Treatment options for MDR & XDR Gram-Negative infections

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MDR	XDR	PDR
not susceptible to at least one agent in at least three antimicrobial classes	not susceptible to at least one agent in all but one or two antimicrobial classes	not susceptible to all agents in all antimicrobial classes

In management of MDR GNB infections

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BIG NOTE

When a MDR gram-negative pathogen is suspected, the early prescription of a broad-spectrum, combination regimen, followed by a prompt de-escalation upon availability of susceptibility tests should be recommended


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Proper Use of β-lactams

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- The use of β-lactams should be maximized by a PK/PD point of view with the administration of high dosages and prolonged infusion strategies maximizing the time above the MIC (t>MIC).
- A loading dose followed by maintenance doses with extended or continuous infusion is recommended

Proper use of antibiotics

- ABxs which should always use in combination therapy

  Rifampin , Fosfomycin and Tygecycline

- Following Abs dose not require loading dose:

  FQs ,AGs ,

  Rifampin ,

  Fosfomycin ,

  Sulbactam

Mechanisms of resistance of Gram-negative bacteria

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1-The most common mechanism of resistance is production of b-lactamases,

2- Down-regulation of porins

3-Efflux pumps, most common in *P. aeruginosa*-

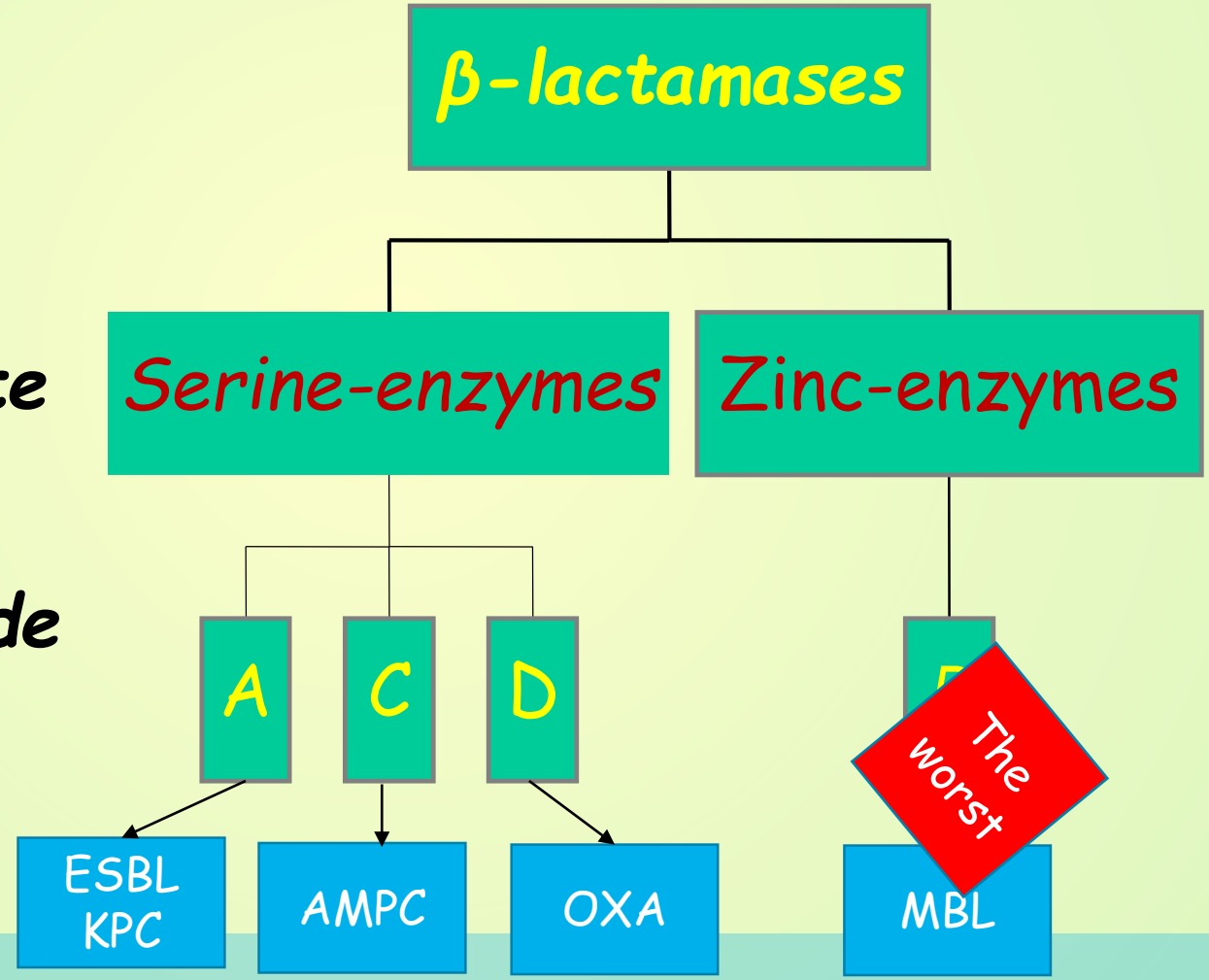
Ambler Classification of β-Lactamases

In this classification,β-Lactamases are classified according to their amino-acid structure into four molecular classes(class A-D)

All are carbapenemase producing except ESBLs

tive site

Nucleotide sequence



β-Lactamases – Class A

Enzymes	Spectrum	Epidemiology
ESBL: TEM, SHV, CTX-M,	Penicillins, Cephalosporins (except cefamycins), Aztreonam. Inhibited by β-lactamase inhibitors	Community and nosocomial infections
KPC	Penicillins, Cephalosporins Aztreonam, Carbapenems. Inhibited by β-lactamase	Mainly nosocomial outbreaks

