Management of MDR ESBL Infections: Update

Adel Mohamad Alansary, MD

Objectives

1. Describe AMR and Egypt.
2. Enumerate Resistance mechanisms of GNB.
3. Illustrate some guidelines.
4. Detail the approach towards treatment.
5. Describe follow-up and parameters of stopping treatment.

AMR and Egypt

Definitions

- MDR: The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories
- XDR: The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories.
- PDR: Non-susceptibility to all agents in all antimicrobial categories.

Abuse of Antimicrobials leads to:

- Patient damage.
- Hospital damage.
- Financial damage.
- Community damage.

Patient Damage

Side effects.

Toxicity.

Idiosyncrasy.

Allergy.

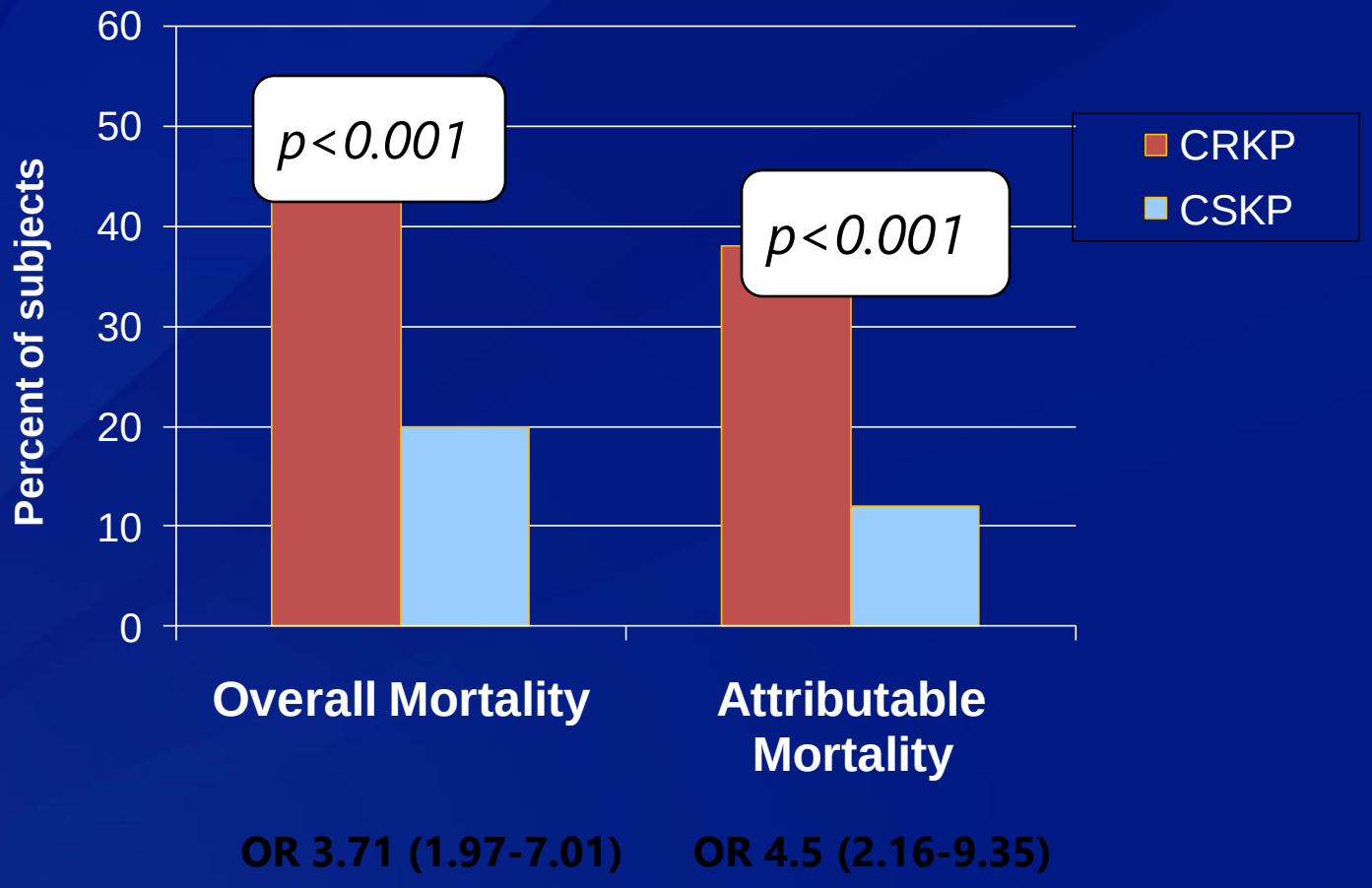
Hospital damage

COST.

RESISTANCE.

POOR PATIENT OUTCOME.

Mortality associated with carbapenem resistant (CR) vs susceptible (CS) Klebsiella pneumoniae (KP)



