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IDM
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

Faculty of Health Sciences
Division of Medical Microbiology

NATIONAL HEALTH LABORATORY SERVICE

Stewardship of reserve antibiotics in South Africa

Adrian Brink

Professor and Head, Division of Medical Microbiology, Department of Pathology, NHLS and Faculty of Health Sciences, University of Cape Town, Cape town, South Africa

Scope of presentation

- Introduction
- Stewardship of colistin in South Africa
- Stewardship of new β-lactam-β-lactamase inhibitors in South Africa
- Conclusions

Introduction

Introduction

- The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts at local, national and global levels,

- Antibiotics are classified into three groups, Access, Watch and Reserve, taking into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance, to emphasize the importance of their appropriate use.

- The 2021 update of the AWaRe classification includes an additional 78 antibiotics not previously classified, bringing the total to 258.

- It is a useful tool:
  - For monitoring antibiotic consumption
  - Defining targets
  - Monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance.

https://www.who.int/publications/i/item/2021-aware-classification

Introduction

- **The Reserve Group**
- This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms.

- Reserve group antibiotics should be treated as “last resort” options.

- Selected Reserve group antibiotics are listed as individual medicines on the WHO Model Lists of Essential Medicines when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the WHO Priority Pathogens List1, notably carbapenem resistant Enterobacterales.

https://www.who.int/publications/i/item/2021-aware-classification

Introduction

Aztreonam	Monobactams
Carumonam	Monobactams
Cefiderocol	Other-cephalosporins
Ceftaroline-fosamil	Fifth-generation cephalosporins
Ceftazidime/avibactam	Third-generation-cephalosporins
Ceftobiprole-medocaril	Fifth-generation cephalosporins
Ceftolozane/tazobactam	Fifth-generation cephalosporins
Colistin_IV	Polymyxins
Colistin_oral	Polymyxins
Dalbavancin	Glycopeptides
Dalfopristin/quinupristin	Streptogramins
Daptomycin	Lipopeptides
Eravacycline	Tetracyclines
Faropenem	Penems
Fosfomycin_IV	Phosphonics
Iclaprim	Trimethoprim-derivatives
Imipenem/cilastatin/relebact	Carbapenems
Lefamulin	Pleuromutilin
Linezolid	Oxazolidinones

