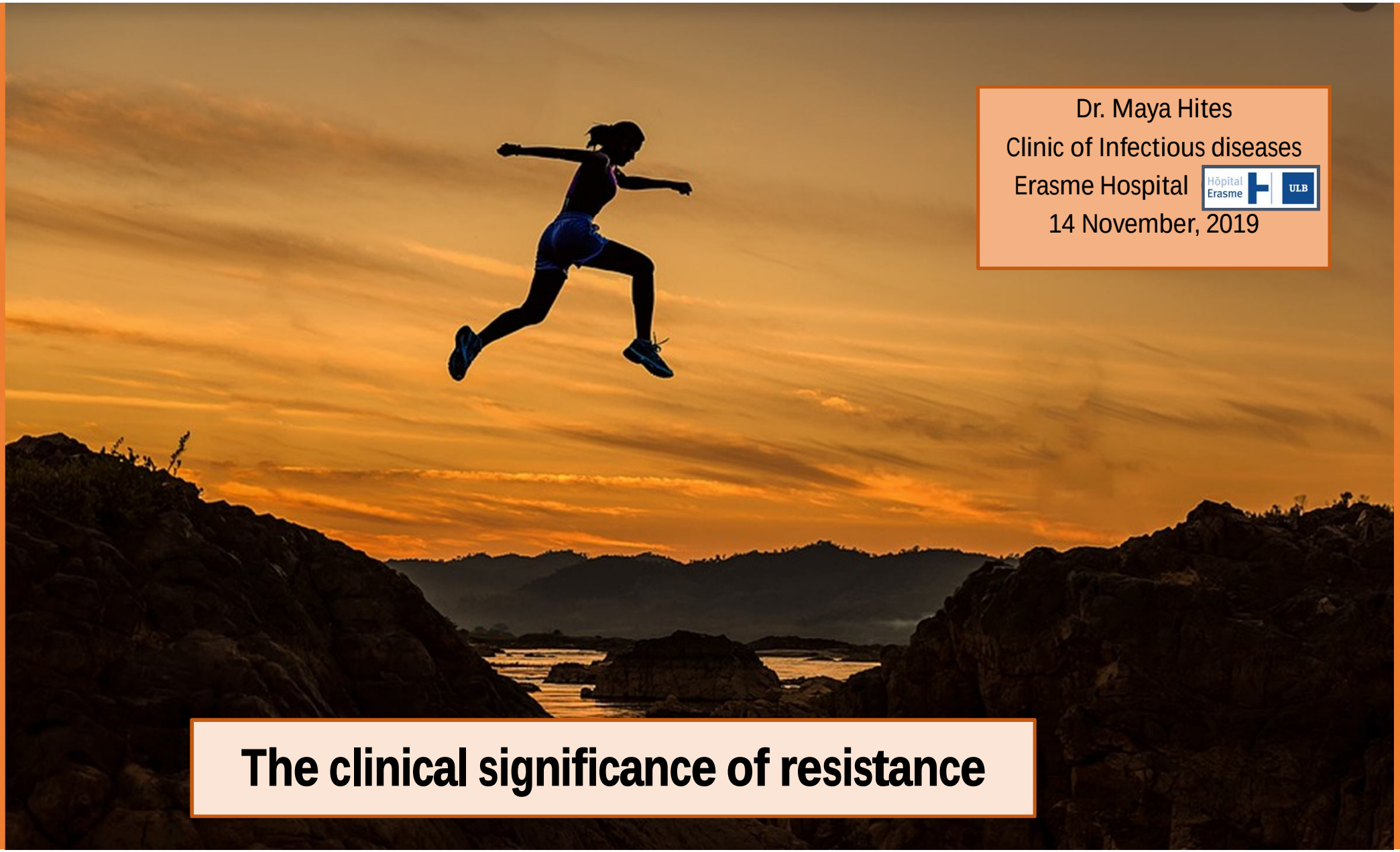


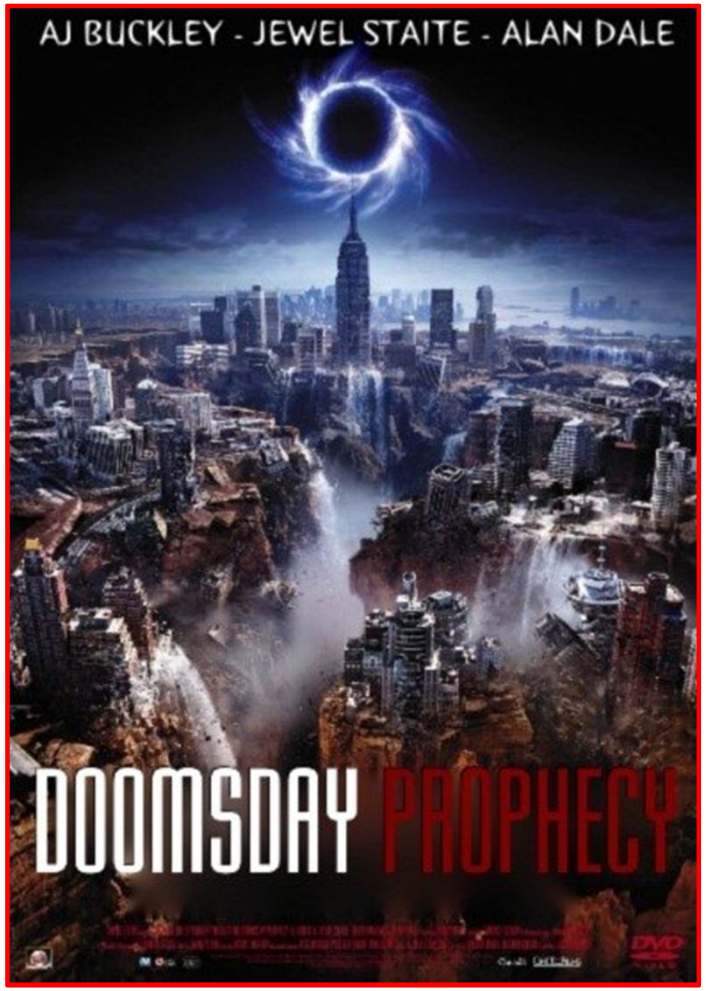
Dr. Maya Hites
Clinic of Infectious diseases
Erasme Hospital
14 November, 2019

The clinical significance of resistance

No conflicts of interest

- Moderator on a session on Isavuconazole for Pfiezer

The near future.....



Or...

Is there some light at the end of the tunnel?

Plan

- 4 clinical cases to illustrate the clinical significance of multi-drug resistant (MDR) Gram-negative bacteria (GNB):
  - 2 cases of septic shock in the ICU
  - 1 case of chronic osteomyelitis
  - 1 case of a pulmonary abscess
- Conclusions

Case n°1: 70 years old male

- Transferred to Erasme hospital from a hospital in Italy (after a **2 weeks** stay) for a Cerebral hemorrhage due to an arterio-venous malformation
  - Unconscious $E_3V_TM_4$, intubated
  - Information on previous bacteria colonization:

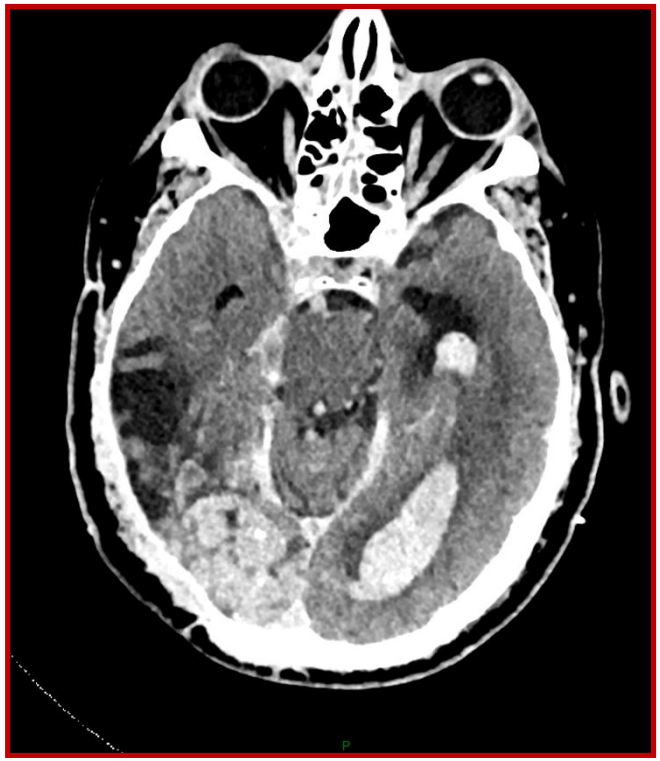
Klebsiella pneumoniae:	
Ampicillin	R
Amoxi-clav	R
Pipera + Tazobactam	R
Temocillin	R
Cefuroxime	R
Cefotaxime	R
Ceftazidime	R
Cefepime	R
Aztreonam	R
Imipenem	R
Meropenem	R
Gentamicin	R

Amikacin	S
Cotrimoxazole	R
Ciprofloxacin	R
Minocycline	R

In:
- Rectal swab
- Tracheal aspirate
- Urine

Case n°1: 70 years old male

- Upon arrival: septic shock, without an obvious infectious foci
  - Catheters are changed,
  - Microbiological samples:
    - Urines
    - Broncho-tracheal aspirate
    - Blood cultures
    - catheters
    - Rectal swab
    - Screening for MRSA
  - Empirical antibiotic therapy started:
    - Meropenem high dose (HD): 2g x 3/day in 3h +
    - Amikacin: 30 mg/kg +
    - Colistin: 12 MIU loading dose, followed by 3 MIU x 3/day
    - Tigecycline HD: 200 mg loading dose, followed by 100 mg x 2/day
    - Vancomycin: 45 mg/kg, followed by 30 mg/kg/day in continuous infusion



Determinants of increased risk of MDR infections in the ICU

Table 1 Determinants of increased risk of MDRB infection at ICU admission and during the ICU stay

Predictors of MDRB infection	At ICU admission	During the ICU stay
Patient features	Co-morbid illness/immunosuppression/recent hospital and/or ICU stay	Higher severity of acute illness/Invasive interventions
Type of infection	Hospital-acquired > healthcare-associated > community-acquired	ICU-acquired > others
Antimicrobial selection pressure	Prior antibiotics*/antifungals	Antibiotics*/antifungals in the ICU
Colonization status	Previously documented colonization with MDRB	In-ICU acquisition of MDRB
Local epidemiology	Epidemiology of MDRB in community/hospital/areas recently traveled to	Local epidemiology of MDRB in the ICU
Infection prevention measures	Poor hygiene practices in hospital	Poor hygiene practices in the ICU

MDRB multidrug-resistant bacteria, *ICU* intensive care unit

*Especially if agents with broad-spectrum and/or potent activity against intestinal anaerobes

But the Positive Predictive Value (PPV) is only 50%!

Timsit JF et al. Intensive Care Med. 2019. 45: 172-189.

Mono or combination therapy for MDR GNB?

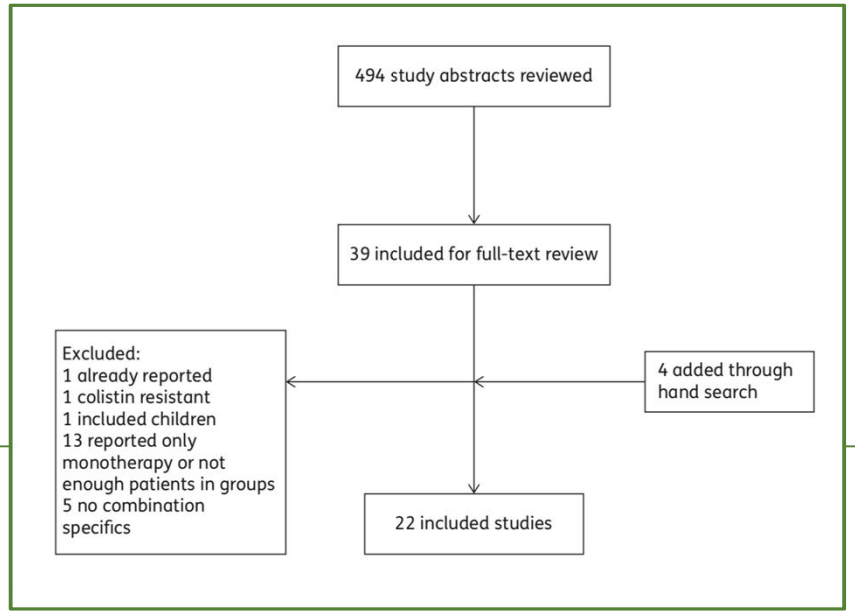
J Antimicrob Chemother 2017; **72**: 29–39
doi:10.1093/jac/dkw377 Advance Access publication 13 September 2016

Journal of Antimicrobial Chemotherapy

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Oren Zusman[1]*, Sergey Altunin[2,3]†, Fidi Koppel[2], Yael Dishon Benattar[2,4], Habip Gedik[5] and Mical Paul[2,3]

[1]Department of Medicine E, Rabin Medical Center, Petah-Tiqva, Israel; [2]Infectious Diseases Unit, Rambam Medical Center, Haifa, Israel; [3]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel; [4]The Cheryl Spencer Department of Nursing, University of Haifa, Haifa, Israel; [5]Department of Infectious Diseases and Clinical Microbiology, MoH Bakirkoy Sadi Konuk Training and Research Hospital, Istanbul, Turkey