THE MOST PREVALENT ENZYME BETWEEN EB SPP.

MDR GNB resistant infections, Matteo Bassetti,et al. IJM 2016

KPC enzymes of class A

- Initially reported fr K. pneumoniae isolates in several northeastern U.S. out aks,
- KPCs have been found wo wide in multiple other GN species, such as E. coli, Citrobacter nterobacter, Salmonella, Serratia, and P. aeruginosa.
- Mainly nosocomial

Inhibitated just by BLBLIs

MDR GNB resistant infections, Matteo Bassetti,et al. IJM 2016

Metallo β-lactamases – Class B

Enzymes	Spectrum	Epidemiology
Metallo β-lactamases (VIM, IMP,SPM, SIM,GIM ,NDM)	Penicillins, Cephalosporins Carbapenems Not inhibited by b-lactamase inhibitors	Nosocomial outbreaks and endemic situations

Monobactams susceptible only

are expressed by both enterics and *P. aeruginosa*

MDR GNB resistant infections, Matteo Bassetti,et al. IJM 2016

AmpC type β-Lactamases – Class C

Enzymes	Spectrum	Epidemiology
AmpC type (CMY-2, FOX-1, others)	Penicillins, cephalosporins (except cefepime), and monobactams Not inhibited by β-lactamase inhibitors	Community and nosocomial infections

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

β-Lactamases – Class D

Enzymes	Spectrum	Epidemiology
Oxacillinase (OXA) (OXA-23 ,24,58,146, others)	Penicillin, Aztreonam and Carbapenems Not inhibited by β-lactamase inhibitor	Nosocomial outbreak

are mostly expressed in *P. aeruginosa* and *A. baumannii*

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Carbapenemase resistant Enterobacteriacae (CPE)

Mechanisms of resistance to carbapenems:

1) *Carbapenemase production,*

2) *Combination of Class C enzymes expression (encoded by chromosomal or plasmid genes) or some ESBL*

3) *loss or structural modification of porins*

4) *Changes in PBPs (less frequently)*

Treatment options for CRE

Antibiotics that:

- Permeabilize the bacterial cell membrane (e.g., polymyxins),
- Interfere with cell wall synthesis (e.g., fosfomycin), or
- Inhibit protein synthesis (e.g. AGs or Tigecycline)

may decrease the MIC , sufficiently , so that it is exceeded when a carbapenem is co-administered.

Therefore, combination therapy should be strongly considered.