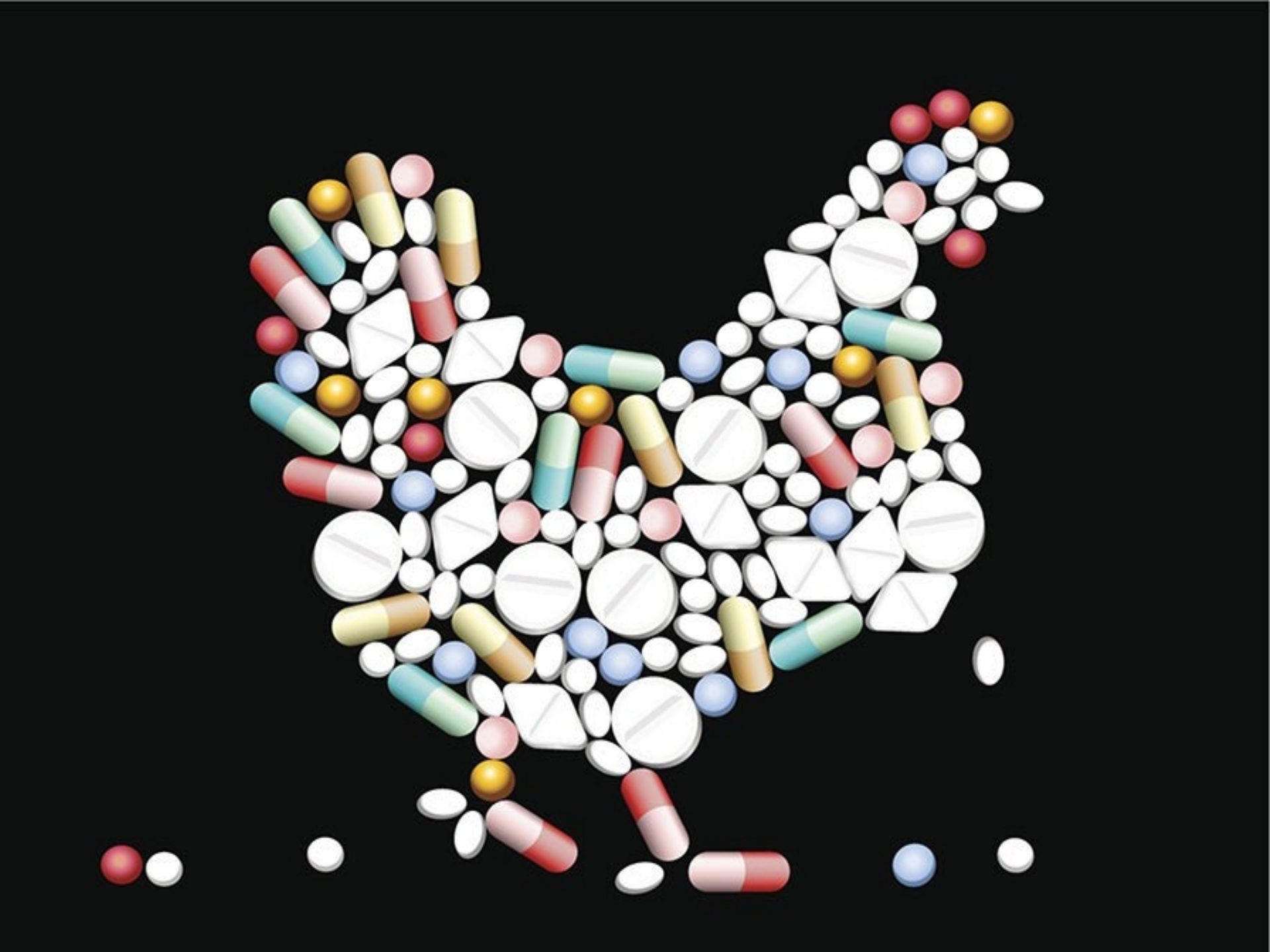
https://www.who.int/publications/i/item/2021-aware-classification

Introduction

Meropenem/vaborbactam	Carbapenems
Minocycline_IV	Tetracyclines
Omadacycline	Tetracyclines
Oritavancin	Glycopeptides
Plazomicin	Aminoglycosides
Polymyxin-B_IV	Polymyxins
Polymyxin-B_oral	Polymyxins
Tedizolid	Oxazolidinones
Telavancin	Glycopeptides
Tigecycline	Glycylcyclines

https://www.who.int/publications/i/item/2021-aware-classification

Stewardship of colistin in South Africa



Emergence of plasmid mediated colistin resistance

SAMJ IN PRACTICE

CLINICAL ALERT

Emergence of plasmid-mediated colistin resistance (MCR-1) among *Escherichia coli* isolated from South African patients

J Coetzee, C Corcoran, E Prentice, M Moodley, M Mendelson, L Poirel, P Nordmann, A J Brink

Coetzee J et al. *S Afr Med J* 2016;106(5):449-450

Emergence of plasmid mediated colistin resistance

- A countrywide surveillance program of RSA poultry farms revealed that colistin resistance in *E. coli* strains increased substantially -19 of 24 (79%) colistin-resistant cultures from the last quarter of 2015 contained MCR-1.

- It was surmised that this sudden increase was likely due to the selection of MCR-1-containing strains where colistin was being used .

- Of critical importance, MCR-1 was detected in clinical isolates of colistin-resistant *E.coli* from hospitalized (n=3) and outpatient based (n=6) patients in South Africa.

- The national and global significance of sudden spread of MCR-1 and the attendant loss of colistin had profound public health implications and confirms the continuum between colistin use in feed animals and colistin resistance in slaughtered animals, food for human consumption, colonized humans, and infected patients.

