: a prospective cohort study

- pneumonia (53%), UTI (18%), bacteremia (16%), others (CNS, peritonitis, wound)
- Colistin (n=55) vs Non-colistin (n=130) (carbapenem 80%)

	Colistin (n=55)	Non-colistin (n=130)
improvement on D6	15%	17%
Mortality	29%	26%
Microbiological Eradication	93%	94%

Rosa Reina. Intensive Care Med (2005) 31:1058–1065

Treatment of MDR-AB VAP with IV colistin: a comparison with imipenem-susceptible VAP

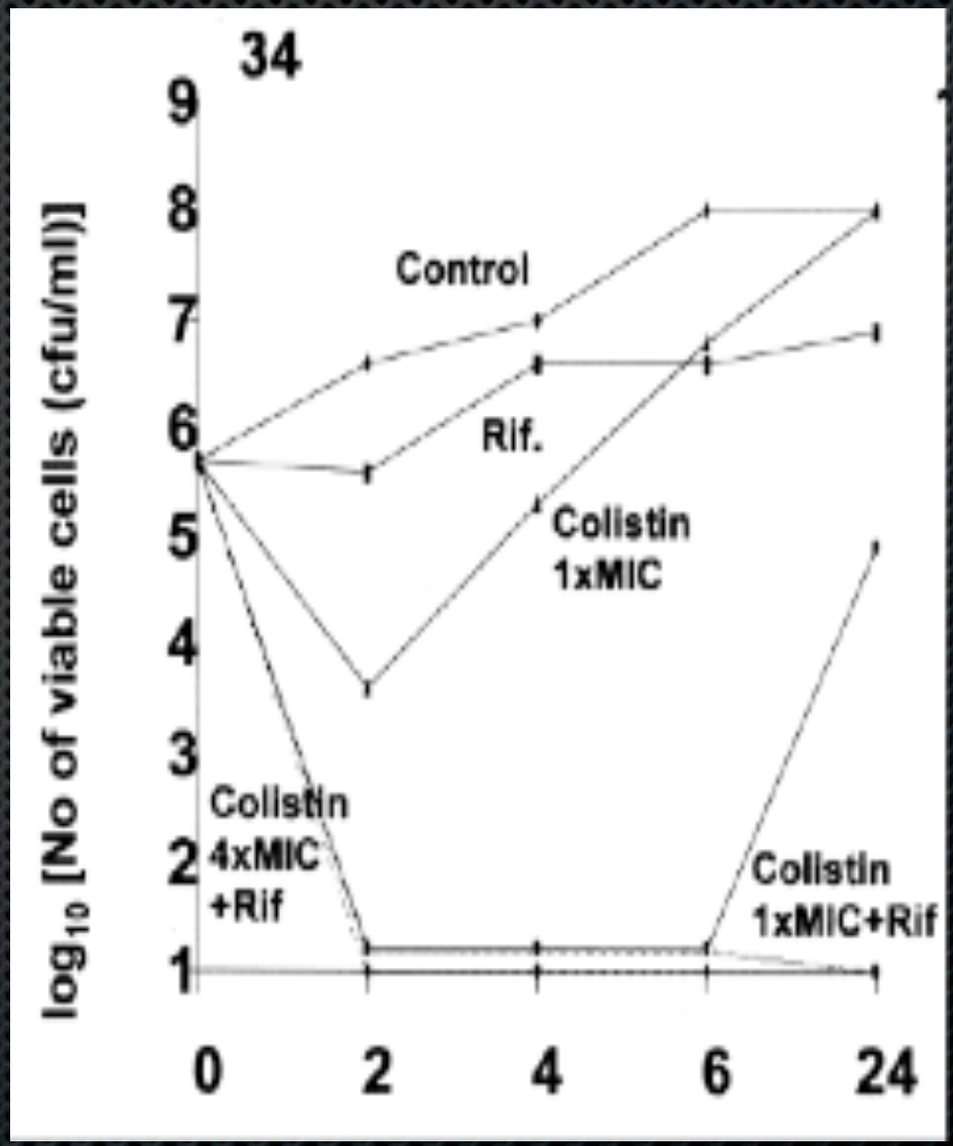
- prospective cohort
- pneumonia (100%)
- colistin (n=21) vs carbapenem+/-others (n=14)

	Colistin (n=21)	Non-colistin (n=14)
Clinical cure	57%	57%
Mortality	38%	36%
Microbiological Eradication	67%	50%

Garnacho-Montero. CID 36:1111–1118.