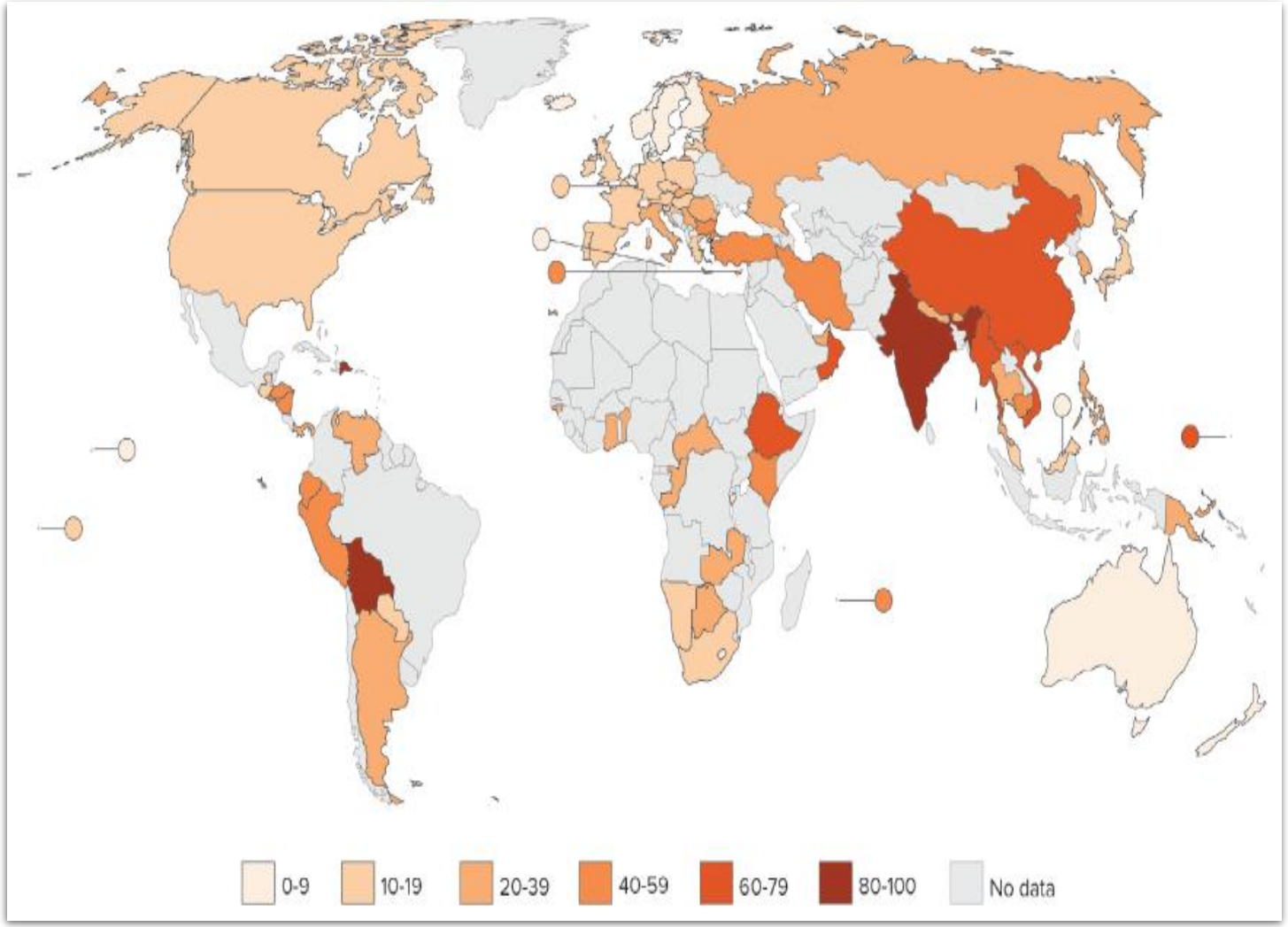
Patel G et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106

Carbapenem Resistant Enterobactericeae and Carbapenems	15 fold 1
ESBL producing organisms and Cephalosoprins	6- 29 fold 3,4

Antimicrobial exposure increases the risks of resistance

- Patel G et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106
- Zaoutis TE et al. *Pediatrics* 2005;114:942-9
- Talon D et al. *Clin Microbiol Infect* 2000;6:376-84

Global Prevalence of ESBL-producing *E. coli* (2011-2014)



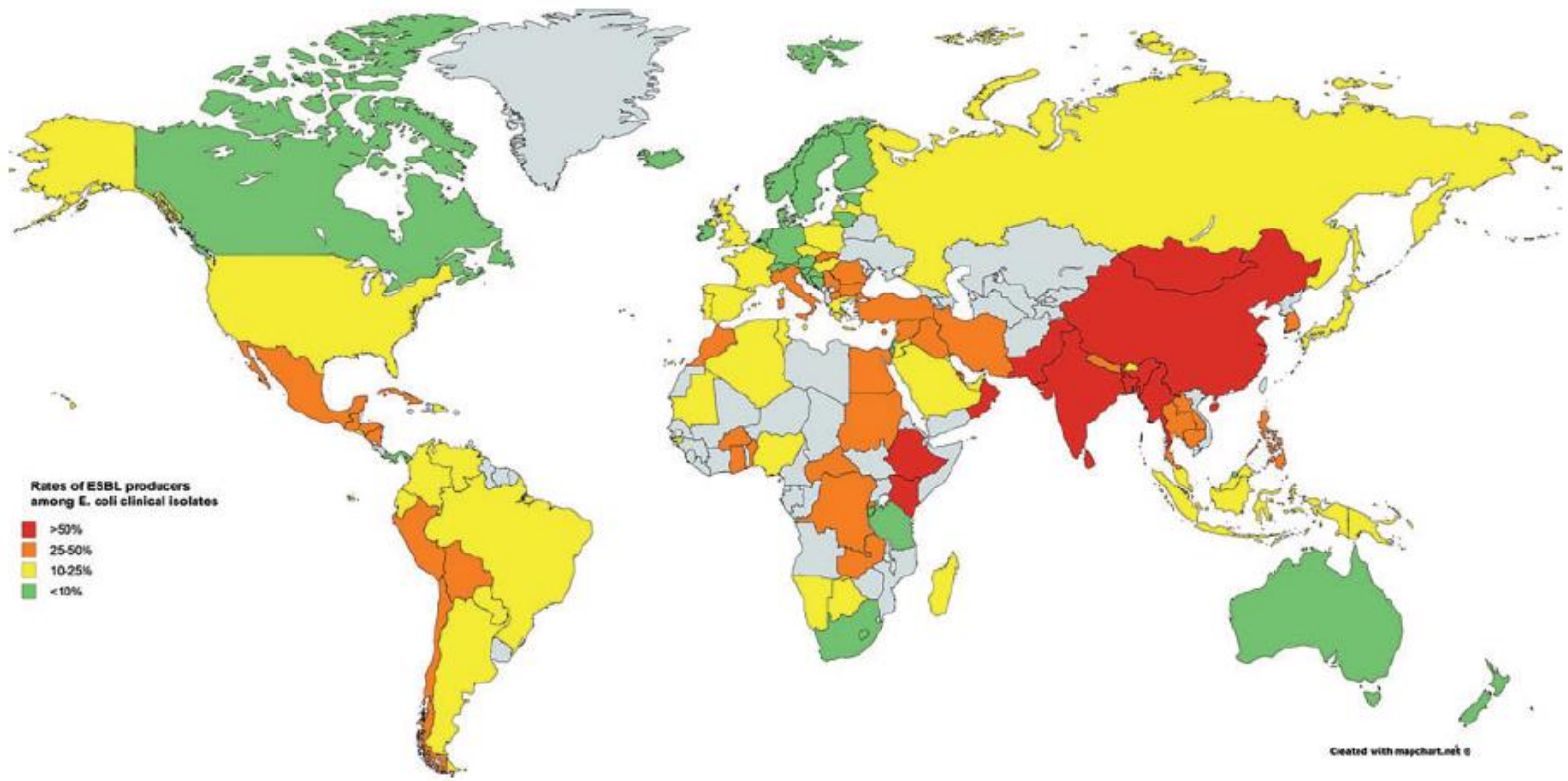
CDDEP report, 2015

Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Established 1991
Journal of Travel Medicine, 2017, Vol 24, Suppl 1, S44–S51
doi: 10.1093/jtm/taw102
Review