Systematic review of adult:

- Observational studies
- Randomized controlled trials (RCTs)

Primary endpoint: mortality

Results:

Low, quality of evidence from observational studies!

mono vs polymyxin/carban… …studies, 537 patients

m… …overall: **OR of 1.57** (95%CI= 1.06-2.32), 10

on… …patients

mono vs. Tigecycline/ Aminoglycosides or Fosfomycin for *Klebsiella pneumoniae* bacteremia: **OR of 2.09** (95% CI= 1.21-5.6), 7 observational studies, 285 patients

SCIENTIFIC REPORTS
nature research

OPEN

Monotherapy versus combination therapy for multidrug-resistant Gram-negative infections: Systematic Review and Meta-Analysis

Adrian Schmid, Aline Wolfensberger, Johannes Nemeth, Peter W. Schreiber, Hugo Sax & Stefan P. Kuster*

Methods: CPE, MDR or XDR GNB infections

- Primary endpoint: Mortality
- Secondary endpoint: clinical cure
- Databases: OVID MEDLINE, EMBASE, Pubmed, The Cochrane Library, Scopus
- Studies included: Published by December 2016
  - RCT
  - Observational studies

Results:

- 53 studies included (< 8847 initially identified)
  - Pneumonia: 10 studies
  - Blood stream: 15 studies
  - Osteoarticular: 1 study
  - Mixed infections: 27 studies
  - Monotherapy: 1848 patients (41%)
  - Combination therapy: 2666 patients (59%)
- Studies of Good Quality:
  - Case-control studies: 1/6 (17%)
  - Cohort studies: 17/45 (38%)

Results:

- Cure rates: no difference
- Mortality:
  - No differences in case-control studies or RCTs
  - Case-series, cohort studies (n= 45): mortality was lower with combination therapy vs monotherapy:
    RR: 0.83, CI 0.73-0.93, p= 0.002, I2= 24%

Combination therapy>>>> monotherapy in terms of mortality, but quality of evidence is poor!!!

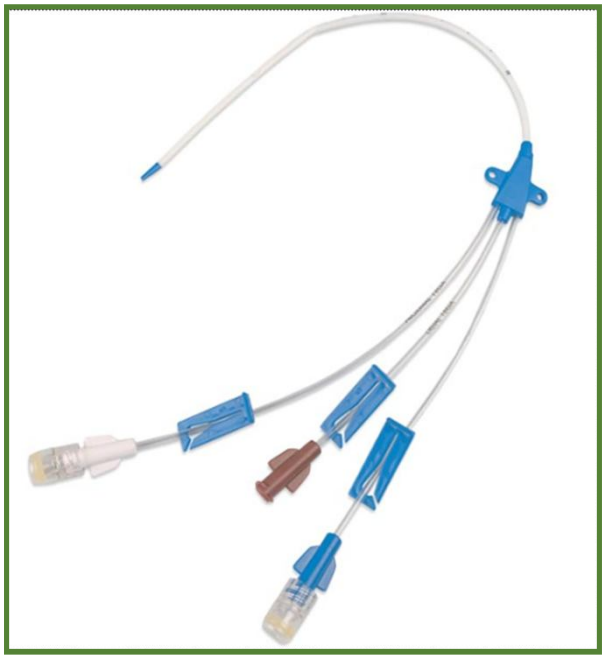
Schmid A et al. Scientific Reports. 2019. 9:15290

Case n°1: 70 years old male

- The following day:
  - 2 blood cultures/2 positive for *Streptococcus sp.*
  - Central venous catheter: 5000 colonies of *Streptococcus sp*

Enterococcus fecalis
Ampicillin S

→ Catheter related infection!



- Clinical evolution:
  - rapid resolution of the septic shock
  - acute renal insufficiency
    - < septic shock
    - < AB: Vancomycin/ Aminoglycosides/ Colistin

- R/
  - Stop Meropenem/Colistin/Tigecycline/Vancomycin/Amikacin
  - Start Ampicillin IV

Infos on *Kl. Pneumoniae:* ESBL + CPE, type KPC

Case n°1: 70 years old male

- **Conclusions:** Colonization with a very resistant pathogen resulted in:
  - Carpet bombing for a severe infection due to a very susceptible pathogen!

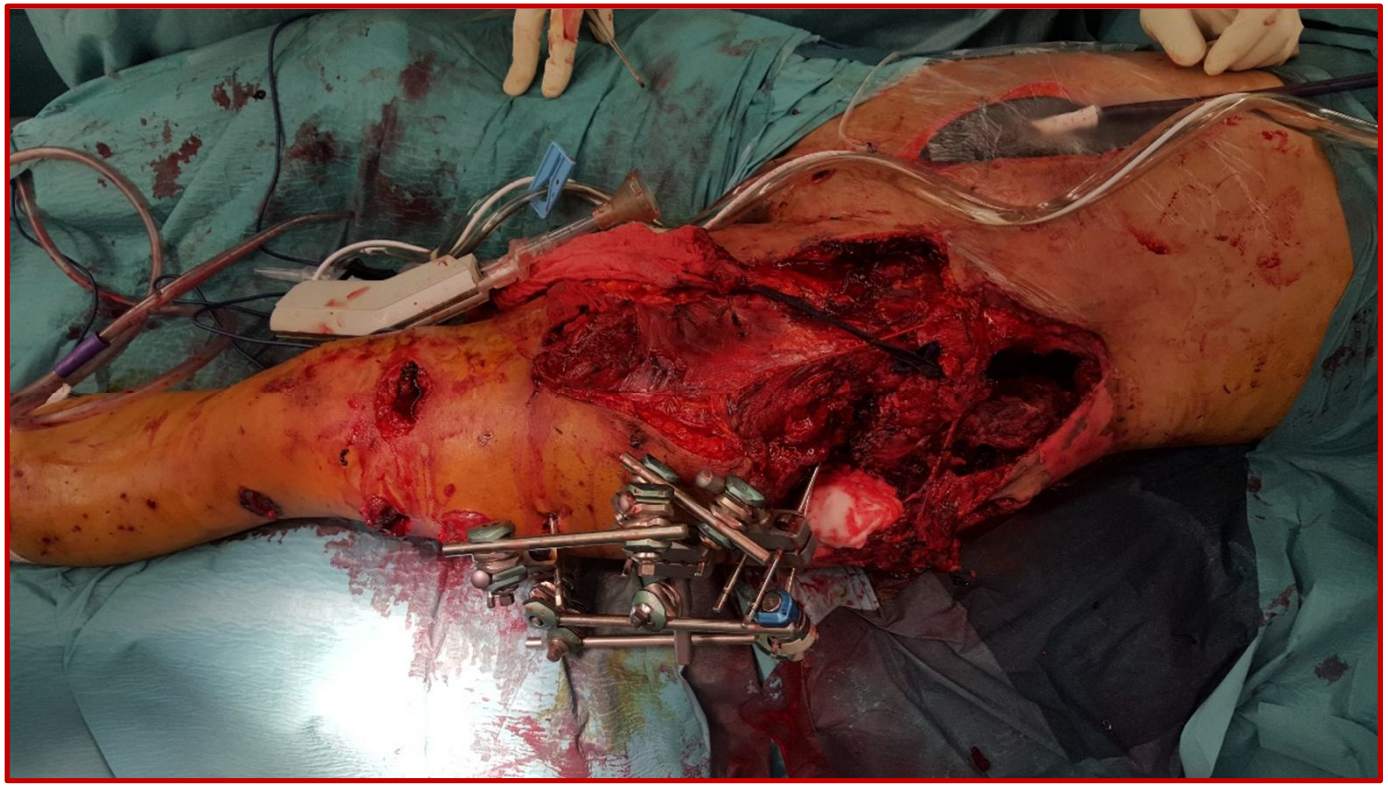
Unnecessary exposure to very large spectrum antibiotics!!!

  - Increased toxicity: Renal insufficiency due to AB toxicity
  - Increased costs: +++++

Case n°2: 31 years old female

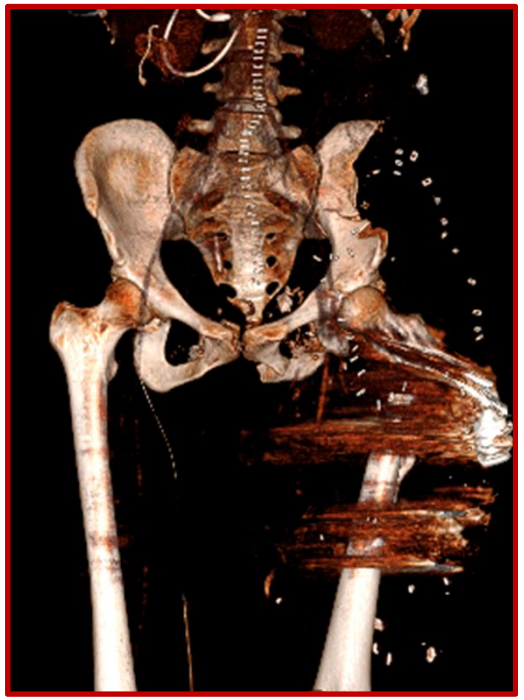
- Admitted to the ICU because victim of a terrorist attack.....

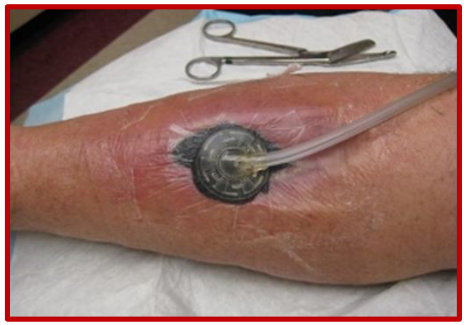
- Hypovolemic shock from extensive bleeding
- 2 cardiac arrests: cardiorespiratory resuscitation (2 x 4 minutes)



Case n°2: 31 years old female

- Stabilization of the patient
  - Massive transfusions
  - Embolisation of bleeding foci
  - **Abdominal surgery:** Laparotomy
    - Clamping of the primitive external Iliaque artery
    - Raphia of the colon & colostomy
    - Extraction of a bolt from the pelvis
    - Vaccum assisted closure (VAC) of the abdominal wall
  - **Orthopedic surgery:**
    - Cleaning of the wound + packing
    - Multifocal fractures of the left proximal femur => External fixator
    - VAC of the left proximal femur





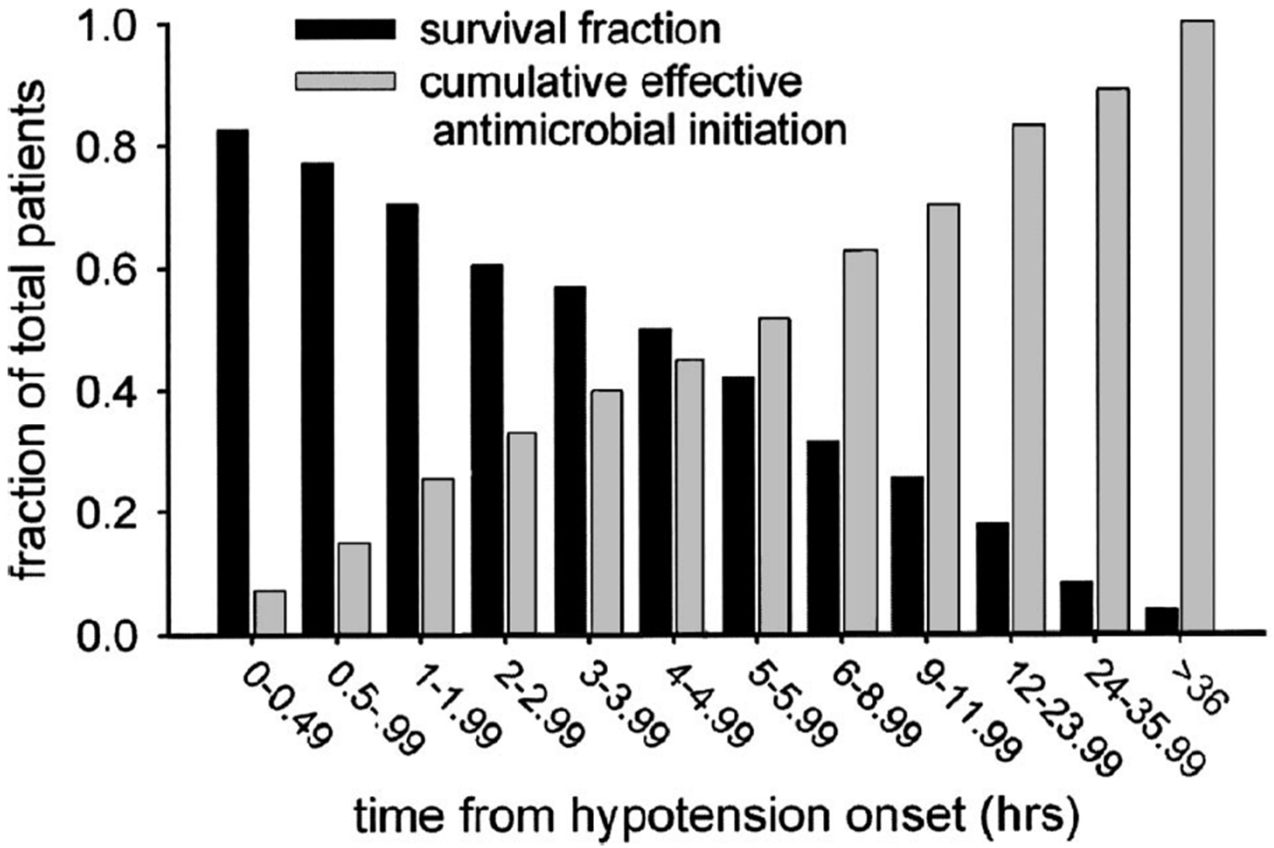
Case n°2: 31 years old female

- **Day 3:** Septic shock due to wound infection of the left thigh, despite treatment with Amoxi-clavulanate
  - Previous microbiological samples: negative
  - **Empiric treatment:**
    - Piperacillin-tazobactam +
    - Amikacin 30 mg/kg +
    - surgical debridement of the wound
- Other pathogens found in the wound: Polymicrobial flora
  - *Pseudomonas aeruginosa*
  - *Enterobacter cloacae complexe*
  - *Enterococcus faecium*
  - *Klebsiella pneumoniae*

Inappropriate empiric antibiotic therapy!