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Treatment options for CPE

Combination therapy is recommended as first-line treatment for patients diagnosed with a severe infection caused by CPE

Criteria for Monotherapy:

- *non-severe infections,*
- *the site of the infection is adequately controlled*
- *a fully active antimicrobial, with an adequate infection site penetration, can be prescribed,*

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

What is the 1st -line therapy for a patient with an infection caused by CPE?

- Treatment recommendations in CRE infections are mostly based on the accumulating clinical experience from KPC and should be based on several aspects.
- ***Combination treatment*** containing two or three active drugs has shown significant advantages over monotherapy in terms of survival for KPC infections.
- Tumbarello *et al.* supported the use of carbapenems for the treatment of KPC, but with some fundamental conditions, such as low carbapenem MIC for the infecting organism (≤8 mg/L), optimal PK/PD exposure to carbapenem, and combination with another active compound

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Tumbarello M et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 2015

Combination therapy for CRE

If MIC value for Carbapenem is ≤8-16 mg/L

HD Carbapenem administered by EI

+

one or two fully active agent

(Colistin, Tigecycline, AG , Fosfomycin)

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Combination therapy for CRE

If MIC value for Carbapenem is >8-16 mg/L

- In this case, carbapenems are probably ineffective, especially if the MIC value is >16 mg/L.
- A combination therapy regimen that includes at least two completely active antimicrobials, according to the susceptibility study and the site of the infection (colistin, AGs, fosfomycin and tigecycline)

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Double-carbapenem regimen for CPE

- Double-carbapenem regimen (ertapenem plus HD meropenem or doripenem) has shown to enhance efficacy over either agent alone in previous in vitro and in vivo studies and has been recently considered a possible therapeutic strategy in KPC with high carbapenem MIC or colistin resistance.
- The proposed rationale is that ertapenem has a higher affinity to the KPC enzyme, therefore acting as a suicide substrate and allowing the second carbapenem to be protected from the KPC carbapenemase.
- Controlled clinical data, however, are needed to determine the efficacy of this treatment.

MDR GNB-resistant infections, Matteo Bassetti,et al. IJM 2016

Treatment options for CRE

Tigecycline

- Clinical use of Tigecycline for MDR infections has been heterogeneous, but seem to be effective and safe in the treatment of CRE as part of a combination regimen especially when administered at higher doses
- The mean serum concentrations and the urinary concentrations of tigecycline are low.

usually display activity against CRE and CRAB, but not CRPA, since P. aeruginosa is inherently resistant

Infections produced by MDR A. baumannii

Therapeutic options for *A. baumannii*

- Carbapenems
- Sulbactam,
- Aminoglycosides,
- polymyxins and
- Tigecycline

Mechanisms of carbapenem resistance in MDR A. baumannii (CRAB)

Carbapenemases :

1-The most important : acquired Oxacillinases (class D)

a) OXA-23-like, (the most prevalent)

b) OXA-24-like,

c) OXA-58-like

d) OXA-143-like

2-MBLs (class B), and class A (less frequent).

- *A. baumannii also produces a class C chromosomal cephalosporinase with an irrelevant role in establishing resistance to carbapenems*

-J.M. Aguado et al, Management of MDR GNB infections in SOT recipients: SET/GESITRA-SEIMC/REIPI recommendations, 2017,Spain

Colistin in treatment of MDR AB

- Monotherapy with colistin or polymyxin B, has not proven to be more effective than their comparators in VAP caused by this MO.
- The main limitation of these studies lies in the heterogeneity of the patients enrolled and in the variability of the colistin dosage.
- The use of colistin monotherapy can lead to hetero-resistant mutants and failure in microbiological eradication can reach up to 30%

-J.M. Aguado et al, Management of MDR GNB infections in SOT recipients: SET/GESITRA-SEIMC/REIPI recommendations, 2017,Spain

Sulbactam in treatment of MDR AB

- In strains susceptible to colistin and
- demonstrating a low MIC for sulbactam (≤4 mg/L), the use of sulbactam may be preferable in the directed therapy based on its better safety profile and to preserve colistin.