Coetzee J et al. *S Afr Med J* 2016;106(5):449-450

Emergence of plasmid mediated colistin resistance

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

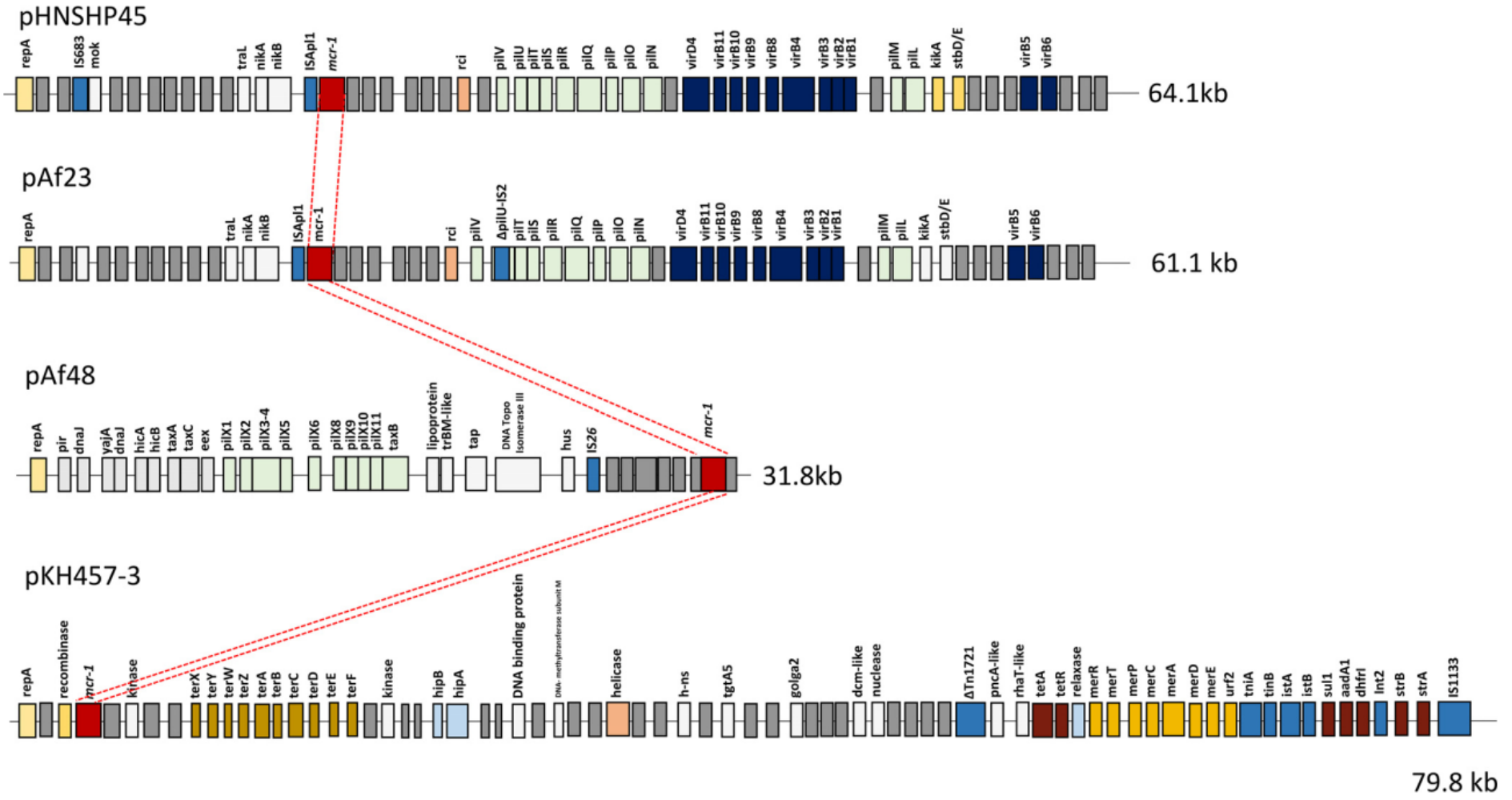
Genetic Features of MCR-1-Producing Colistin-Resistant *Escherichia coli* Isolates in South Africa