Antibiotics	*Klebsiella pneumoniae*
	S/I/R
Ampicillin	R
Amoxicillin-clavulanic acid	R
Piperacillin -tazobactam	R (MIC > 128 mg/L)
Temocillin	R
Cefuroxime	R
Ceftazidime	R
Ceftriaxone	R
Cefotaxime	R
Cefepime	R
Aztreonam	R
Imipenem	I
Meropenem	R
Ertapenem	R
Gentamicin	S
Amikacin	I (MIC= 16 mg/L)
Tobramycin	R
Cotrimoxazole	S
Ciprofloxacin	R
Minocycline	S

Inappropriate empiric antibiotic treatment



Retrospective study on 2154 patients in septic shock

Kumar A et al. Crit Care Med. 2006.34(6): 1589-96.

The role of AMR in initial antibiotic treatment failure

- Retrospective observational study on patients with healthcare associated pneumonia
- July 2013 –June 2014
- Countries:
  - Brazil
  - France
  - Italy
  - Russia
  - Spain

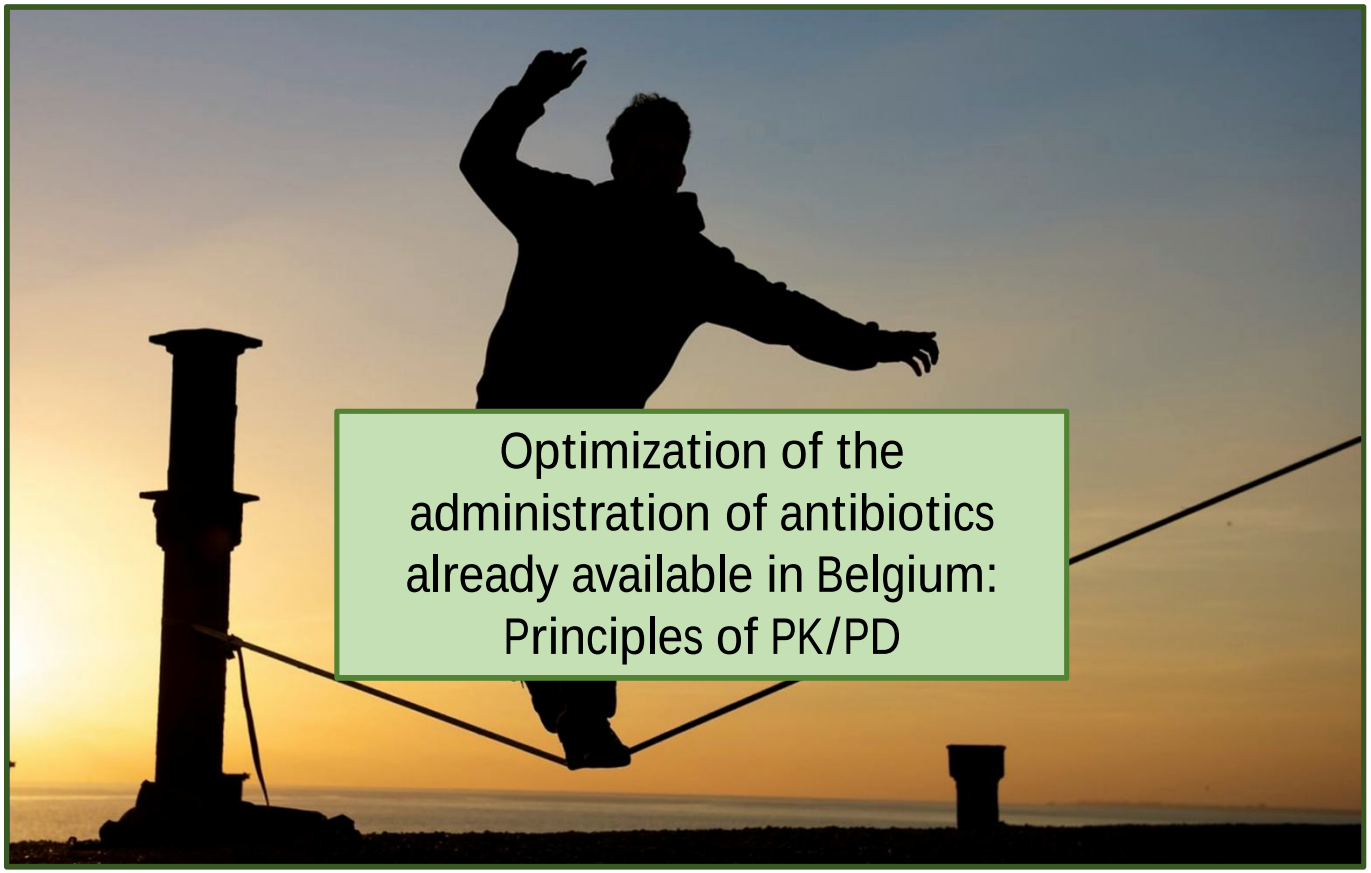
Statistical predictors of initial antibiotic treatment (IAT) failure.

Potential risk factor	Univariate analysis Odds ratio (95% CI)	*p*-value	Multivariate analysis[a] Odds ratio (95% CI)	*p*-value
Age, years				
18–44[b]	Reference	0.262	–	–
45–64	1.28 (0.64, 2.59)		–	–
≥65	1.65 (0.86, 3.16)		–	–
Gender				
Female[b]	Reference	0.350	–	–
Male	1.23 (0.80, 1.89)		–	–
Country				
Spain[b]	Reference	<0.001	Reference	
Brazil	4.01 (1.88, 8.58)		2.07 (0.56, 7.68)	0.010
France	1.18 (0.64, 2.15)		0.85 (0.31, 2.36)	NS
Italy	0.35 (0.19, 0.65)		0.17 (0.05, 0.57)	NS
Russia	1.67 (0.85, 3.28)		0.86 (0.27, 2.79)	NS
Number of days in hospital before start of IAT				
0–7[b]	Reference	0.152	–	–
8–14	1.92 (0.99, 3.75)		–	–
15–30	1.14 (0.51, 2.54)		–	–
>30	2.14 (0.61, 7.54)		–	–
Intensive care unit admission (yes if initial admission or transfer)				
No[b]	Reference	0.028	–	–
Yes	1.59 (1.05, 2.41)		–	–
Deyo–Charlson Comorbidity Score				
0[b]	Reference	0.175	–	–
1–2	1.63 (0.96, 2.75)		–	–
3–4	1.88 (1.01, 3.48)		–	–
≥5	1.34 (0.71, 2.56)		–	–
Resistance to third-generation cephalosporins (%) for site				
No	Reference	0.262	–	–
Yes	0.99 (0.98, 1.00)		–	–
Resistance to carbapenems (%) for site				
No	Reference	0.059	–	–
Yes	0.99 (0.98, 1.00)		–	–
Combined resistance to third-generation cephalosporins and carbapenems (%) for site				
No	Reference	0.015	–	–
Yes	0.98 (0.97, 1.00)		–	–
Patient-level MDR pathogen				
No	Reference	0.024	Reference	0.007
Yes	1.88 (1.08, 3.27)		3.39 (1.41, 8.16)	
Mechanical ventilation				
No	Reference	<0.001	–	–
Yes	3.77 (2.44, 5.82)		–	–

Ryan K et al. J Infecxtion. 2018. 77: 9-17.

Case n°2: 31 years-old F

- She will survive!



Kl. Pneumoniae: ESBL + CPE, type NDM

Antibiotics	*Klebsiella pneumoniae*	
	S/I/R	MIC (µg/mL)
Ampicillin	R	
Amoxicillin-clavulanic acid	R	
Piperacillin -tazobactam	R	> 128
Temocillin	R	= 256
Cefuroxime	R	
Ceftazidime	R	> 64
Ceftriaxone	R	
Cefotaxime	R	> 64
Cefepime	R	> 64
Aztreonam	R	> 64
Imipenem	I	
Meropenem	R	= 32
Ertapenem	R	> 32
Gentamicin	S	< 1
Amikacin	I	= 16
Tobramycin	R	> 8
Cotrimoxazole	S	
Ciprofloxacin	R	= 4
Minocycline	S	
Tigecycline	S	= 0,5
Chloramphenicol	S	
Fosfomycin	S	
Colistin	S	0,25

Case n°2: 31 years old female

- **Treatment (Day 5- Day 70):** debridement of the wound + high dose TDM guided intra-venous antibiotic therapy:
  - Meropenem: 2g x 3-6/d in 3h,
  - Gentamicin: 400 mg/d
  - Tygecycline: 200 mg, 100 mg x 2/d
  - Cotrimoxazole: 880 mg x 2/d
  - Vancomycin
  - Colistin
  - Fosfomycin: 6g x 4/day

Day 71-84

TDM of Meropenem:
- Trough: 1 mg/L
- 180 minutes: 54.9 mg/L
- > 32 mg/L for 40% of time

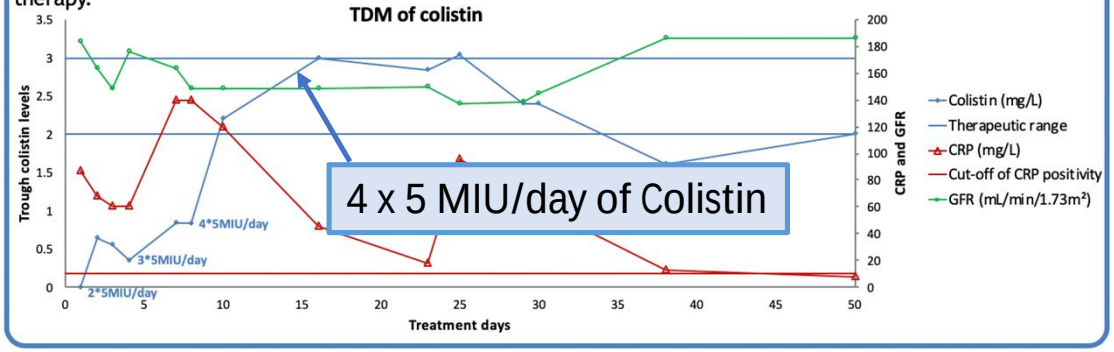
TDM of Gentamicin at
- Trough: < 2 mg/L
- 60 minutes: 10-15 mg/L

Requirement of Very High Doses of Colistin in a Critically Ill Patient with Augmented Renal Clearance

D. Fage[1], A. Herpain[1], G. Deprez[1], F. Wolff[1], M. Hites[1], F. Van Bambeke[1], F. Cotton[1], F. Jacobs[1]
[1] CUB Erasme Hospital ULB, Brussels, BC, Belgium [2] Louvain Drug Research Institute UCL, Brussels, BC, Belgium

RESULTS

The first colistin assay performed on day 4 was largely below the therapeutic target (0.36 mg/L). The recommended maintenance dose was therefore increased to 3*5 MIU per day. On day 7, a new colistin determination showed again a subtherapeutic concentration (0.84 mg/L). As no clinical or biological improvement was noted, the dosage regimen was therefore increased to 4*5 MIU per day on day 8. With this dose, between day 10 and end of therapy (day 51), colistin concentrations remained within therapeutic ranges. The inflammatory biomarkers decreased gradually and the clinical situation improved. Colistin therapy was stopped after two months, because there were no more biological or clinical signs of acute infection. Renal function, followed every day (sCr, GFR and diuresis) remained unchanged during the entire duration of colistin therapy.