-J.M. Aguado et al, Management of MDR GNB infections in SOT recipients: SET/GESITRA-SEIMC/REIPI recommendations, 2017,Spain

Sulbactam in treatment of MDR AB

- A recent RCT reported that treatment with sulbactam (Ampicillin-sulbactam 9-12 gr of Sulbactam) compared to colistin for HCAP had similar adverse effects and similar clinical and microbiological outcomes *.
- Other observational studies have reported similar outcomes with different associations of sulbactam versus their comparators

Combination regimens for treatment of MDR AB infections

Colistin-Carbapenem

- has been analysed only in retrospective studies suggesting that colistin-carbapenem combinations may result in improved clinical responses and survival compared to other regimens and may also limit the emergence of colistin resistance

Colistin and sulbactam or tigecycline :

- has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR A. baumannii

-J.M. Aguado et al, Management of MDR GNB infections in SOT recipients: SET/GESITRA-SEIMC/REIPI recommendations, 2017,Spain

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Combination regimens for treatment of MDR AB infecrtions

Colistin and rifampicin

- has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR A. baumannii, although it offers a higher rate of microbiological eradication
- Despite promising in vitro and animal studies (particularly for rifabutin), the panel does not favor the use of rifamycin.

Colistin and vancomycin

- *has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR A. baumannii and increases the risk of renal toxicity*

-J.M. Aguado et al, Management of MDR GNB infections in SOT recipients: SET/GESITRA-SEIMC/REIPI recommendations, 2017,Spain

National Library of Medicine
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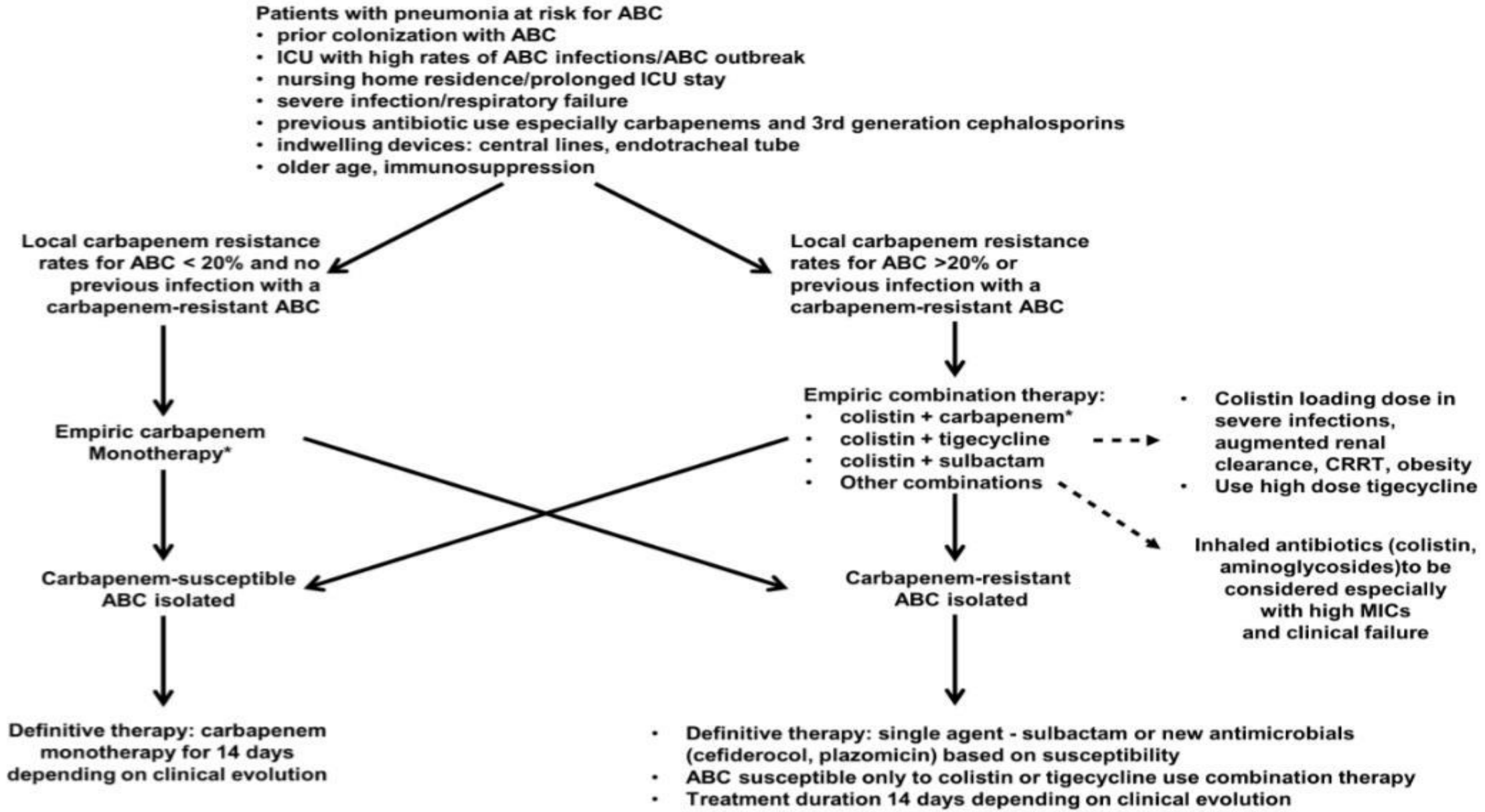
Review