Synergy?

- In-vitro / Animal Studies
- Evidence of **synergy** between colistin and **various antimicrobial agents** (carbapenem, rifampicin, ceftazidime)



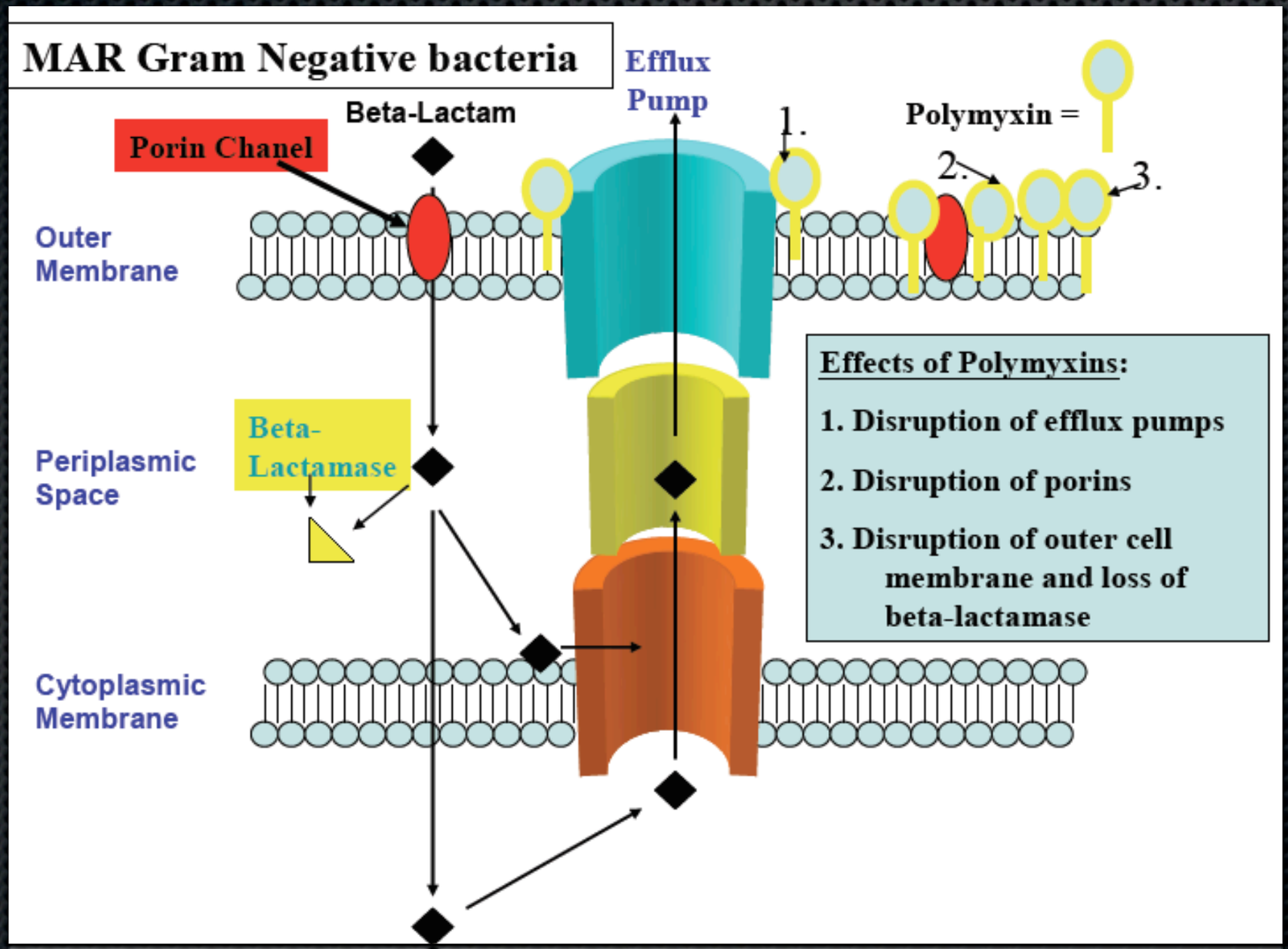
Diagnostic Microbiology and Infectious Disease 40 (2001) 117–120