Review

The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world

Yohei Doi, MD, PhD[1,*], Alina Iovleva, MD[1], and Robert A. Bonomo, MD[2,3,4,5,6]



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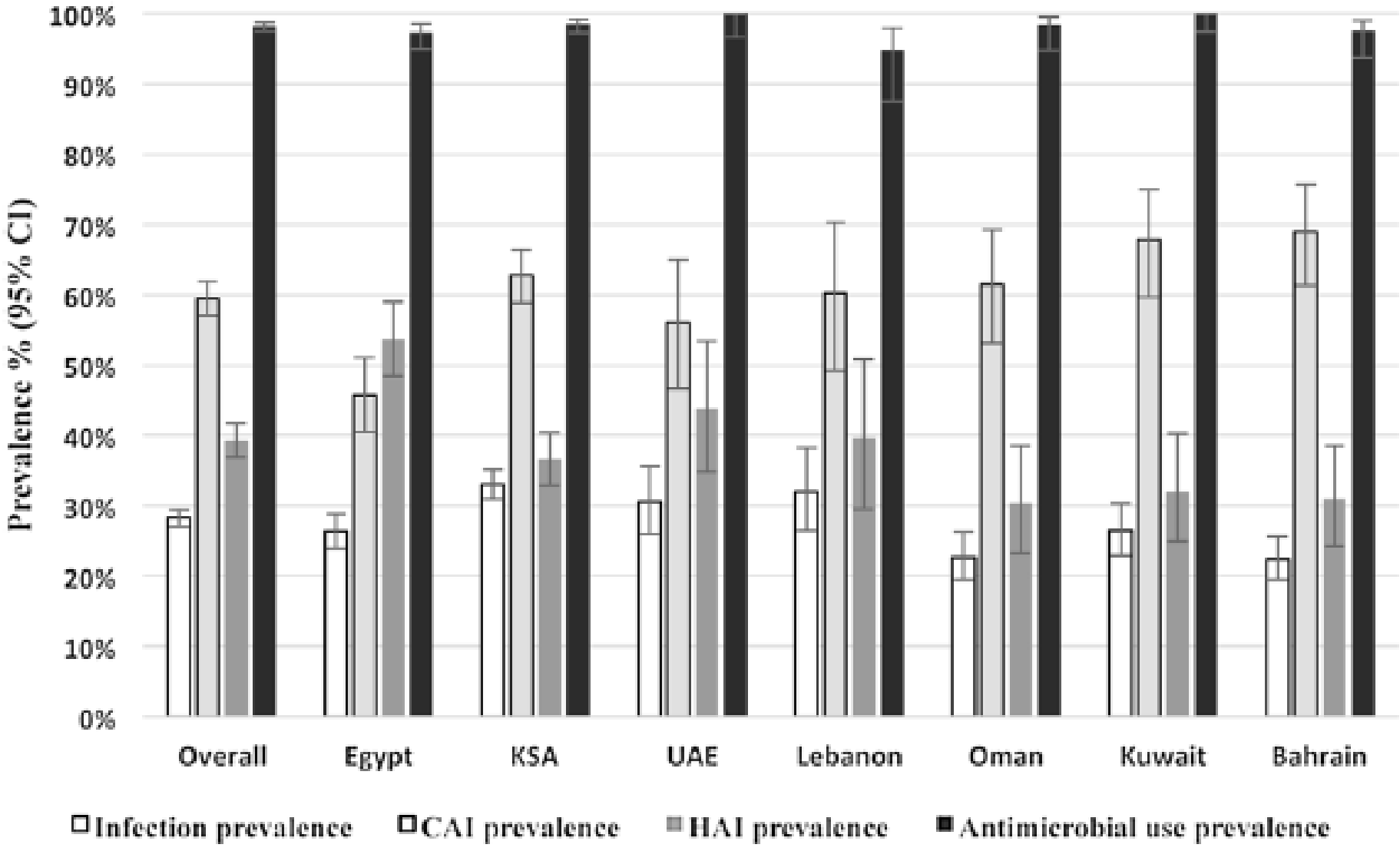
Prevalence of infections and antimicrobial use in the acute-care hospital setting in the Middle East: Results from the first point-prevalence survey in the region

Adel Alothman[a], Abdulhakeem Al Thaqafi[b], Adel Al Ansary[c], Ahmed Zikri[d], Akram Fayed[e], Faryal Khamis[f], Jameela Al Salman[g], Laila Al Dabal[h], Natasha Khalife[i], Tariq AlMusawi[j], Wadha Alfouzan[k], Said El Zein[l], Ramy Kotb[m,*], Yasser Ghoneim[i], Souha S. Kanj[l,**]


Prevalence % (95% CI)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Overall
Egypt
KSA
UAE
Lebanon
Oman
Kuwait
Bahrain
Infection prevalence
CAI prevalence
HAI prevalence
Antimicrobial use prevalence

	Total patients	Hospital type		Infection type		
	(N = 1586)	Secondary (N = 140)	Tertiary (N = 1446)	CAI (N = 944)	HAI (N = 625)	Unknown (N = 17)
Acinetobacter baumannii	49 (3.1%)	2 (1.4%)	47 (3.3%)	16 (1.7%)	32 (5.2%)	1 (9.1%)
Candida albicans	28 (1.8%)	3 (2.1%)	25 (1.7%)	10 (1.1%)	18 (2.9%)	0
Other *Candida sp.*	32 (2.0%)	3 (2.1%)	29 (2.0%)	16 (1.7%)	16 (2.6%)	0
Enterobacter cloacae	17 (1.1%)	5 (3.6%)	12 (0.8%)	7 (0.7%)	10 (1.6%)	0
Enterococcus faecalis	25 (1.6%)	2 (1.4%)	23 (1.6%)	14 (1.5%)	11 (1.8%)	0
Escherichia coli	143 (9.1%)	13 (9.3%)	130 (9.1%)	88 (9.4%)	55 (8.9%)	0
Other *Klebsiella sp.*	25 (1.6%)	0	25 (1.7%)	6 (0.6%)	19 (3.1%)	0
Klebsiella pneumoniae	129 (8.2%)	8 (5.7%)	121 (8.5%)	58 (6.2%)	71 (11.5%)	0
Proteus mirabilis	23 (1.5%)	4 (2.9%)	19 (1.3%)	12 (1.3%)	11 (1.8%)	0
Pseudomonas aeruginosa	137 (8.7%)	10 (7.1%)	127 (8.9%)	46 (4.9%)	90 (14.5%)	1 (9.1%)
Staphylococcus aureus	126 (8.0%)	7 (5.0%)	119 (8.3%)	67 (7.1%)	58 (9.4%)	1 (9.1%)