Acinetobacter Pneumonia: Improving Outcomes With Early Identification and Appropriate Therapy

Cristina Vazquez Guillamet et al. Clin Infect Dis. 2018.

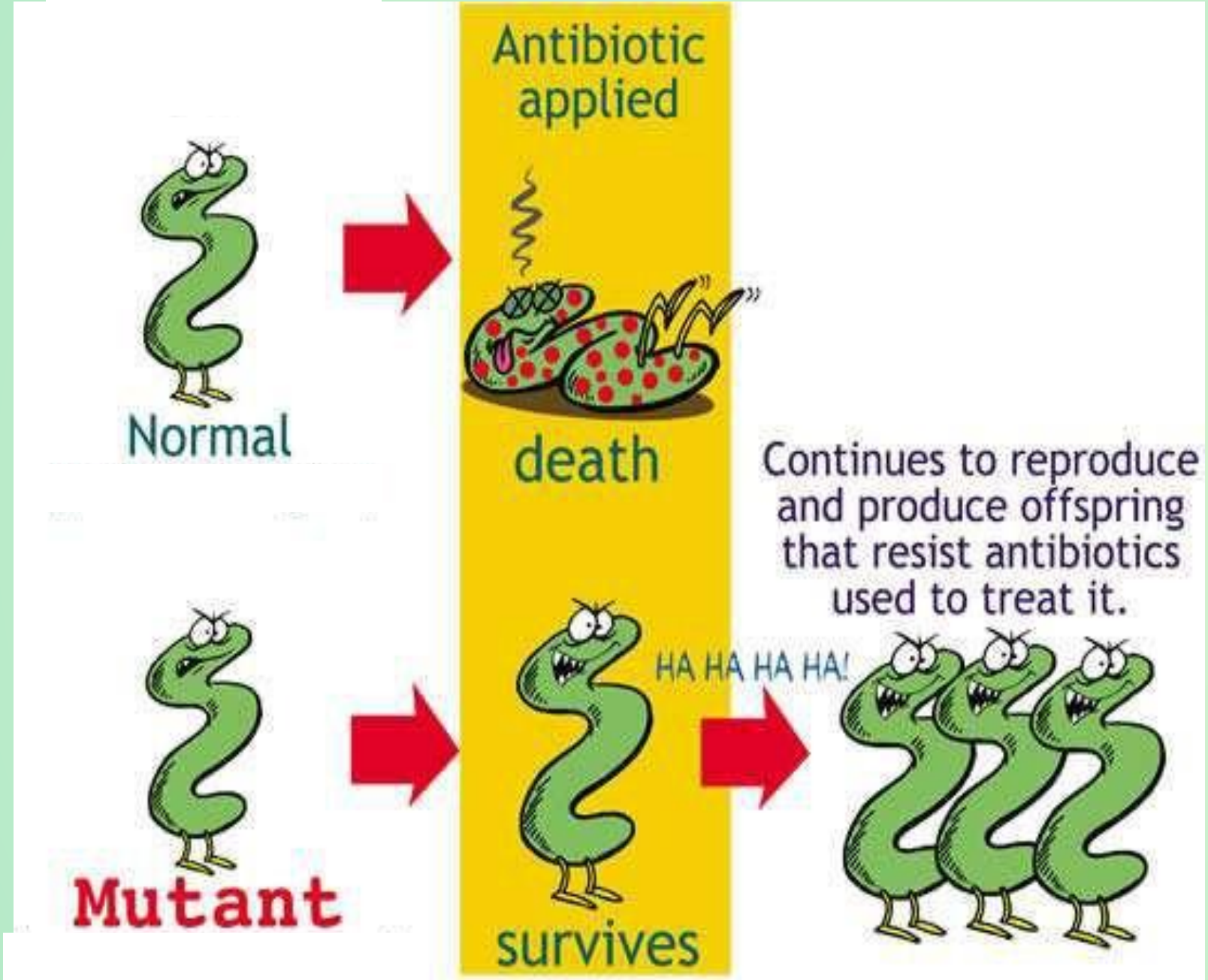

Patients with pneumonia at risk for ABC
• prior colonization with ABC
• ICU with high rates of ABC infections/ABC outbreak
• nursing home residence/prolonged ICU stay
• severe infection/respiratory failure
• previous antibiotic use especially carbapenems and 3rd generation cephalosporins
• indwelling devices: central lines, endotracheal tube
• older age, immunosuppression
Local carbapenem resistance rates for ABC < 20% and no previous infection with a carbapenem-resistant ABC
Local carbapenem resistance rates for ABC >20% or previous infection with a carbapenem-resistant ABC
Empiric carbapenem Monotherapy*
Empiric combination therapy:
• colistin + carbapenem*
• colistin + tigecycline
• colistin + sulbactam
• Other combinations
• Colistin loading dose in severe infections, augmented renal clearance, CRRT, obesity
• Use high dose tigecycline
Inhaled antibiotics (colistin, aminoglycosides)to be considered especially with high MICs and clinical failure
Carbapenem-susceptible ABC isolated
Carbapenem-resistant ABC isolated
Definitive therapy: carbapenem monotherapy for 14 days depending on clinical evolution
• Definitive therapy: single agent - sulbactam or new antimicrobials (cefiderocol, plazomicin) based on susceptibility