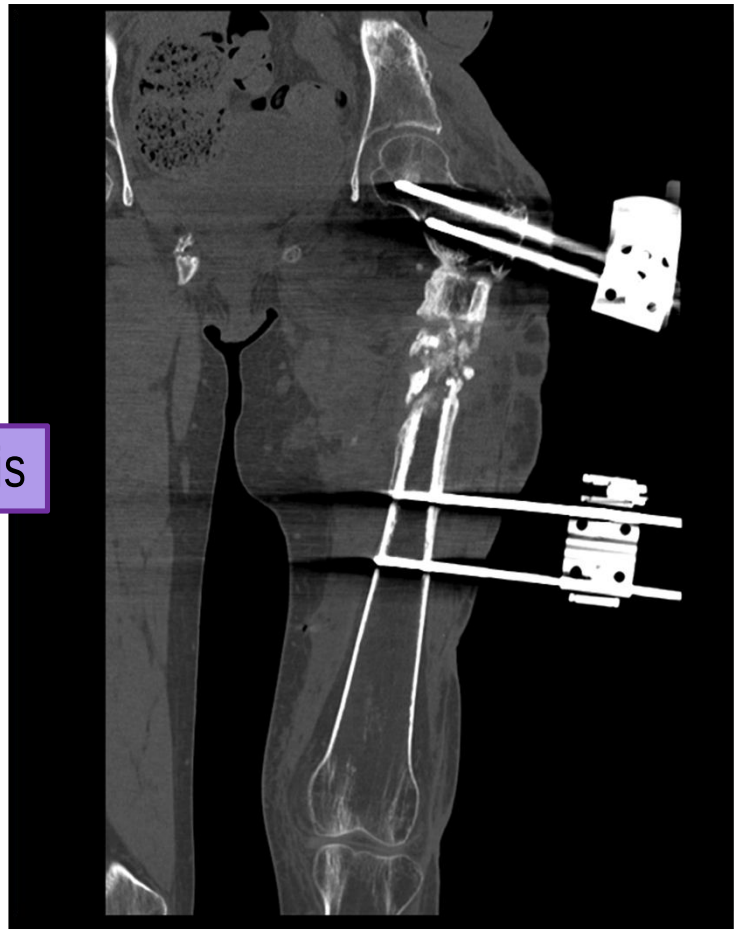
Creatinine clearance > 120 mL/min

Case n°2: 31 years old female

- **Days 100- 169:**
  - Purulent discharge from the orifices of the pins
  - Fistula
  - No consolidation of the left femur

Chronic osteomyelitis

- **Day 170:**
  - change of the external fixator
  - extensive debridement
  - new microbiological samples:
    - *Klebsiella pneumonia*
    - *Staphylococcus aureus*
    - *Mycobacterium xenopi*

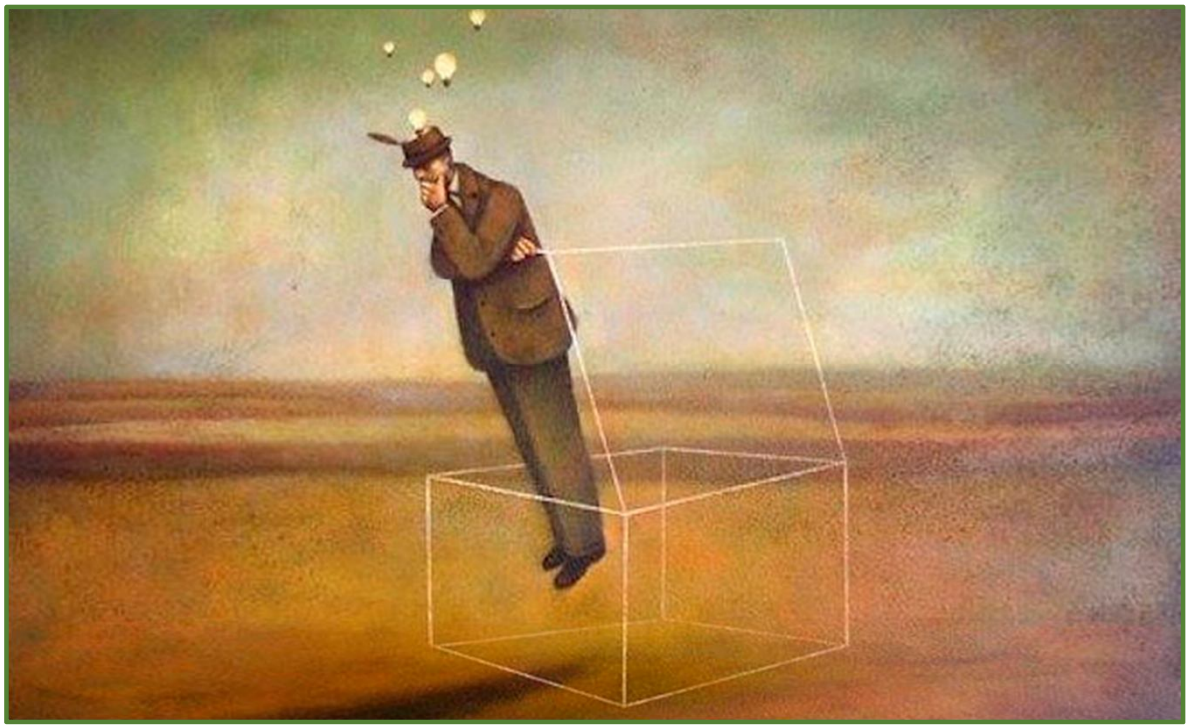


Left hip and thigh (antero-external view)

Antibiotics	*Kl. pneumoniae* 1 (Day 3)		*Kl. pneumoniae* 2 (Day 170)		*Kl. pneumoniae* 3 (Day 170)	
	S/I/R	CMI (µg/mL)	S/I/R	CMI (µg/mL)	S/I/R	CMI (µg/mL)
Ampicillin	R		R		R	
Amoxicillin-clavulanic acid	R		R		R	
Piperacillin -tazobactam	R	> 128	R	> 128	R	
Temocillin	R	= 256		= 256	R	
Cefuroxime	R		R		R	
Ceftazidime	R	> 64	R	> 64	R	
Ceftriaxone	R		R		R	
Cefotaxime	R	> 64	R	> 64	R	
Cefepime	R	> 64	R	> 64	R	
Aztreonam	R	> 64	R	> 64	R	
Imipenem	I		R	> 32	R	
Meropenem	R	> 32	R	> 32	R	
Ertapenem	R	> 32	R	> 32		
Gentamicin	S	< 1	R	> 8	R	
Amikacin	I	= 16	S	< 1	I	
Tobramycin	R	> 8	R	> 8		
Cotrimoxazole	S		R		R	
Ciprofloxacin	R	= 2	R	= 2	R	
Minocycline	S		R		R	
Tigecycline	S	= 0,5	I	= 2	R	
Chloramphenicol	S		S		R	
Fosfomycin	S		R		I	
Colistin	S	0,25	R	> 8	R	> 256

Case n°2: 31 years old female

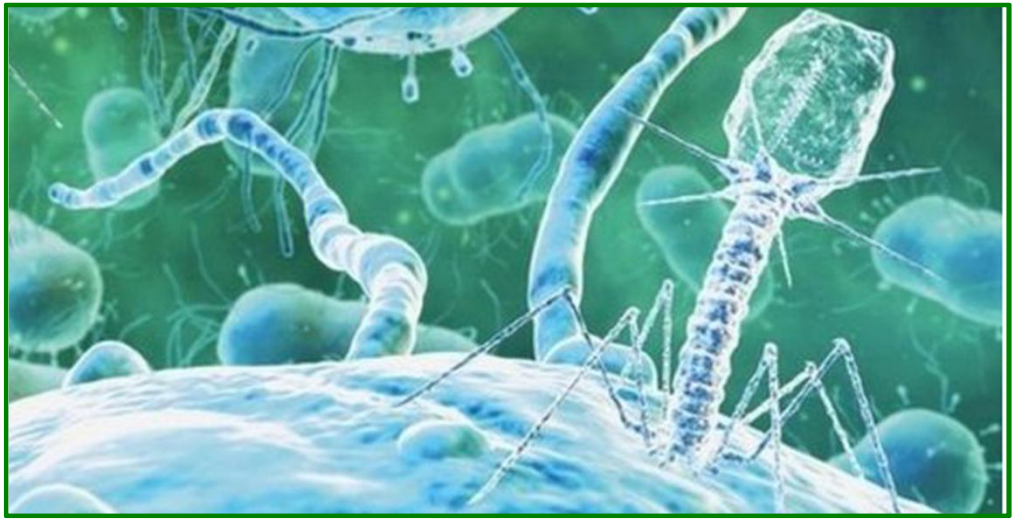
It was time to really start thinking out of the box……



In the meantime…. A new antibiotic treatment was initiated: high dose IV Meropenem/ Colistin/Oxacillin/Clarithromycin/Rifampicin/Ethambutol

Case n°2: 31 years old female

- DNA or RNA viruses that infect bacteria
- Do not infect human cells!
- Ubiquitaire: microbiome, environnement
- 2 phases:
  - Lytic: cell lysis is obligatory for viral replication
  - Lysogenic: integrated in the cell's genome (pro-phage state)



- Phages are species, but also often strain specific → cocktails of multiple phages are required to target multiple species and even strains within a species!
- *In-vitro* studies have shown activity against biofilms

Case n°2: 31 years old female

- **Day 700:** phage cocktail received from the Eliava Institute in Georgia

February 2018

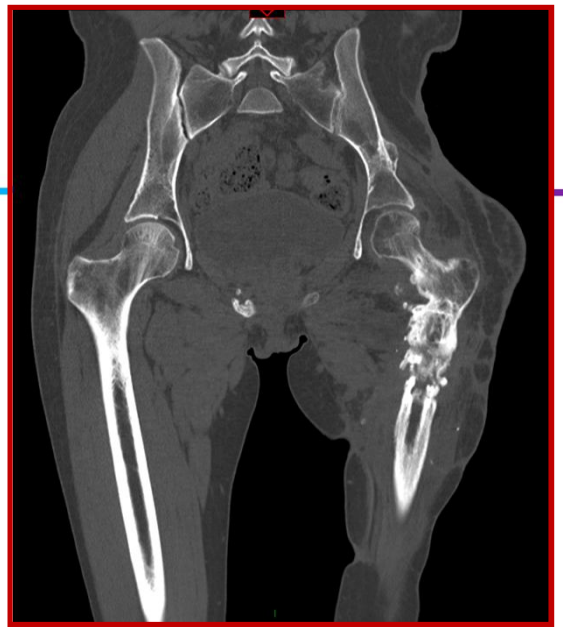
- **Day 701:** verification of the purity of the phage cocktail at the Queen Astrid Military Hospital

- **Day 702:** Surgery
  Large debridement
  Rifampicin impregnated autologous bone grafts
  Catheter placed in the wound for Phage cocktail therapy

End of surgery: 100 mL of
Phage cocktail
(6×10^{10} PFU/ mL) to rinse the wound
+
20 mL x 3/day for 5 days

- **Day 710-798**: New antibiotic combination therapy
  STOP Meropenem/Colistin
  Ceftazidime-avibactam IV (compassionate use) +
  Tigecycline high dose IV (Stop on Day 725 due to Acute pancreatitis (Grade A)+
  Moxifloxacine IV

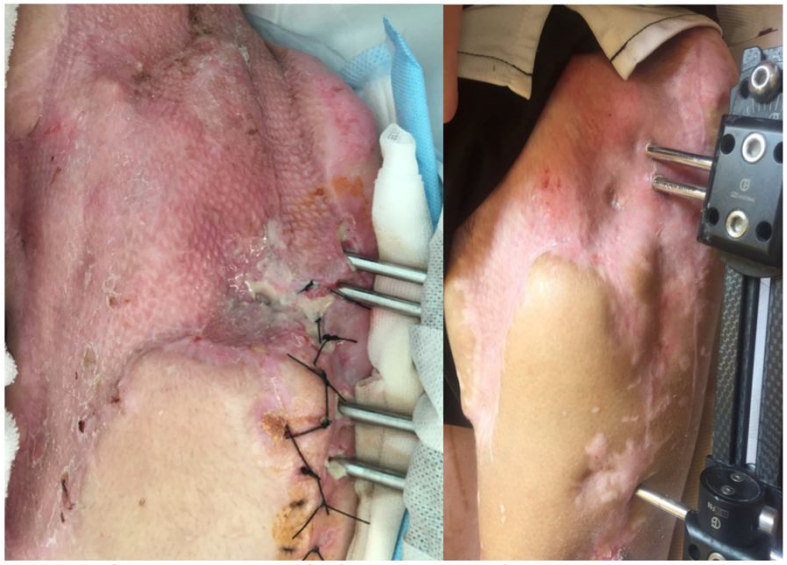
Case n°2: 31 years old f



- **Day 798:**
  - 5 kg weight gain
  - Consolidation of the left femur fracture

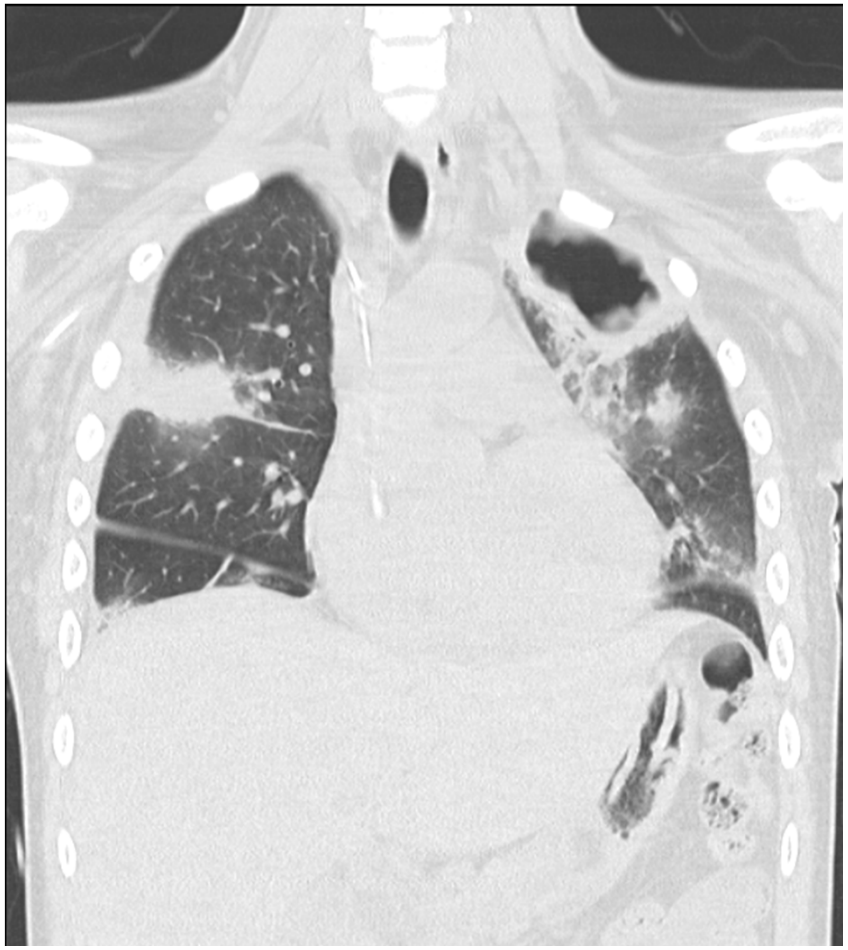
- **Day 806:** removal of external fixator!