	Total patients	Hospital type		Infection type		
	(N = 1586)	Secondary (N = 140)	Tertiary (N = 1446)	CAI (N = 944)	HAI (N = 625)	Unknown (N = 17)
Klebsiella pneumoniae resistance to Third-generation cephalosporins (C3G)						
Susceptibility	40 (32.5%)	3 (37.5%)	37 (32.2%)	24 (46.2%)	16 (22.5%)	0
Intermediate susceptibility	1 (0.8%)	0	1 (0.9%)	1 (1.9%)	0	0
Resistant	77 (62.6%)	4 (50.0%)	73 (63.5%)	24 (46.2%)	53 (74.6%)	0
Unknown	5 (4.1%)	1 (12.5%)	4 (3.5%)	3 (5.8%)	2 (2.8%)	0
Klebsiella pneumoniae resistance to Carbapenems (CAR)						
Susceptibility	67 (54.9%)	3 (37.5%)	64 (56.1%)	34 (66.7%)	33 (46.5%)	0
Intermediate susceptibility	4 (3.3%)	0	4 (3.5%)	2 (3.9%)	2 (2.8%)	0
Resistant	34 (27.9%)	0	34 (29.8%)	6 (11.8%)	28 (39.4%)	0
Unknown	17 (13.9%)	5 (62.5%)	12 (10.5%)	9 (17.6%)	8 (11.3%)	0

ESBLS

Bacteria that produce Beta Lactamase that hydrolyses Pencillins, Cephalosporins, and Aztreonam.

Carbanemases are similar enzymes that specifically hdrolyses Carbapenems.