Laurent Poirel,[a,b] Nicolas Kieffer,[a] Adrian Brink,[c] Jennifer Coetze,[d] Aurélie Jayol,[a] Patrice Nordmann,[a,b,e]

Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Fribourg, Switzerland[a]; INSERM European Unit (LEA) (INSERM, Paris, France), University of Fribourg, Fribourg, Switzerland[b]; Department of Clinical Microbiology, Ampath National Laboratory Services, Milpark Hospital, Johannesburg, South Africa[c]; Department of Clinical Microbiology and Molecular Biology, Ampath National Laboratory Services, National Referral Laboratory, Centurion, South Africa[d]; University of Lausanne and University Hospital Center, Lausanne, Switzerland[e]

Citation Poirel L, Kieffer N, Brink A, Coetze J, Jayol A, Nordmann P. 2016. Genetic features of MCR-1-producing colistin-resistant *Escherichia coli* isolates in South Africa. Antimicrob Agents Chemother 60:4394–4397. doi:10.1128/AAC.00444-16.

Emergence of plasmid mediated colistin resistance



Poirel et al AAC 2016;60:4394-4397

The One Health stewardship of colistin in SA

The One Health stewardship of colistin as an antibiotic of last resort for human health in South Africa

Marc Mendelson, Adrian Brink, Joey Gouws, Nontombi Mbelle, Vinny Naidoo, Troy Pople, Natalie Schellack, Moritz van Vuuren, Helen Rees, on behalf of the South African One Health Stewardship Sub-Committee of the Ministerial Advisory Committee on Antimicrobial Resistance

Mendelson et al. *Lancet ID* 2018 http://dx.doi.org/10.1016/S1473-3099(18)30119-1

The One Health stewardship of colistin in SA

- "Increasing reliance on antibiotics of last resort to treat the rising numbers of MDR and XDR bacterial infections in humans has focused attention on how we steward shared-use antibiotics across human and animal health

- South Africa has reacted to this threat by performing a situational analysis and review of existing legislation concerning colistin use in animals and humans, to inform action"

- "The experiences shared in this paper, outline the process, institution of governance with widespread stakeholder engagement, surveillance, and interventions that the country has undertaken towards optimising shared use of colistin

Mendelson et al. *Lancet ID* 2018 http://dx.doi.org/10.1016/S1473-3099(18)30119-1

The One Health stewardship of colistin in SA

SAVC
SOUTH AFRICAN VETERINARY COUNCIL

Colistin use by veterinarians

Dear Member

It is recommended that Colistin not be used in food producing animals at all, unless the veterinarian can justify its use at the hand of a sensitivity test and as a very last resort to treat an animal. Any conduct to the contrary would be regarded by Council as unprofessional conduct.

Please read the message from the Registrar of Medicines addressed to all veterinarians.

Stewardship of new β-lactam-β-lactamase inhibitors (BLICs) in South Africa

Stewardship of BLICs in SA

Southern African Journal of Infectious Diseases
ISSN: (Online) 2313-1810, (Print) 2312-0053

AOSIS

Page 1 of 10 Guideline

Best practices: Appropriate use of the new β-lactam/β-lactamase inhibitor combinations, ceftazidime-avibactam and ceftolozane-tazobactam in South Africa