- Microbiological samples taken for culture on **day 806** remained negative for the first time!



Case n°3: 16 years old male

- Transfer from another institution for left upper lobectomy for a pulmonary abscess due to a Pan-R ***Pseudomonas aeruginosa***
- History: Hemolytic anemia, treated with Sirolimus + Methylprednisolone
- Patient admitted 7 weeks earlier for a necrotizing pneumonia- no pathogen identified upon admission, but 4 weeks after admission, Multi-R Pseudomonas aeruginosa identified
- Anti-infective agents received since admission:
  - Ceftriaxone
  - Meropenem + Vanco + Ambisome IV
  - Colistin + Zyvoxid + Tobramycin IV, then aerosols



Case n°3: 16 years old male

- Last microbiological sample: 2 weeks prior to transfer:

	MIC (mg/L)
Colistin	2
Piperacillin/tazobactam	16
Ceftazidime/avibactam	>32
Ceftazidime	48
Meropenem	32
Amikacin	12
Tobramycin	S

- Treatment upon transfer:
  - Colistin IV: 235, 000 UI x 3/day
  - Linezolid PO 600 mg x 2/day
  - Tobramycin aerosols 160 mg x 2/day

- Re-adaptation of treatment :
  - Colistin: 3 MUI x 2/d + TDM
  - Piperacillin-tazobactam: 4 g loading dose, then 16 g/d in continuous infusion
  - Tobramycin IV 400 mg/d

TDM Piperacillin: 172.5 mg/L

Serum creatinine: 2.74 mg/dL
Creatinine Clearance (8h urine collect: 30 mL/min)

Case n°3: 16 years old male

11/04/2019 15:20 UMT388 CAPPELLO Matteo Biopsie ou autre prélèvement profond (pulmonai

11/04/2019 15:20 Biopsie ou autre prélèvement profond (pulmonaire)

Examen direct

Polynucléaires	(2+)
Hématies	(1+)
Flore	Présence de
Bacilles gram négatif	(2+)

Culture aérobie

Culture aérobie	1. Pseudomonas aeruginosa 3+
	1
Pipéra. +Tazobactam	R
Ceftazidime	R
Céfépime	R
Aztreonam	R
Imipénem	R
Méropéneme	R
Gentamicine	R
Amikacine	R
Tobramycine	R
Ciprofloxacine	R
Colistine	S

CMI Amikacine R (CMI = 128 µg/mL)
CMI Aztreonam R (CMI = 64 µg/mL)
CMI Céfépime R (CMI = 64 µg/mL)
CMI Ceftazidime R (CMI = 64 µg/mL)
CMI Ceftazidime/avibactam R (CMI = 32 µg/mL)
CMI Ceftozolam/tazobactam S (CMI = 4 µg/mL)
CMI Ciprofloxacine R (CMI = 16 µg/mL)
CMI Colistine S (CMI = 4 µg/mL)
CMI Gentamicine R (CMI = 64 µg/mL)
CMI Imipéneme R (CMI = 32 µg/mL)
CMI Méropéneme R (CMI = 32 µg/mL)
CMI Pipéracilline +Tazobactam R (CMI = 256 µg/mL)
CMI Tobramycine R (CMI = 16 µg/mL)

No mechanisms of resistance identified

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

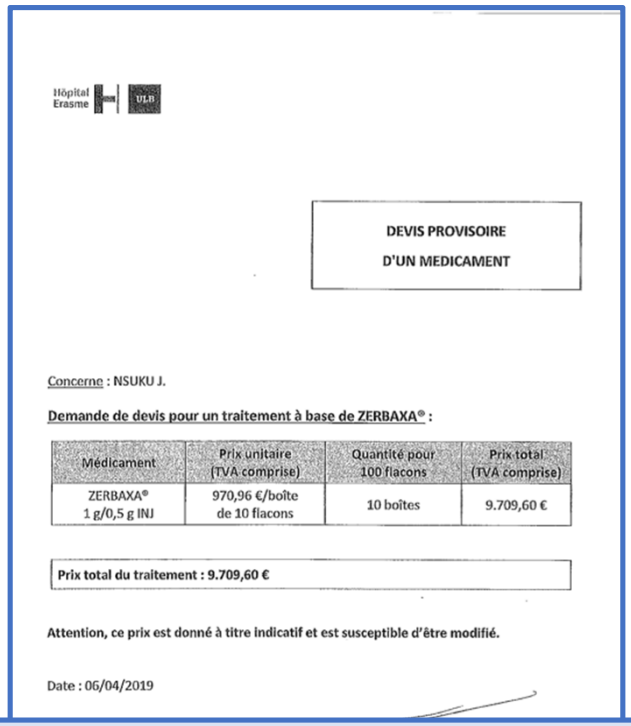
Ghady Haidar,[1] Nathan J. Philips,[2] Ryan K. Shields,[1,3,4] Daniel Snyder,[2] Shaoji Cheng,[4] Brian A. Potoski,[1,3,5] Yohei Doi,[1] Binghua Hao,[4] Ellen G. Press,[1] Vaughn S. Cooper,[2] Cornelius J. Clancy,[1,4,6a] and M. Hong Nguyen[1,3,4a]

[1]Department of Medicine, University of Pittsburgh, [2]Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, [3]Antibiotic Management Program, and [4]XDR Pathogen Laboratory, University of Pittsburgh Medical Center, [5]Department of Pharmacy and Therapeutics, University of Pittsburgh, and [6]VA Pittsburgh Healthcare System, Pennsylvania

- Retrospective study on 21 patients
  - 18 with respiratory infections
- Success rate: 13/21 (71%)
- Emergence of R (*de novo* mutations): 3/21 (14%)

Case n°3: 16 years old male

- Ceftolozane-tazobactam was imported + Fond de Solidarité was solicited to pay for treatment
- Re-adaptation of treatment :
  - Colistin: 2 MUI x 2/day + TDM
  - Meropenem: 2g x 2/day + TDM
  - Ceftolozane-tazobactam 1.5 x 3/day
- Stop all AB treatment 5 weeks later



Hôpital Erasme | ULB

DEVIS PROVISOIRE
D'UN MEDICAMENT

Concerne : NSUKU J.

Demande de devis pour un traitement à base de ZERBAXA® :

Médicament	Prix unitaire (TVA comprise)	Quantité pour 100 flacons	Prix total (TVA comprise)
ZERBAXA® 1 g/0,5 g INJ	970,96 €/boîte de 10 flacons	10 boîtes	9.709,60 €

Prix total du traitement : 9.709,60 €

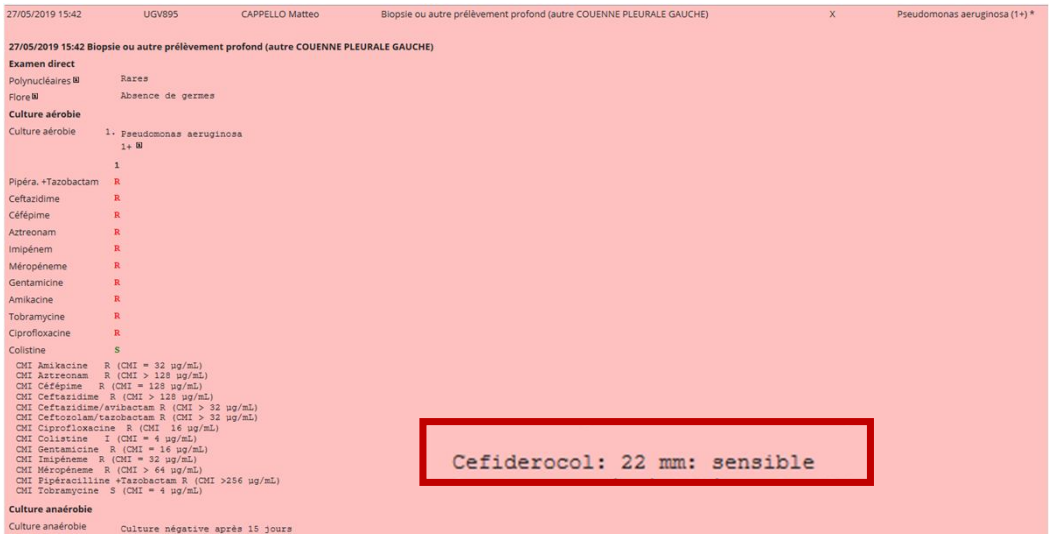
Attention, ce prix est donné à titre indicatif et est susceptible d'être modifié.

Date : 06/04/2019

Increase in air leaks → need for lower lobectomy as well, 4 weeks after upper lobectomy

Case n°3: 16 years old male

- 10 days after lower lobectomy: fever + increase in inflammatory syndrome <empyema
- Culture of lung:



27/05/2019 15:42 UGV895 CAPPELLO Matteo Biopsie ou autre prélèvement profond (autre COUENNE PLEURALE GAUCHE) X Pseudomonas aeruginosa (1+) *

27/05/2019 15:42 Biopsie ou autre prélèvement profond (autre COUENNE PLEURALE GAUCHE)

Examen direct

Polynucléaires [N] Rares
Flore [N] Absence de germes

Culture aérobie

Culture aérobie 1. Pseudomonas aeruginosa 1+ [N]

1

Pipéra. +Tazobactam	R
Ceftazidime	R
Céfépime	R
Aztreonam	R
Imipénem	R
Méropéneme	R
Gentamicine	R
Amikacine	R
Tobramycine	R
Ciprofloxacine	R
Colistine	S

CMI Amikacine R (CMI = 32 µg/mL)
CMI Aztreonam R (CMI > 128 µg/mL)
CMI Céfépime R (CMI = 128 µg/mL)
CMI Ceftazidime R (CMI > 128 µg/mL)
CMI Ceftazidime/avibactam R (CMI > 32 µg/mL)
CMI Ceftozolam/tazobactam R (CMI > 32 µg/mL)
CMI Ciprofloxacine R (CMI 16 µg/mL)
CMI Colistine I (CMI = 4 µg/mL)
CMI Gentamicine R (CMI = 16 µg/mL)
CMI Imipéneme R (CMI = 32 µg/mL)
CMI Méropéneme R (CMI > 64 µg/mL)
CMI Pipéracilline +Tazobactam R (CMI >256 µg/mL)
CMI Tobramycine S (CMI = 4 µg/mL)

Culture anaérobie

Culture anaérobie Culture négative après 15 jours

Cefiderocol: 22 mm: sensible

- Thoracic drain + Antibiotics for 6 weeks:
  - Compassionate use of Cefiderocol +
  - Colistin IV +
  - Tobramycin aerosol

<u>Cephalosporine siderophore</u>

- Uses iron pumps to traverse the membrane of the GNB → AB arrives directly in the cytoplasme to bind to « Penicillin-binding proteins » → inhibition of bacteria wall synthesis
- **<u>Shoengi study:</u>** Meropenem + Zyvoxid vs. Cefiderocol for VAP due to GNB

- Discharged from the hospital, and is doing well, after
  - 5 months of hospitalization
  - Left lung pneumectomy

Conclusions

- These cases illustrate several points concerning resistant GNB:
  - Acquisition of MDR GNB is definitely a risk in hospitalized patients. Prior AB treatment ++++++
  - Risk for subsequent infections due to MDR GNB is significantly higher for hospitalized patients with MDR GNB colonization than in patients without colonization.
  - Patients colonized by MDR GNB may nevertheless develop infections due to very susceptible bacteria.
  - Risk of inappropriate empiric antibiotic regimens is greater when there is an infection due to a MDR GNB.
  - Health care costs are significantly increased when there are infections due to MDR GNB due to:
    - Longer hospitalisations
    - Longer treatments
    - Use of second to last line antibiotics

Conclusions: Infections due to MDR GNB

- Patients are exposed to significant antibiotic pressure because of administration of many antibiotics and at high dosage regimens to try to treat the infection

- Patients are at greater risk for adverse events due to antibiotics than patients treated for multi-susceptible pathogens:
  - Possible hearing loss < aminoglycosides
  - Renal tubulopathy < Colistin
  - Renal insufficiency < Colistin/ Aminoglycosides
  - Acute pancreatitis < high dose Tigecycline
  - Neutropenia < high dose meropenem

- Despite combination therapy, bugs continue to get more R!!!!