Resistance Mechanisms

Mechanisms

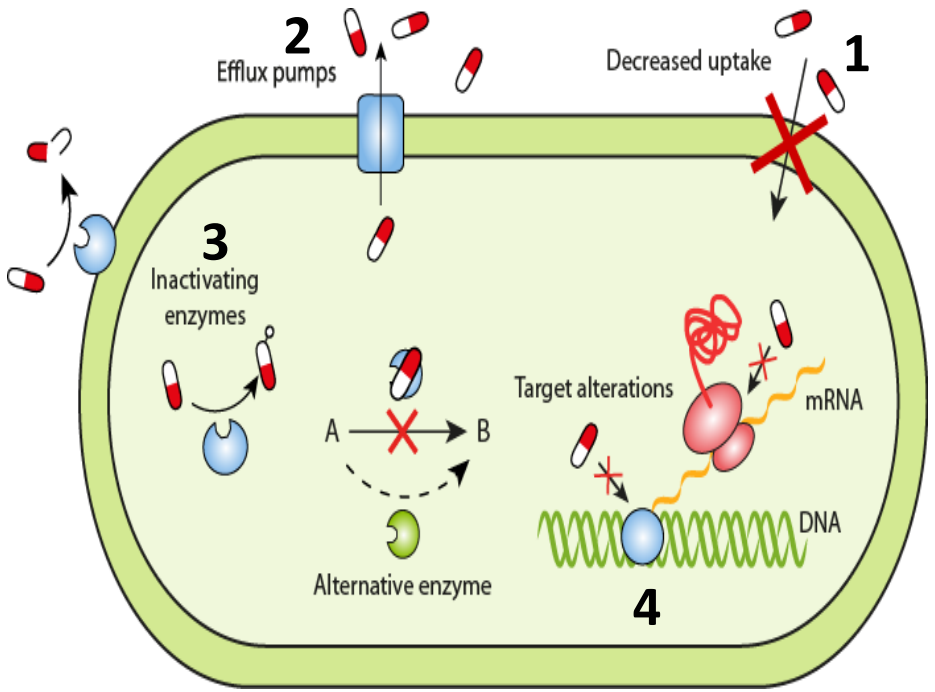
Biofilms

Efflux Pumps

Hydrloases, Lactamases

Target enzyme deletion

Mechanisms of resistance in gram-negative bacteria

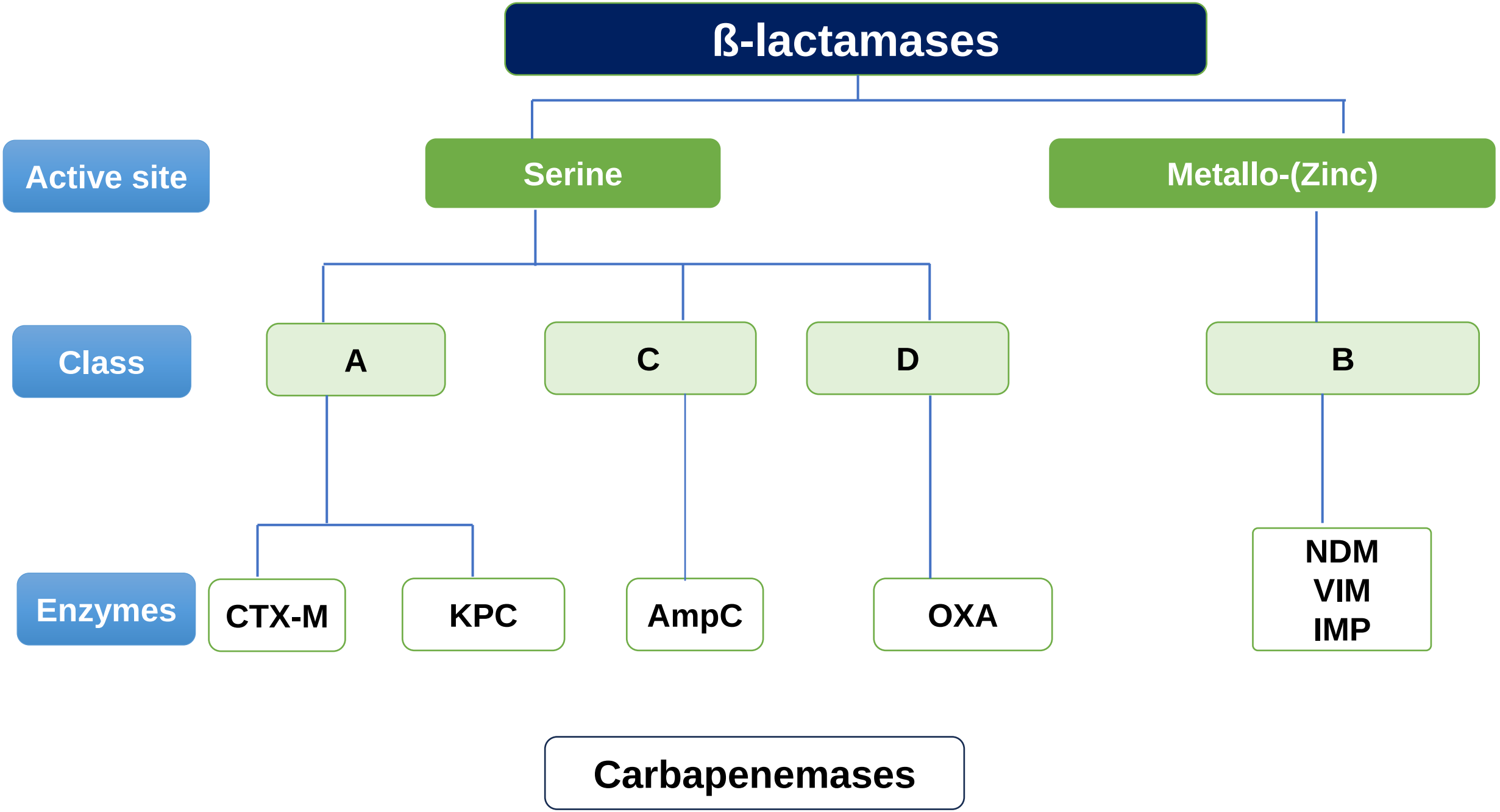


1-Decreased uptake (Porin deletion)

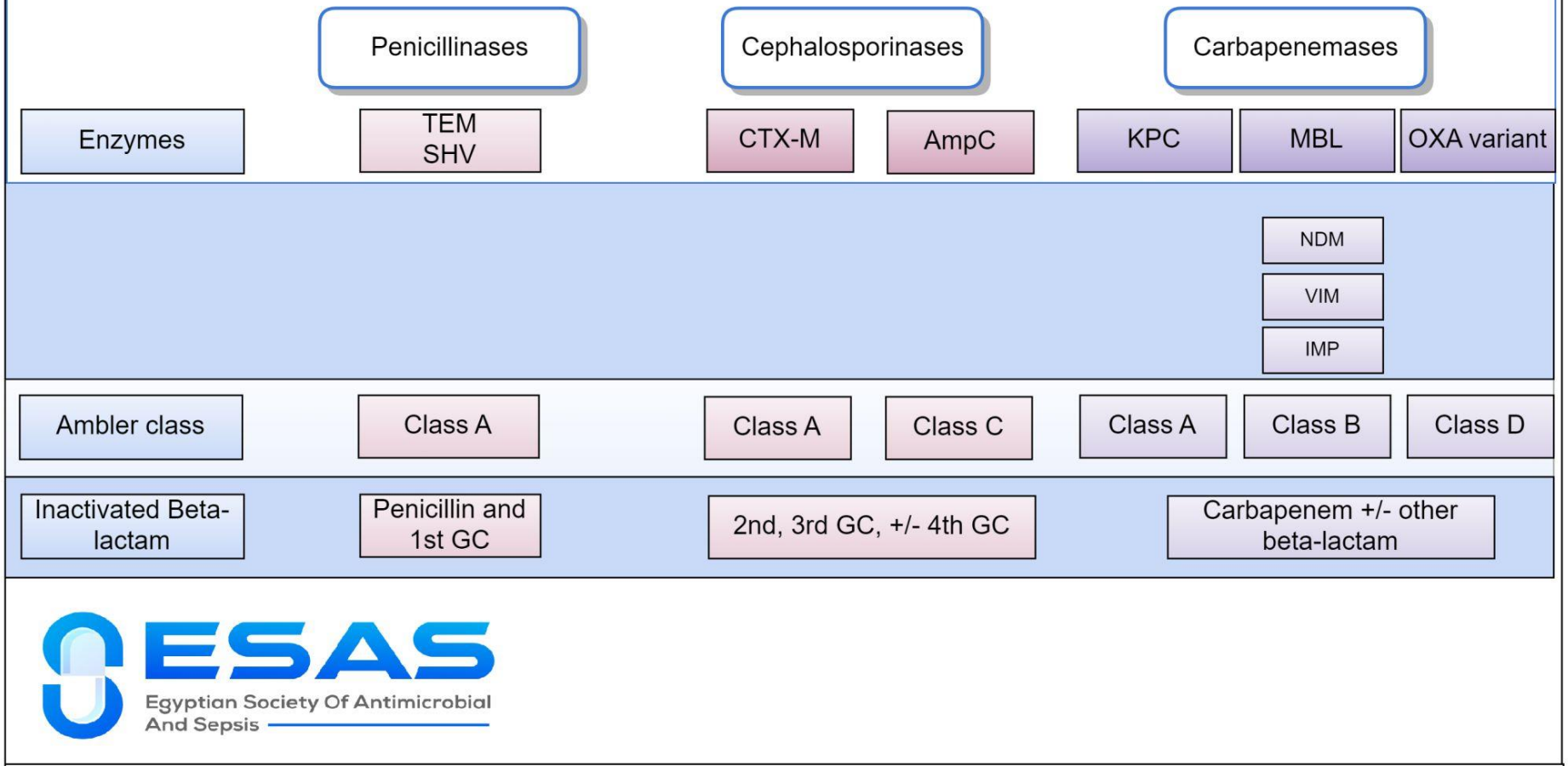
2-Efflux pumps

3-Inactivating enzymes (ex: ß-lactamases)