In-vitro Study

- Pre-exposing beta-lactam resistant strains to colistin may restore activity to the beta-lactam
- **Control**: meronem MIC90 = 8
- **pre-expose to colistin:** meronem MIC90 = 1.5
- **NOT** all isolates would demonstrate the pheonmonen

Ullman, M et al ICAAC 2008

Disruption of outer cell membrane



Limited human studies in Colistin combination therapy

Toxicity of Colistin

Nephrotoxicity- in the PAST

- Studies in 60s to 70s reported **incidence of up to 50%**
- Many **NOT include definition** of nephrotoxicity
- **HIGHER total daily doses** than now recommended
- **Koch-Weser et. al.** (Ann Intern Med **1970**, 72:857)
  - 288 patients / 317 courses
  - colistin dosage: <1g to >2g per day
  - renal insufficiency: 63 courses
  - acute tubular necrosis: 6 patients

Nephrotoxicity-Nowadays

Treatment Outcomes			
Outcomes	Colistin (n=78)	Non-colistin (n=15)	p Value
Nephrotoxicity	24 (39.8%)	10 (66.7%)	0.02
Neurotoxicity	0	0	

- Nephrotoxicity in colistin group < non-colistin group
- Mild and reversible
- Other contributing factors: nephrotoxic drug, hypovolemia

Pornpan et al. Int J Infect Dis (2007) 11, 402—406

Toxicity-
Less than Previously Thought

- Intensive Care Med. 2007 Jul;33(7):1162-7. Epub 2007 May 25
- Rosa Reina. Intensive Care Med (2005) 31:1058–106

Possible Mechanisms

- Nephrotoxicity of polymyxins may be partly due to their D-amino acid content and fatty acid component
- Proposed mechanism: **polymyxin increases membrane permeability**, resulting in an increased influx of cations, anions, and water, leading to cell swelling and lysis

Colistin-Neurotoxicity

- Toxicity of polymyxins: a **systematic review of the evidence from old and recent studies** (Critical Care 2006, 10:R27)
  - **Old studies:** incidence up to 30%
  - **Recent studies**: lower incidence
  - 4 out of 24 studies had patients developing neurotoxicity
  - 2 patient had diffuse muscular weakness
  - 1 seizure
  - 2 polyneuropathy

Dilemmas of Colistin: PK/PD

- Not known if data from in vitro testing with colistin sulphate are predictive of in vivo activity of CMS
- **Limited** pharmacokinetic data
- **Limited** pharmacodynamic data
- **Optimal dosing regimen** as yet undetermined

Commercial Preparation of CMS

Colomycin Injection ®
(Europe / HK)

Coly-Mycin M Parenteral ®
(USA / Australia)

This 2 parenteral products are <u>not</u> equal

Commercial Preparation of CMS

Colomycin Injection ® (Europe / HK)	≠	Coly-Mycin M Parenteral ® (USA / Australia)

This 2 parenteral products are not equal

Commercial Preparations of Colistin methanesulphonate (CMS)

Colomycin Injection ®
(Europe / HK)

0.5 million IU
(40mg of CMS)
1 million IU
(80mg of CMS)
2 million IU
(160mg of CMS)

Coly-Mycin M Parenteral ®
(USA/Australia)

150mg CBA
(400mg of CMS)

CBA = Colistin Base Activity

Commercial Preparations of Colistin methanesulphonate (CMS)

Colomycin Injection ® (Europe / HK)

0.5 million IU
(40mg of CMS)
1 million IU
(80mg of CMS)
2 million IU
(160mg of CMS)