- Increased Paper work ++++++
  - Compassionate use programs
  - Ethics committee (Phages, Cefiderocol)
  - Importation of new antibiotics
  - Fonds Spécial de Solidarité (FSS)

Conclusions

- These cases also illustrate the benefit/need to:
  - work in a multi-disciplinary fashion
  - collaborate
  - “think out of the box”: novel therapeutic approaches, new antibiotics….
- Outcomes were positive for our patients. However, it is impossible to determine if this was due to the:
  - Use of phages
  - Use of different new antibiotics
  - Agressive source control, etc…

Efficacy of these novel treatments for MDR pathogens will still have to be demonstrated!

- Risk of developing rapid R to these last line drugs is a reality

Conclusions

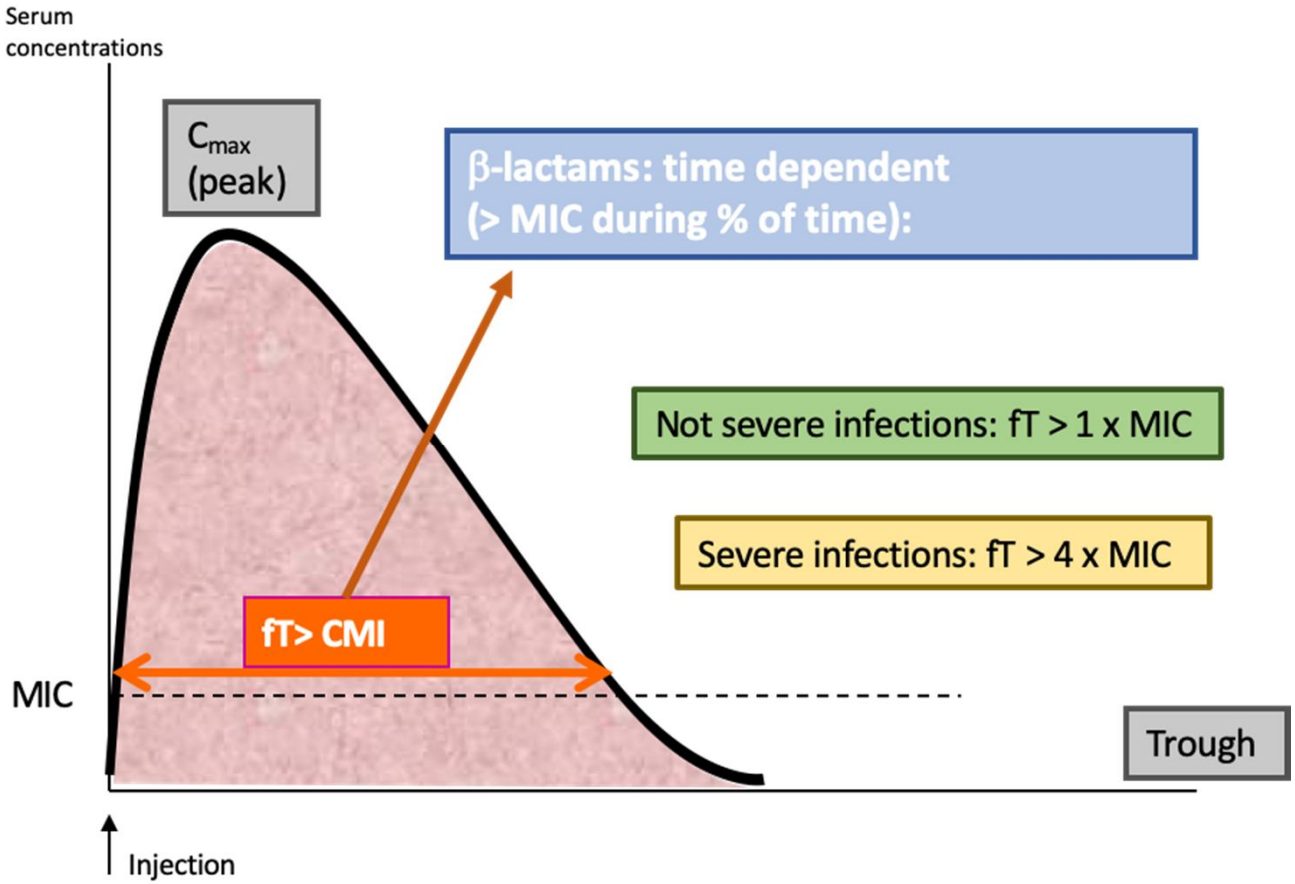
- Treating infections due to MDR GNB is very challenging!
  - Need for individualized treatments: the optimal treatment for one patient with a MDR GNB infection may not be the optimal one for another!
  - Importance of source control!

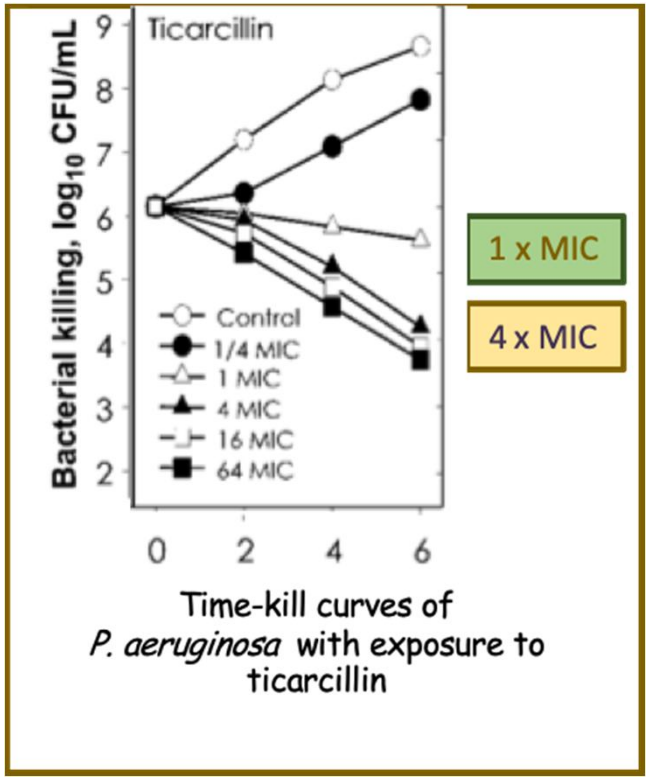
- When treating these infections, it is important to take into account the:
  - patient
  - severity of the infection
  - site of the infection
  - Antibiogram (+ enlarged Antibiogram)
  - MIC of the pathogen

Infectious disease specialists + microbiologists (people knowledgeable in this domain) are needed to treat these infections in an optimal fashion → **best outcomes for our patients!**


Thank you for your attention!
Some light at the end of the tunnel?

PK/PD index for Beta-Lactams





Craig WA et al. Scand J Infect Dis Suppl 1990; 74: 63-70.

Meropenem

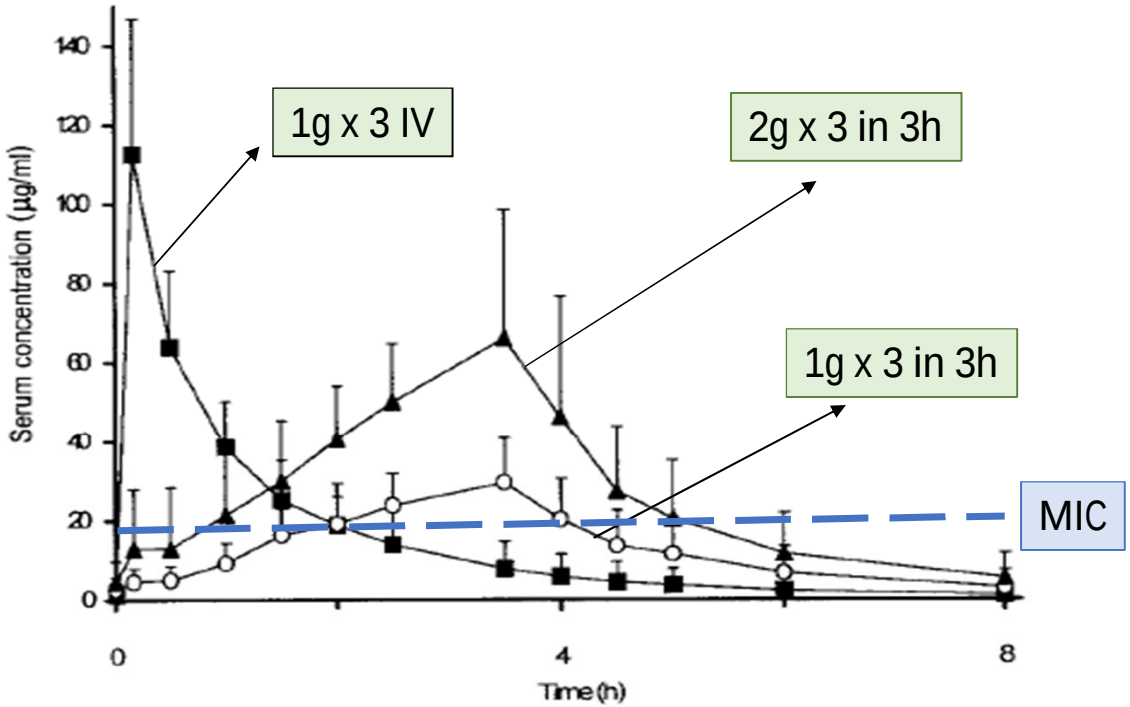


FIG. 1. Mean serum meropenem concentration-time data for nine patients with VAP following administration of 1 g by bolus injection (filled squares), 1 g by a 3-h infusion (open circles), and 2 g by a 3-h infusion (filled triangles).

Jaruratanasirikul et al. Antimicrob Agents Chemother. 2005. doi: 10.1128/AAC.49.4.1337-1339.2005

AAC Journals.ASM.org

Optimal Meropenem Concentrations To Treat Multidrug-Resistant *Pseudomonas aeruginosa* Septic Shock

Fabio Silvio Taccone,[a] Frédéric Cotton,[b] Sandrine Roisin,[c] Jean-Louis Vincent,[a] and Frédérique Jacobs[d]

TABLE 1 Meropenem regimens, concentrations, and pharmacodynamics during therapy[a]

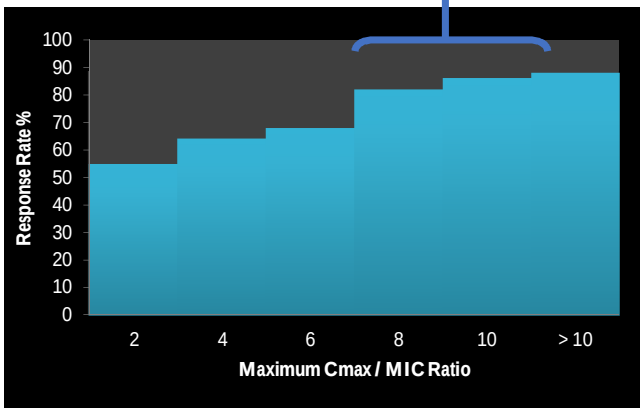
Day of therapy	MEM dose	Time of sampling	MEM concn (mg/liter)	MIC (mg/liter)	% T > 4× MIC
1	1 g q8h				
2	1 g q8h	2 h	12.3	2	37
		8 h	<2.0		
5	1 g q8h	2 h	13.4	2	39
		8 h	<2.0		
9	2 g EI q8h	3 h	17	4	39
		8 h	3		
15	3 g EI q6h	3 h	43	8	51
		6 h	19		

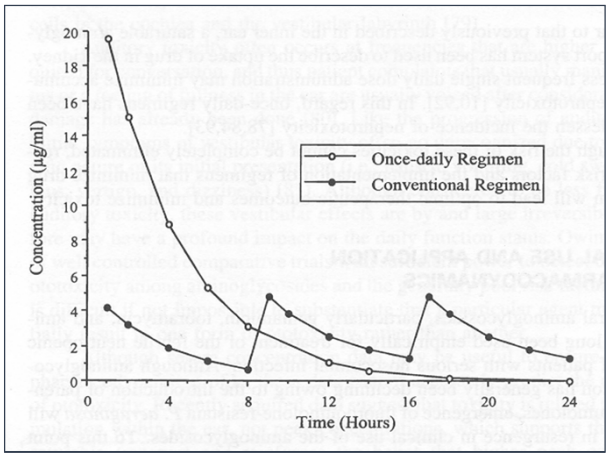
[a] MEM, meropenem; q8h and q6h, every 8 h and 6 h; EI, extended infusion (over 3-h period); 2 h, 3 h, 6 h, and 8 h, 2, 3, 6, and 8 h after the onset of MEM administration; T > 4× MIC, time above 4 times the MIC.