4-Alteration of target binding sites

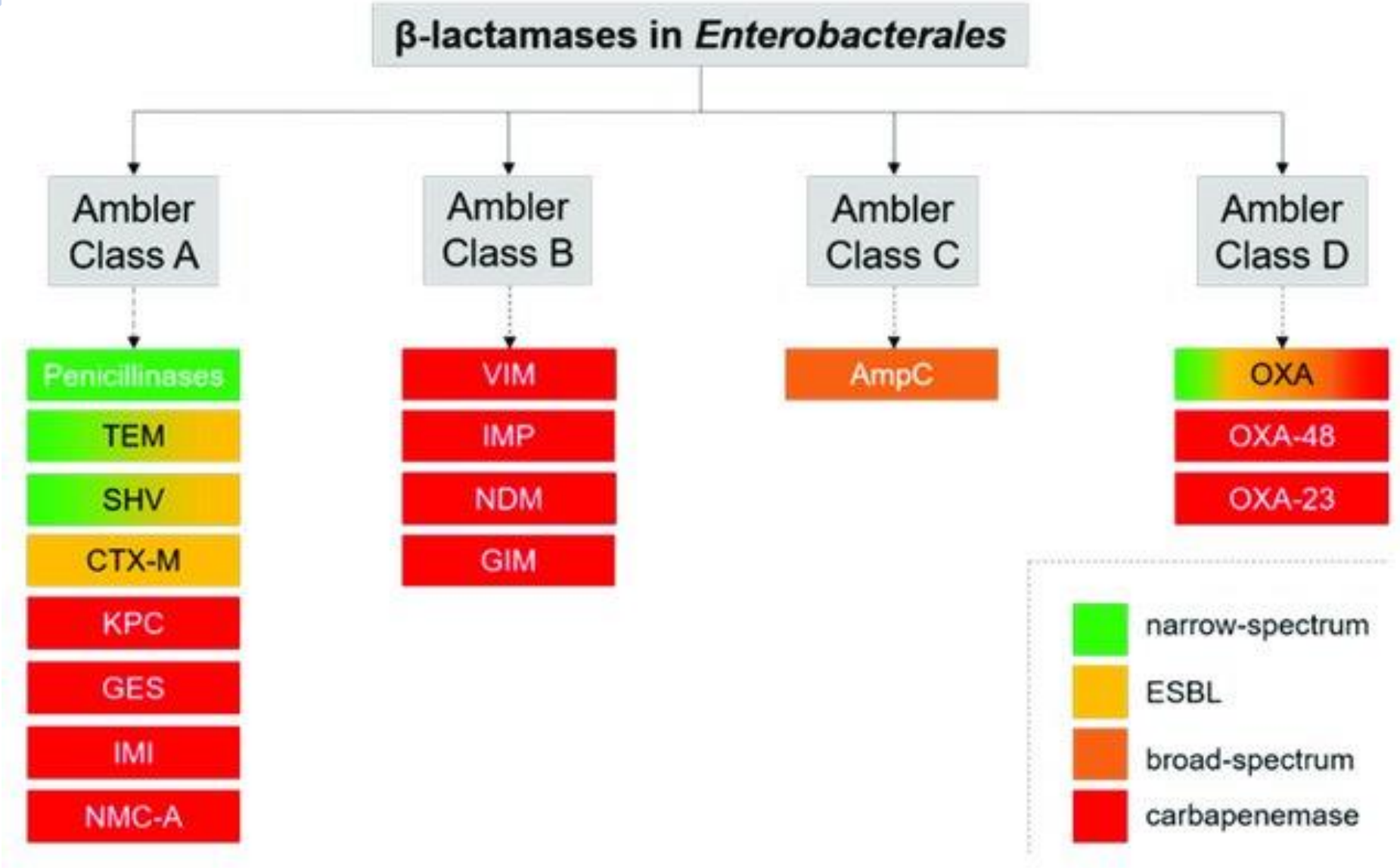

ß-lactamases
Active site
Serine
Metallo-(Zinc)
Class
A
C
D
B
Enzymes
CTX-M
KPC
AmpC
OXA
NDM
VIM
IMP
Carbapenemases

Beta-lactamases classification



ESAS
Egyptian Society Of Antimicrobial And Sepsis

KPC: Klebsiella pneumoniae carbapenemase, MBL: Metallo-beta lactamases, OXA: oxacillinase beta lactamase, 1st GC: 1st generation cephalosporin, 2nd GC: 2nd generation cephalosporin, 3rd GC: 3rd generation cephalosporin, 4th GC: 4th generation cephalosporin


β-lactamases in *Enterobacterales*
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
Penicillinases
TEM
SHV
CTX-M
KPC
GES
IMI
NMC-A
VIM
IMP
NDM
GIM
AmpC
OXA
OXA-48
OXA-23
narrow-spectrum
ESBL
broad-spectrum
carbapenemase

Guidelines

Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control 2018;7:58.

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

ESBLs: MIC to ceftriaxone >2

- Klebsiella
- Proteus
- E. Coli
- CTXM
- TEM
  SHV

Cystitis

- Nitrofurantoin
- TMP-SMX
- Ciprofloxacin
- Levofloxacin
- Carbapenems
- Aminoglycosides
- Fosfomycin

cUTI or Pyelonephritis

- TMP-SMX
- Ciprofloxacin
- Levofloxacin
- Carbapenems

Infections outside UT

- Meropenem
- Imipenem/Cilastatin
- Ertapenem
- Transition to TMP/SMX or quinolones if susceptibility is demonstarted

PRINCIPLES

Management Principles

- Knowledge of national and local resistance epidemiology which means that you know the mechanisms of resistance that you have in your institution or in the country and what are the treatment options that you have against them.
- Interpretation of rapid diagnostic testing:
  - PCR Biofire, Qiagen
  - Gene Expert
  - MIC
- Deescalation to definitive therapy after confirmation of diagnosis.
- Carbapenem sparing when possible.
- Reducing level of care to non hospital setting.

Empiric Therapy

- Most likely pathogen.
- Likely source of infection.
- Patient specific factors.
- Previous isolation of MDR organisms.
- Antimicrobial exposure.
- Local susceptibility patterns.

Selecting the Empiric Antimicrobial

A. Patient Considerations:
    A. Likely source of infection.
    B. Potential organisms involved.
    C. Severity of illness, comorbidities.

B. Patient History:
    A. Prior infection or colonization, culture results.
    B. Health care exposure
    C. Travel history
    D. Antimicrobials given

Selecting the Empiric Antimicrobial

A. Place Considerations:
    A. Rates of MDR organisms
    B. Local Antibiograms.
B. Comorbidities:
    A. Advanced Age.
    B. Immunosuppression
    C. Immobility
    D. Use of indwelling devices.
    E. International travel: South Asia MTR rates 71%, northern Africa 42%.