8mg/kg/day
of CMS

480mg/day or
6MU/day for
60kg BW

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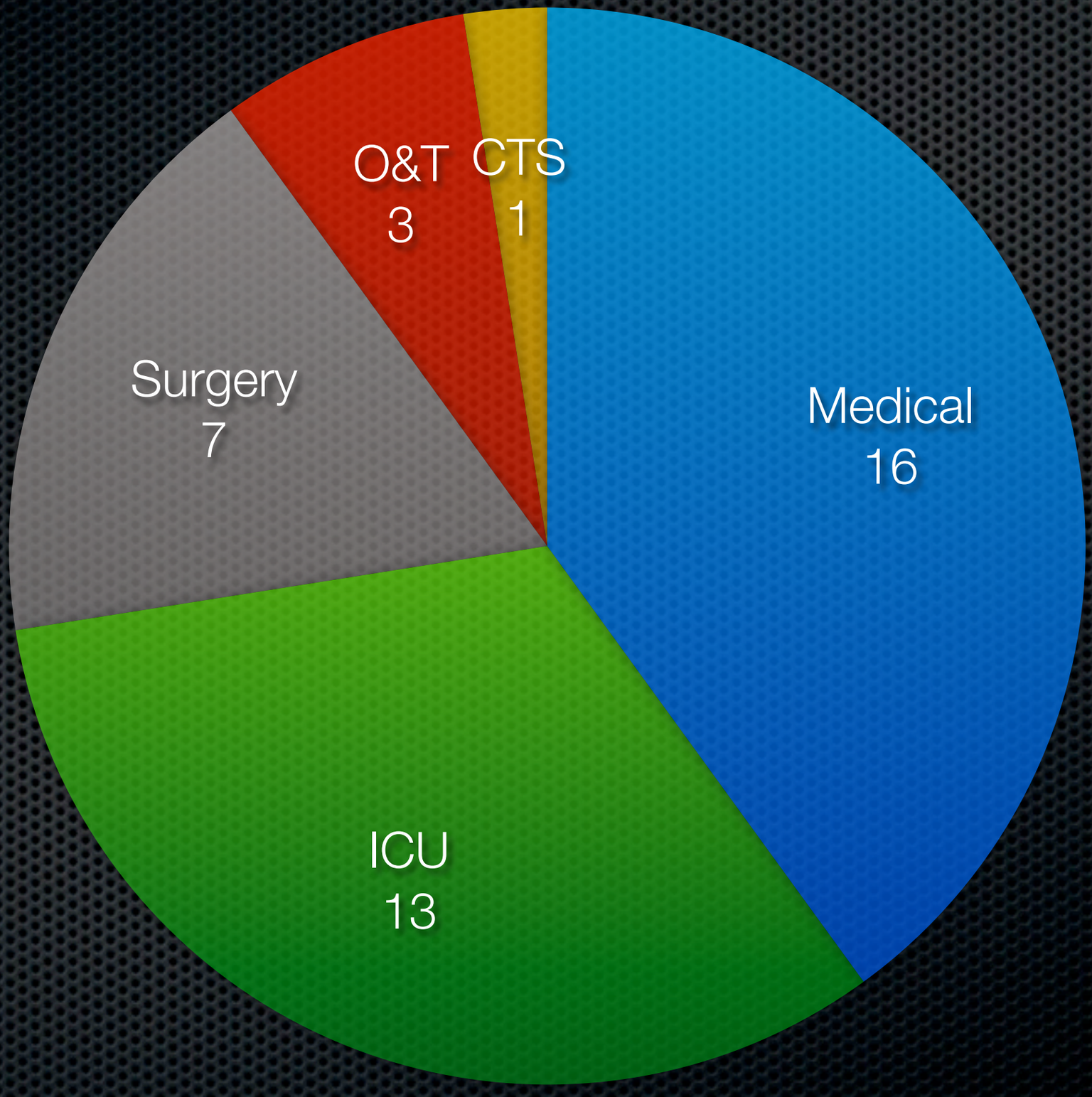
Commercial Preparations of Colistin methanesulphonate (CMS)

Colomycin Injection ® (Europe / HK)