Taccone and al. Antimicrob Agents Chemother. 2012. doi:10.1128/AAC.06389-11

Aminoglycosides

8-10 x MIC





Moore, J Infect Dis 1987

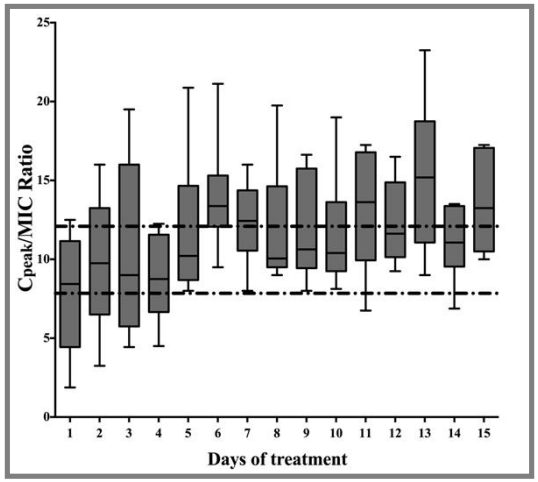
- PK/PD index:
  Cmax/MIC > 8-10
- 1 time/day:
  - Better efficacy
    - High Cmax/MIC
    - Post-antibiotic effect
  - Less Toxicity

J Antimicrob Chemother 2016; **71**: 1386–1394
doi:10.1093/jac/dkv491 Advance Access publication 31 January 2016

Journal of Antimicrobial Chemotherapy

A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study

Alexandre Brasseur[1], Maya Hites[2], Sandrine Roisin[3], Frédéric Cotton[4], Jean-Louis Vincent[1], Daniel De Backer[1], Frédérique Jacobs[2] and Fabio Silvio Taccone[1]*



- Clinical response: 8/15 patients
- Discharged from the hospital alive: 5/15 patients
- 100% recuperation of the renal function: 4/5 patients

Colistin

Acts as a detergent: Perturbs the cellular membrane

- Bactericidal effect: concentration-dependent
  - PK/PD index = $AUC_{0\text{-}24}$/MIC
  - Narrow therapeutic window:
    - Efficacy: ≥ 2 mg/L
    - Risk of nephrotoxicity: ≥ 2,5 mg/L

- <u>If creatinine CL >80 mL/min:</u>

+/- impossible to attain therapeutic serum concentrations because CMS is cleared++++

→ Bi-therapy is needed!

Creatinine clearance (mL/min)	CBA en MUI/jour
0	4
5 à < 30	5
30 à < 40	6
40 à < 50	7
50 à < 60	8
60 à < 80	9
80 à < 90	10
> 90	12 et/ou bi-therapy

Nation RL, et al. *Clin Infect Dis*. 2017; 64(5): 565-571 .

Open Forum Infectious Diseases

MAJOR ARTICLE

Higher MICs (>2 mg/L) Predict 30-Day Mortality in Patients With Lower Respiratory Tract Infections Caused by Multidrug- and Extensively Drug-Resistant *Pseudomonas aeruginosa* Treated With Ceftolozane/Tazobactam

Olga Rodríguez-Núñez,[1] Leonor Periañez-Parraga,[2] Antonio Oliver,[3] Jose M. Munita,[4,5] Anna Boté,[6] Oriol Gasch,[6] Xavier Nuvials,[7] Aurélien Dinh,[8] Robert Shaw,[9] Jose M. Lomas,[9,10] Vicente Torres,[11] Juanjo Castón,[12] Rafael Araos,[5] Lilian M. Abbo,[13] Robert Rakita,[14] Federico Pé[15] Samuel L. Aitken,[16] Cesar A. Arias,[4,5] M. Luisa Martín-Pena,[17] Asun Colomar,[18] M. Belén Núñez,[19] Josep Mensa,[1] José Antonio Martínez,[1] and Alex S

Antimicrobial Agents and Chemotherapy®

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne bla_{KPC-3} Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,[a,b] Liang Chen,[c] Shaoji Cheng,[a] Kalyan D. Chavda,[c] Ellen G. Press,[a] Avin Snyder,[a] Ruchi Pandey,[c] Yohei Doi,[a] Barry N. Kreiswirth,[c] M. Hong Nguyen,[a,b] Cornelius J. Clancy[a,b,d]

Treatment

2-3 drugs > 1 drug

Carbapenem (MIC ≤ 8 mg/L) + tigecyclin + colistin

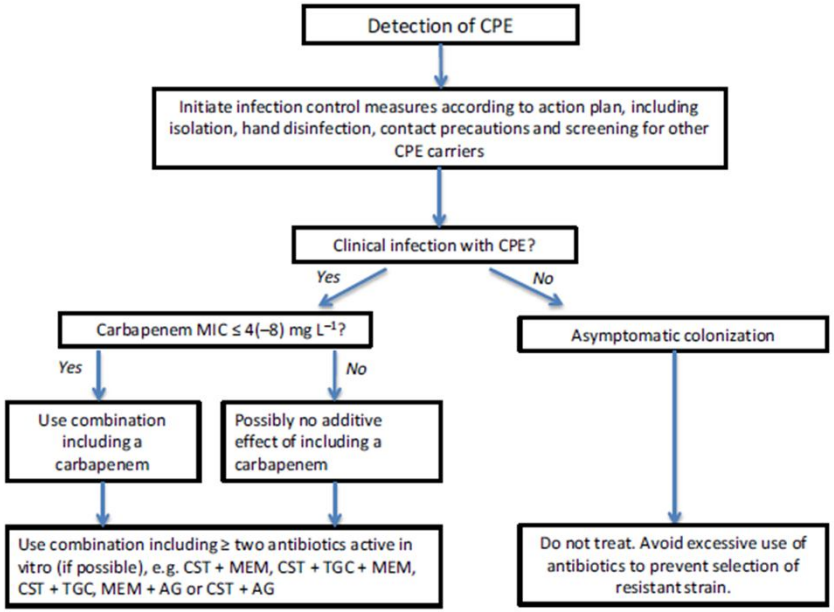


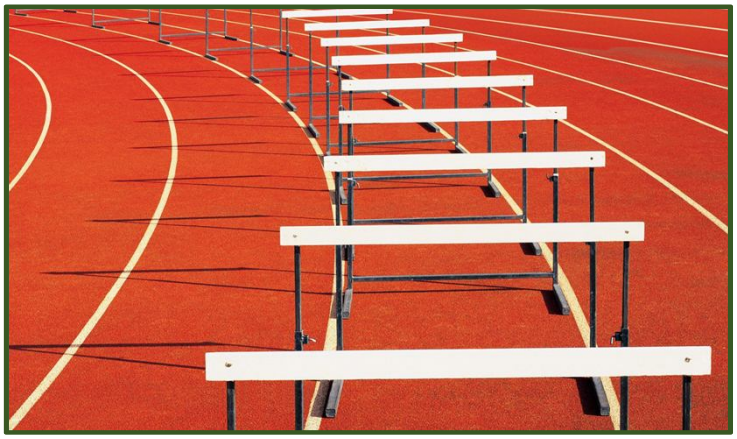
Fig. 5 *Decision tree for management of patients infected or colonized with carbapenemase-producing Enterobacteriaceae (CPE). Note that existing clinical evidence for the choice of therapy is limited and based on the results from retrospective studies. CST, colistin; MEM, meropenem; AG, aminoglycoside; TGC, tigecycline.*

Journal of Internal Medicine, 2015, 277; 501–512

Tangden J Inter Med 2015; 277: 501-512

Conclusions

- Although this case report provides hope for further use of phage therapy in other patients with multi-drug resistant infections, **significant hurdles** remain before alternative strategies such as phage therapy can be widely adopted into clinical practice



More research and money are urgently needed!

Estimated needed investment of ≥ 1.1 billion €
(committed in the next 3 years + spent within 8 years to truly initiate a pipeline of translational projects that would develop new therapies)

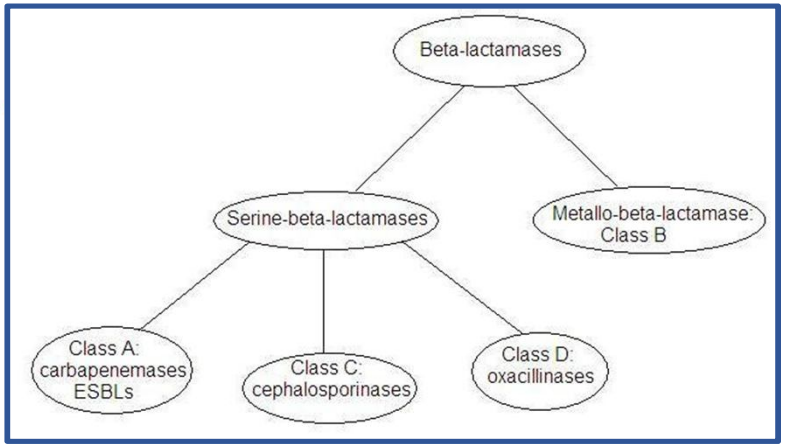
Czaplewski L et al. Lancet Infect Dis 2016; 16: 239-51.

	Target	Product name, reference	Phase as of January–March, 2015	Earliest anticipated registration	Probability of registration by 2025	Risk-adjusted cost of projects; current phases, subsequent phases (£ million)	Pipeline investment needed for additional phase 2 validation (£ million)
Antibodies							
Merck	*Clostridium difficile*	Bezlotoxumab[112,113]	Phase 3 ongoing	2017	–	–	–
MedImmune	*Staphylococcus aureus*	MEDI4893[114]	Phase 2 ongoing	2021	–	–	–
Aridis	*Pseudomonas aeruginosa*	AR-101[115]	Phase 2a complete	2021	–	–	–
Aridis	*S aureus*	AR-301[115]	Phase 2a ready	2022	–	–	–
MedImmune	*P aeruginosa*	MEDI3902[3]	Phase 1 ongoing	2023	–	–	–
XBiotech	*S aureus*	514G3[23]	Phase 1 ongoing	2023	–	–	–
Aridis	*P aeruginosa*	Aerucin[23]	IND ready	2025	–	–	–
Combined	–	–	–	–	183%	60, 120	–
Probiotics							
Seres	*C difficile*	SER-109[109]	Phase 3 ready	2018	–	–	–
Rebiotix	*C difficile*	RBX2660[115]	Phase 2 ongoing	2019	–	–	–
Shire (Viropharma)	*C difficile*	VP20621[122]	Phase 2 ready	2022	–	–	–
Combined	–	–	–	–	124%	52, 53	–
Lysins							
Intron Biotechnology	*S aureus*	SAL200[97]	Phase 1 ongoing	2022	–	–	–
ContraFect	*S aureus*	CF-301[93]	Phase 1 ongoing	2022	–	–	–
Combined	–	–	–	–	26%	12, 28	135
Bacteriophages							
Wild-type bacteriophages							
AmpliPhi	*C difficile*	AmpliPhage-004[123]	Pre-phase 1	2023	–	–	–
AmpliPhi	*P aeruginosa*	AmpliPhage-001[123]	Pre-phase 1	2023	–	–	–
Engineered bacteriophages							
Phico Therapeutics	*P aeruginosa*	PT-3.1[34]	Pre-phase 1	2023	–	–	–
Combined	–	–	–	–	9%	13, 57	135
Immune stimulation							
Akthelia	*C difficile*	Phenylbutyrate/vitamin D[34,35]	Phase 2 ready	2021			
Various	Various	Bacterial extracts[83]	Phase 1 ready	2022			
Combined	–	–	–	–	43%	0, 55	–
Vaccines							
Sanofi Pasteur	*C difficile*	*C difficile* toxoid vaccine[124]	Phase 3	2019	–	–	–
Valneva	*P aeruginosa*	IC43[125,126]	Phase 2 and Phase 3 ongoing	2019	–	–	–
Valneva	*C difficile*	IC84[126]	Phase 2 ongoing	2021	–	–	–
Pfizer	*S aureus*	SA4Ag[127]	Phase 2 ready	2021	–	–	–
Combined	–	–	–	–	188%	74, 66	–
Antimicrobial peptides							
Roche	*P aeruginosa*	POL7080[128]	Phase 2 ongoing	2022	–	–	–
Novacta Biosystems	*C difficile*	NVB302[129]	Phase 1 ongoing	2022	–	–	–
Adenium	*S aureus*	AP-138[64]	Pre-phase 1	2023	–	–	–
Adenium	Urinary tract infection	AP-139[64]	Pre-phase 1	2023	–	–	–
Adenium	*C difficile*	AP-114[64]	Pre-phase 1	2023	–	–	–
Combined	–	–	–	–	52%	16, 104	135
Other peptides							
Various	Gram-negative and Gram-positive	–	Preclinical	2027	–	–	604*