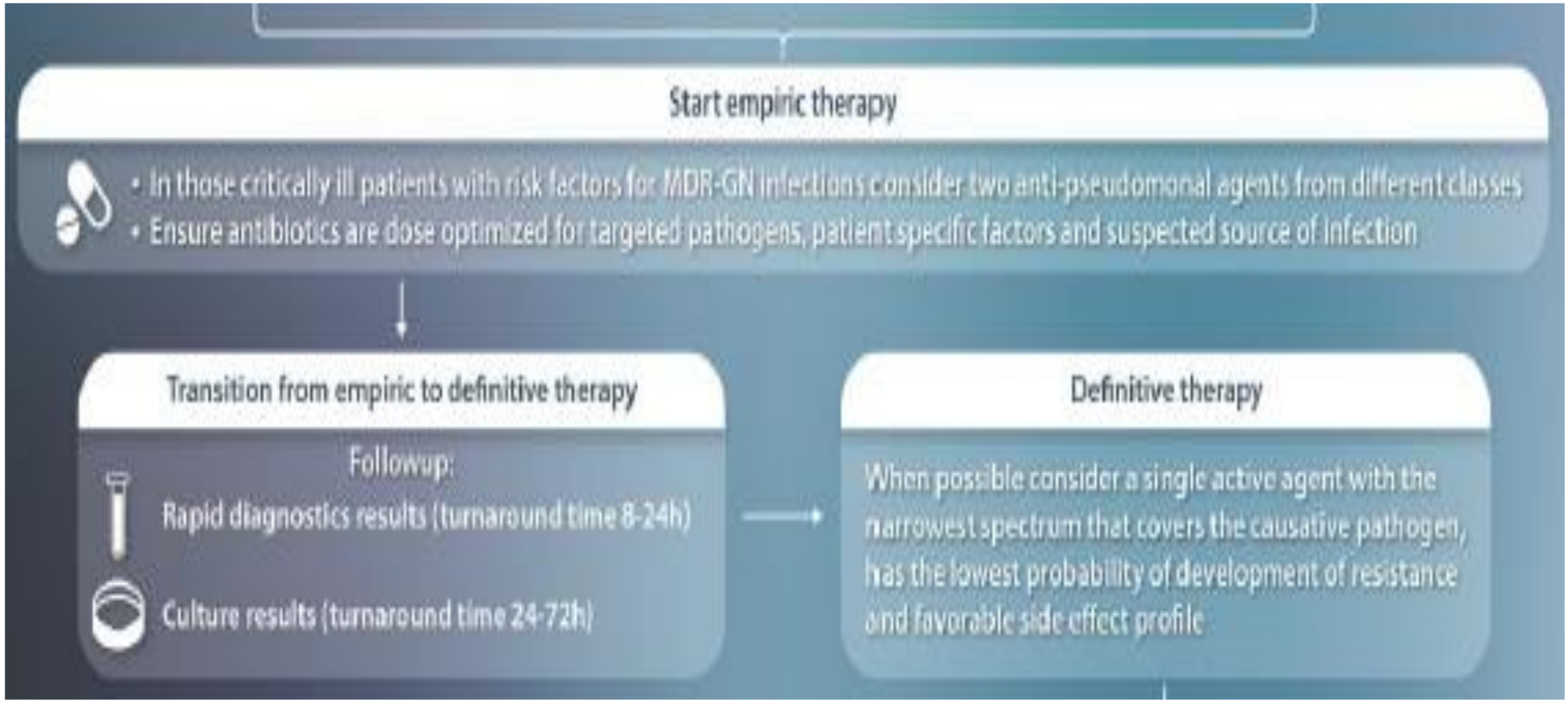
Distribution of pathogens associated with reported ICU-acquired Infections, 01 January 2018 - 31 August 2018

Organism	ICU-acquired Pathogens			BSI			Pneumonia			UTI		
	n = 27			n = 27			n = 0			n = 0		
	No.	%	Rank	No.	%	Rank	No.	%	Rank	No.	%	Rank
Candida albicans	1	3.7	2	1	3.7	2	0	0	1	0	0	1
Pseudomonas spp.	1	3.7	2	1	3.7	2	0	0	1	0	0	1
S. aureus	1	3.7	2	1	3.7	2	0	0	1	0	0	1
Others	24	88.9	1	24	88.9	1	0	0	1	0	0	1


Determining empiric therapy
Assess severity of illness
Have lower threshold to consider broad-spectrum therapy in unstable patients
Assess MDR-GN risk factors
• Previous colonization or infection
• Previous antibiotic use
• Older age
• Bedridden
• Recent hospitalization
• Indwelling devices
• Immunosuppression
• Recent travel
Review local resistance rates
Local antibiograms (hospital/unit specific if available) and outbreaks