• ABC susceptible only to colistin or tigecycline use combination therapy
• Treatment duration 14 days depending on clinical evolution

What Is the Role of Cefiderocol Therapy for the Treatment of Infections Caused by CRAB

- Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance to other agents precludes their use.
- When cefiderocol is used to treat CRAB infections, the panel suggests prescribing the agent as part of a combination regimen.

Table 1. Dosing Recommendations for *Acinetobacter* Pneumonia

Antibiotic	Loading Dose	Maintenance Dosing	Extended Infusion
Parenteral			
Ampicillin/Sulbactam	…	8 g / 4 g every 8 h	4 h infusion
Sulbactam	…	4 g every 8 h	4 h infusion
Colistin base	360 mg (9 million IU)	140 mg every 12 h (4.5 million IU every 12 h)	…
Polymyxin B	2 mg/kg	1.25 mg/kg every 12 h	…
Tigecycline[a]	200 mg	100 mg every 12 h	…
Meropenem	…	2 g every 8 h	3–4 h infusion[b]
Minocycline	200 mg	100–200 mg every 12 h	…
Rifampicin[d]	…	600 mg every 12 h	…
Fosfomycin[d]	…	12–24 g/d (divided 3–4 doses)	…
Cefiderocol[c]	…	2 g every 8 h	3–4 h infusion[b]
Plazomicin[c]	…	15 mg/kg every 24 h	…
Eravacycline[c]	…	1.5 mg/kg every day	…
Aerosol	…		
Colistin base	…	2 million IU every 8 h	…
Amikacin/Fosfomycin[c]	…	300 mg/120 mg every 12 h	…


Antibiotic applied
Normal
death
Continues to reproduce and produce offspring that resist antibiotics used to treat it.
HA HA HA HA!
Mutant
survives

Thank You!