- Vaccins
- Modulation du microbiome
- Bactériophages
- Facteurs anti-virulents

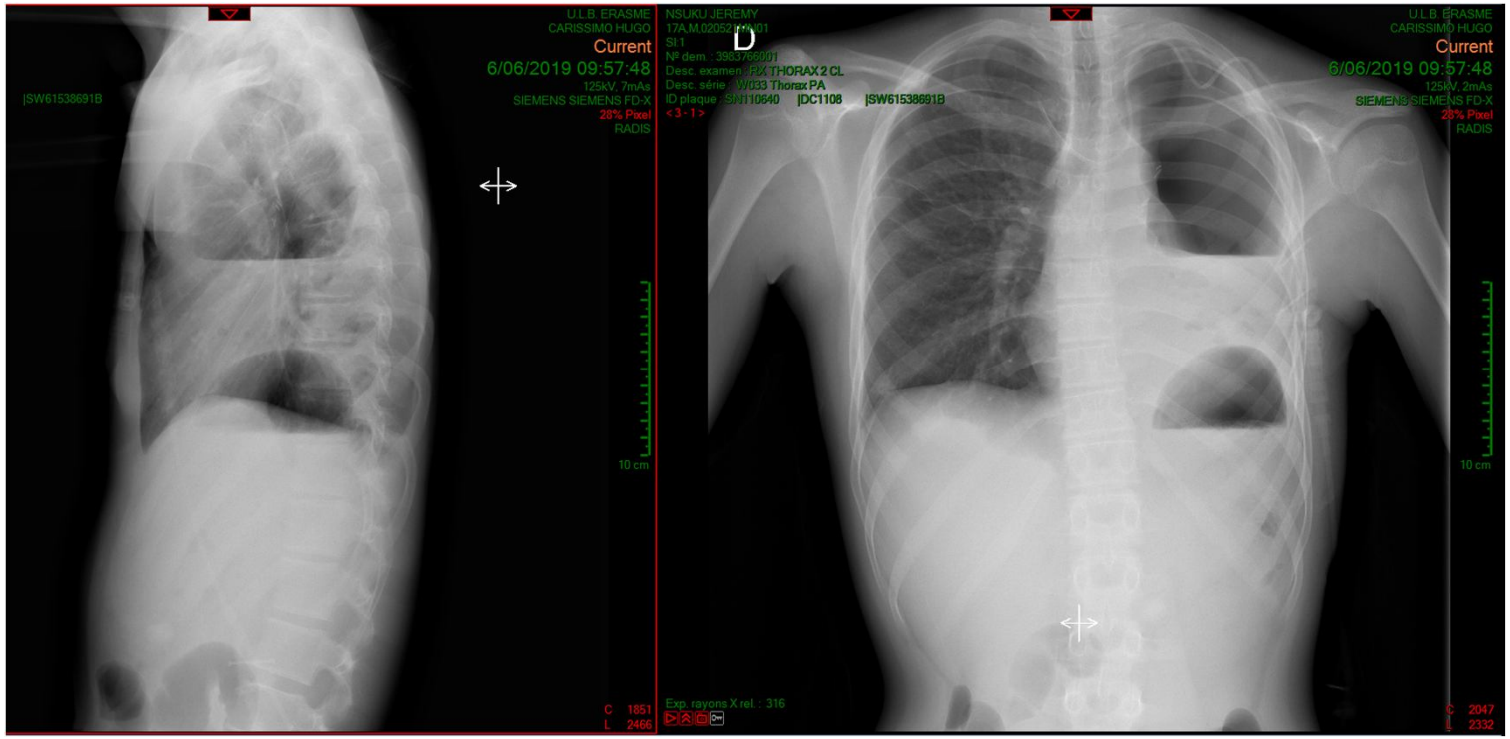
Czaplewski L et al. Lancet Infect Dis. 2016. 16: 239-51.

Les β-lactamases



Ambler classification	Description or characteristics	Examples of enzymes	Bacterial strains
Class A (serine β-lactamase)	Cephalosporinases (ESBLs) Usually clavulanic acid susceptible, except for KPC	TEM, SHV, CTX-M, **KPC**, VEB	*Enterobacteriaceae*, *Pseudomonas* spp.
Class B (metallo-β-lactamase or MBL)	Contain metal ion (Zn) Carbapenemases Not inhibited by clavulanic acid Inhibited by aztreonam	**IMP, VIM, NDM**	*Enterobacteriaceae*, *Acinetobacter* spp., *Pseudomonas* spp.
Class C (AmpC β-lactamase – serine β-lactamase)	Resistant to clavulanic acid Intrinsic in certain species of Gram-negative	CMY, DHA	*Enterobacteriaceae*
Class D (serine β-lactamase)	Oxacillinases Susceptible to clavulanic acid Carbapenemase	**OXA**	*Enterobacteriaceae* (OXA-48 like), *Acinetobacter* spp.

Note: Enzymes in bold are carbapenemases.


U.L.B. ERASME
CARISSIMO HUGO
Current
6/06/2019 09:57:48
125kV, 7mAs
SIEMENS SIEMENS FD-X
28% Pixel
RADIS
|SW61538691B
10 cm
C 1851
L 2466
NSUKU JEREMY
SI:1
D
Desc. examen : RX THORAX 2 CL
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ID plaque : SN110640 |DC1108 |SW61538691B
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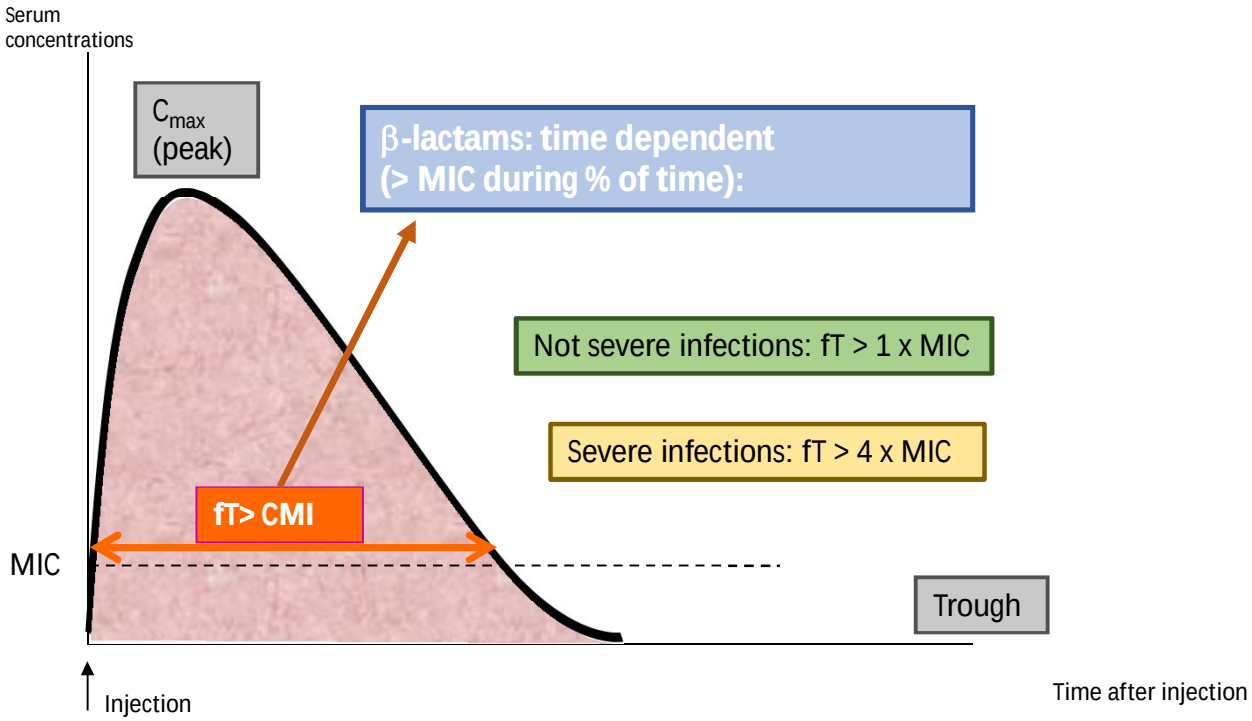
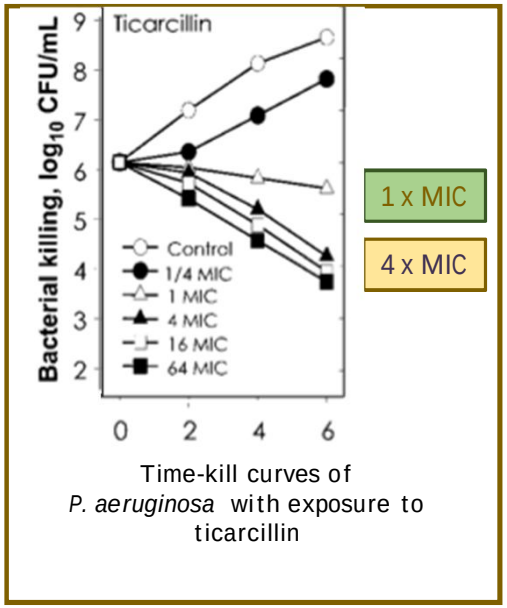
U.L.B. ERASME
CARISSIMO HUGO
Current
6/06/2019 09:57:48
125kV, 2mAs
SIEMENS SIEMENS FD-X
28% Pixel
RADIS
10 cm
Exp. rayons X rel. : 316
C 2047
L 2332

PK/PD index for Beta-Lactams

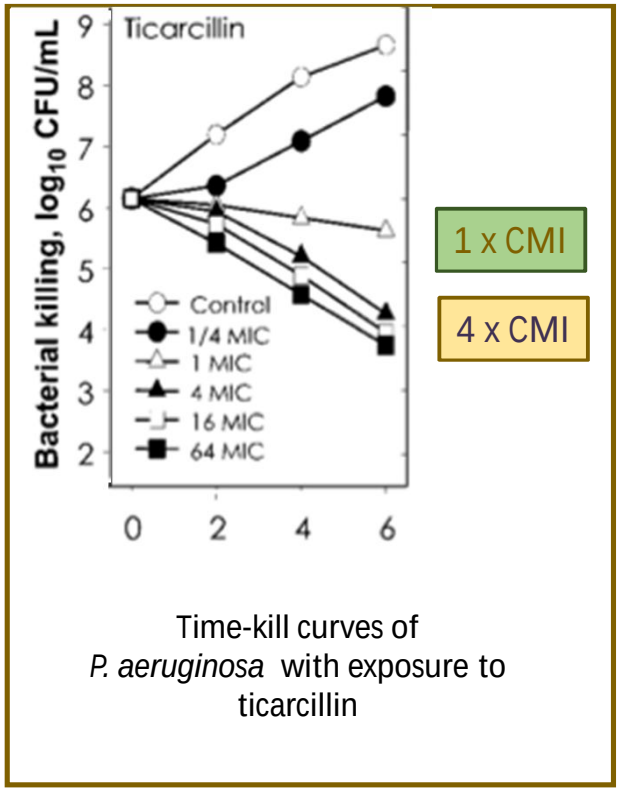




Time-kill curves of *P. aeruginosa* with exposure to ticarcillin

Craig WA et al. Scand J Infect Dis Suppl 1990; 74: 63-70.

Mais..... parfois il est impossible d'optimiser le traitement



Time-kill curves of *P. aeruginosa* with exposure to ticarcillin

Craig WA et al. Scand J Infect Dis Suppl 1990; 74: 63-70.

Antibiotiques	*Kl. pneumoniae*	
	S/I/R	MIC (µg/mL)
Ampicillin	R	
Amoxicillin-clavulanic acid	R	
Piperacillin -tazobactam	R	> 128
Temocillin	R	= 256
Cefuroxime	R	
Ceftazidime	R	> 64
Ceftriaxone	R	
Cefotaxime	R	> 64
Cefepime	R	> 64
Aztreonam	R	> 64
Imipenem	R	> 32
Meropenem	R	> 32
Ertapenem	R	> 32
Gentamicin	R	> 64
Amikacin	R	> 128
Tobramycin	R	> 64
Cotrimoxazole	R	
Ciprofloxacin	R	= 2

Conclusions

- The clinical consequences of infections due to resistant pathogens:
  - Carpet bombing empiric therapy for patients colonized with very resistant pathogens
  - Inappropriate empiric antibiotic regimens
  - Higher mortality
  - Higher morbidity
- Acquisition of MDR GNB are common in hospitalized patients
- Risk for subsequent infection is significantly higher for hospitalized patients with initial AMR GNB colonization than patients without colonization
- 9.1-39% of inpatients initially colonized with AMR GNB developed subsequent infection during the same hospital stay

Risk stratify for AMR: prior colonization

- Observational study
- 817 patients , 125 MDR-GNB culture-positive , 692 MDR-GNB culture-negative
- **Aim**: to determine frequency and risk factors for subsequent MDR-GNB infection and mortality associated with previous MDR-GNB culture status.

positive MDR-GNB culture from either surveillance or clinical culture of any anatomical site

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Risk stratify for AMR

Risk for Subsequent MDR-GNB Infection after Hospital Discharge

	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
LTCF residence	2.59	(1.43–4.70)	0.002	–	–	–
Malignancy	1.41	(0.95–2.09)	0.09	1.66	(1.12–2.47)	0.012
Long-term urinary catheter	1.72	(1.00–3.00)	0.05	–	–	–
Antibiotics exposure	3.54	(2.03–6.17)	< 0.001	2.20	(1.25–3.90)	0.007
Receiving tracheal intubation	2.39	(1.25–4.56)	0.008	–	–	–
MDRGNB culture positive	7.19	(5.08–10.19)	< 0.001	5.35	(3.72–7.71)	< 0.001

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