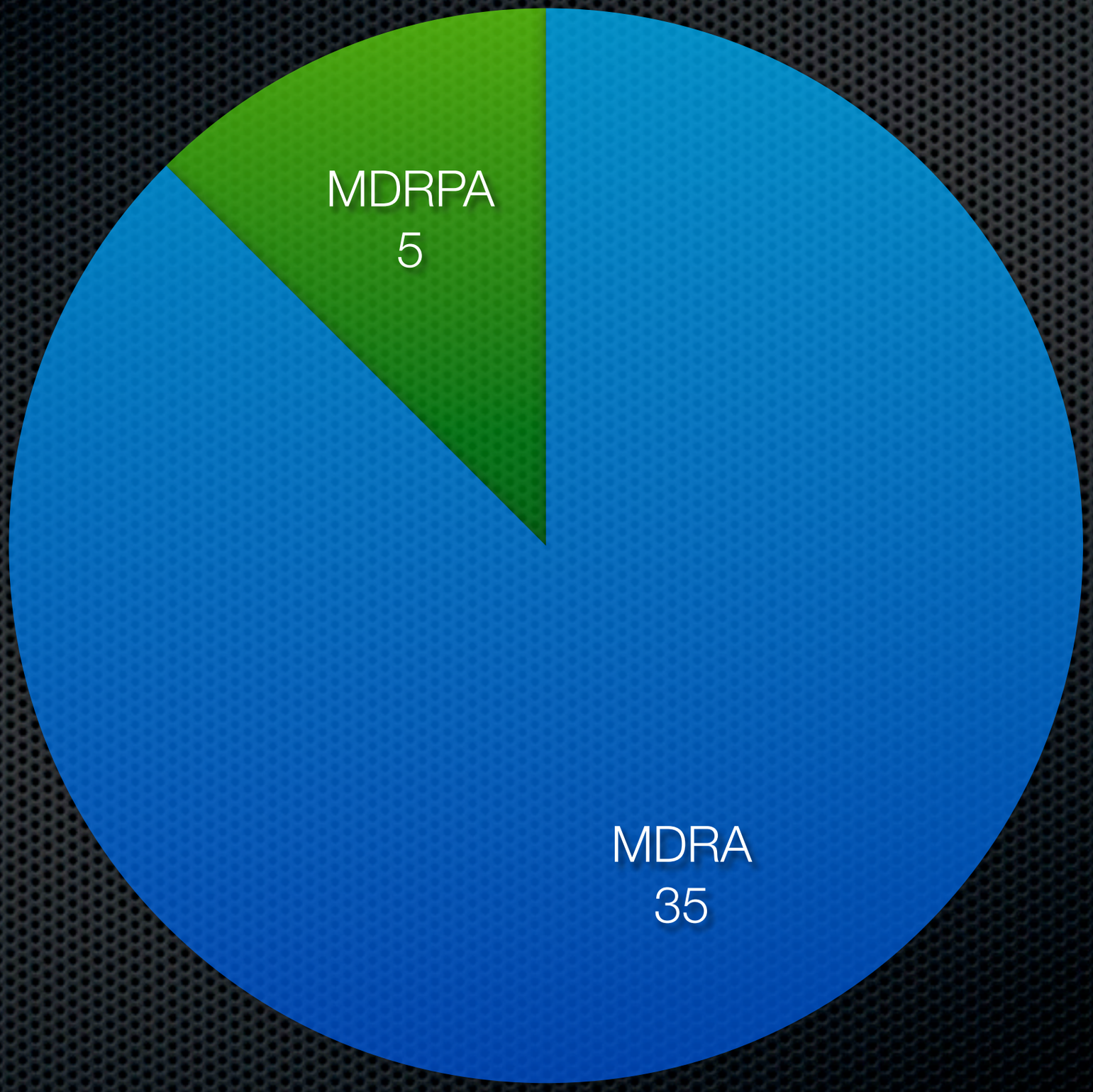
0.5 million IU (40mg of CMS) **1 million IU** (80mg of CMS) **2 million IU** (160mg of CMS)	480mg/day or 6MU/day for 60kg BW

Our Experience in Colistin Use.....