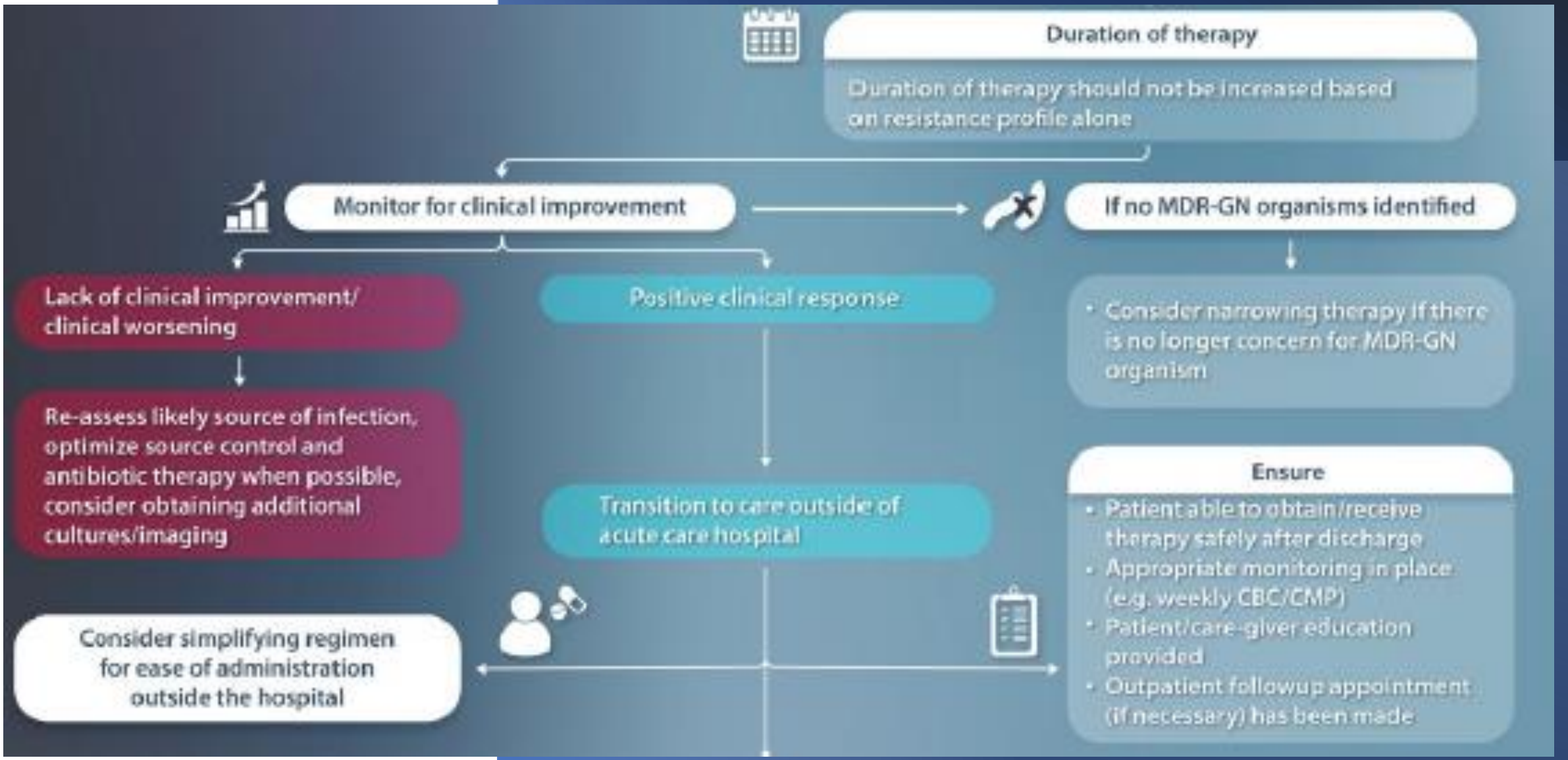
Selecting the Empiric Antimicrobial

A. Drug Factors:
    A. Penetration Power.
    B. Toxicity
    C. Combination therapy
    D. Dosing
    E. TDM


Start empiric therapy
• In those critically ill patients with risk factors for MDR-GN infections consider two anti-pseudomonal agents from different classes
• Ensure antibiotics are dose optimized for targeted pathogens, patient specific factors and suspected source of infection
Transition from empiric to definitive therapy
Followup:
Rapid diagnostics results (turnaround time 8-24h)
Culture results (turnaround time 24-72h)
Definitive therapy
When possible consider a single active agent with the narrowest spectrum that covers the causative pathogen, has the lowest probability of development of resistance and favorable side effect profile

Transition to Targeted Therapy

- Gram Stain
- Traditional Culture
- MIC
- Synergy Testing
- RDT
- Radiology

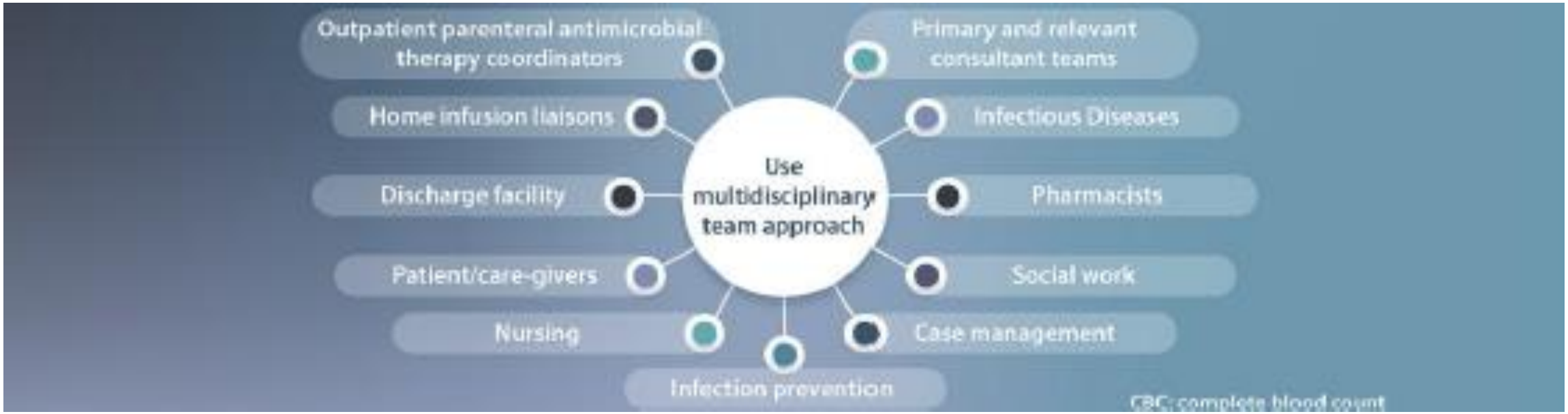

Duration of therapy
Duration of therapy should not be increased based on resistance profile alone
Monitor for clinical improvement
If no MDR-GN organisms identified
Lack of clinical improvement/ clinical worsening
Positive clinical response
Consider narrowing therapy if there is no longer concern for MDR-GN organism
Re-assess likely source of infection, optimize source control and antibiotic therapy when possible, consider obtaining additional cultures/imaging
Transition to care outside of acute care hospital
Ensure
Patient able to obtain/receive therapy safely after discharge
Appropriate monitoring in place (e.g. weekly CBC/CMP)
Patient/care-giver education provided
Outpatient followup appointment (if necessary) has been made
Consider simplifying regimen for ease of administration outside the hospital

Duration of Therapy

- Clinical Response
- What else could it be?
- PCT

PCT in deescalation

- A single randomized trial (ProVAP) directly evaluated use of procalcitonin algorithms versus standard care in 101 patients with known or suspected VAP.
- In the procalcitonin group, stopping antibiotics when the procalcitonin level was <0.5 ng/mL or had decreased by ≥80 percent from peak resulted in a significant 27 percent reduction in antibiotic use (median 10 versus 15 days) without increasing adverse outcomes.


Use multidisciplinary team approach
Outpatient parenteral antimicrobial therapy coordinators
Primary and relevant consultant teams
Home infusion liaisons
Infectious Diseases
Discharge facility
Pharmacists
Patient/care-givers
Social work
Nursing
Case management
Infection prevention
CBC: complete blood count

THANK YOU