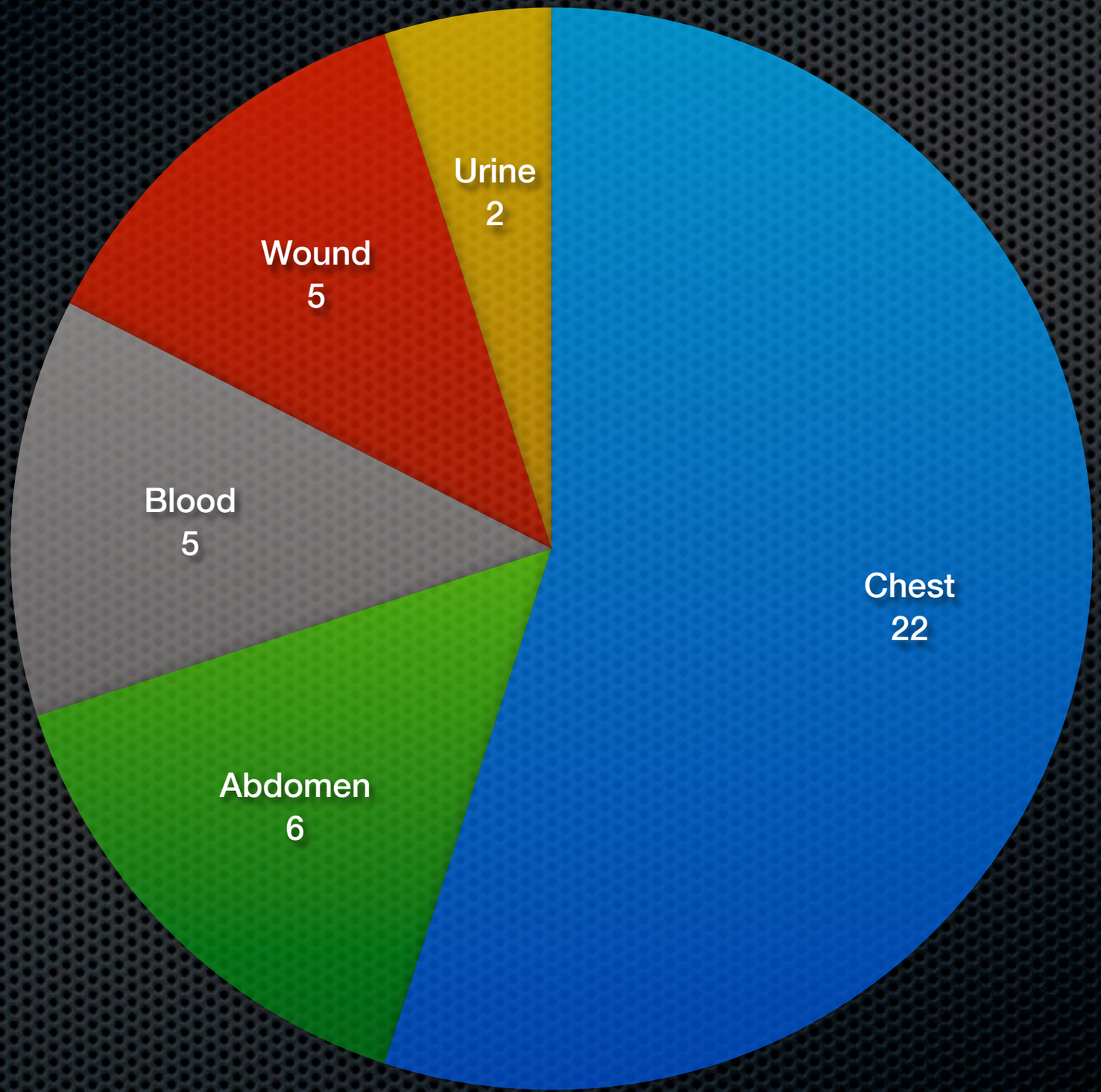
Specialities



MDROs



Site of Isolation



Results

N = 40

RFT deterioration after use	8
All-cause Hospital Mortality	25 (63%)
Microbiological clearance	17/28 (60%) 12 (undetermined)

Bring Home Messages

- MDROs – emerging threat locally and globally
- **Tigecycline**
  - no interpretative MIC breakpoint
  - raised MIC associated with worse prognosis
  - resistance could develop during treatment
  - not a good choice for serious and bloodstream infection
- **Colistin**
  - low resistance rate
  - efficacy appears to be promising
  - less nephrotoxic / neurotoxic than previously thought
  - requires further studies on pharmacokinetics and pharmacodynamics

Thank You