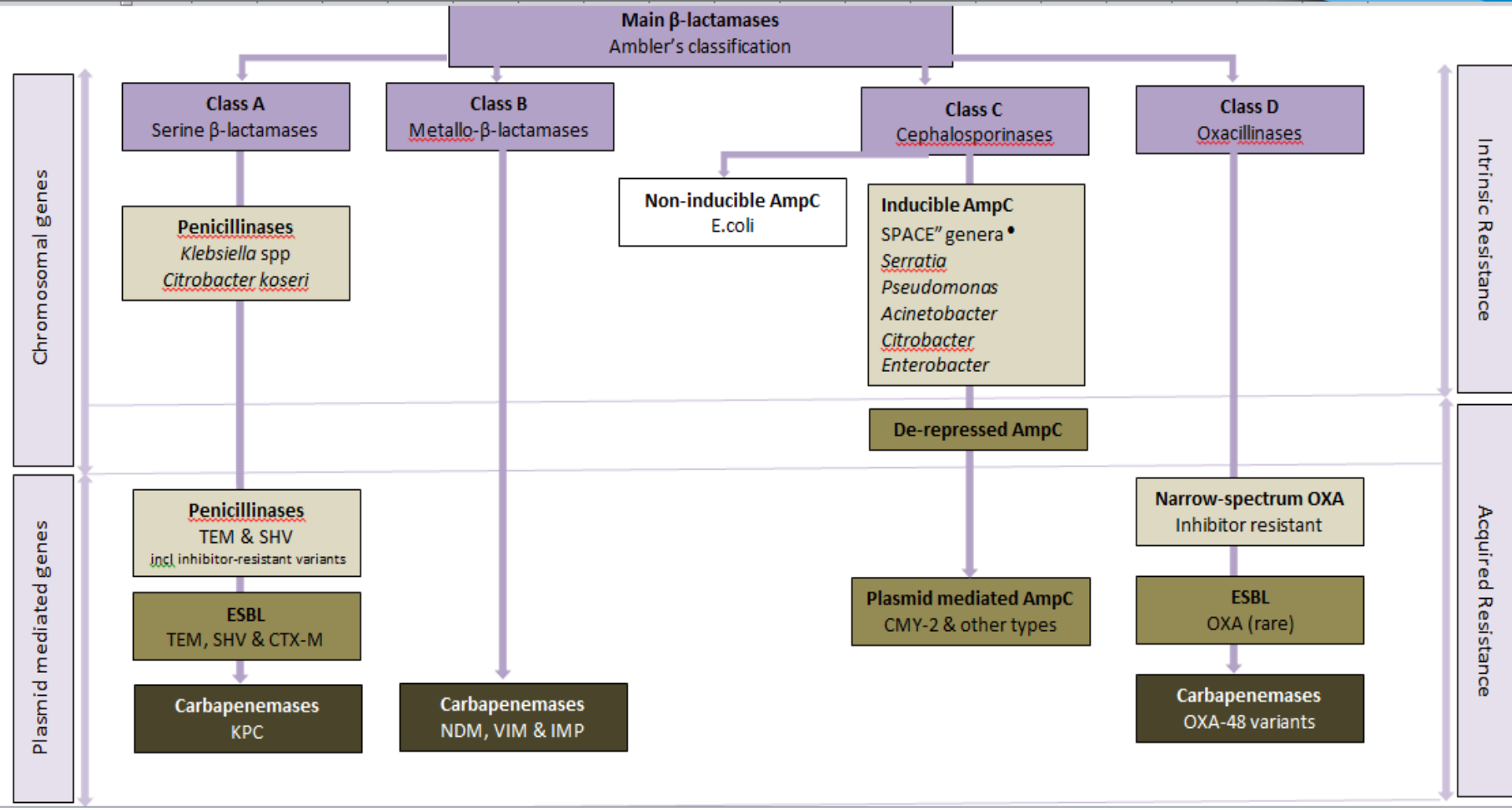
Authors:
Adrian J. Brink[1]
Jennifer Coetzee[2]
Guy A. Richards[3]
Charles Feldman[4]
Warren Lowman[5,6,7]
Hafsah D. Tootla[8]
Malcolm G.A. Miller[9]
Abraham J. Niehaus[10]
Sean Wasserman[11,12]
Olga Perovic[13,14]
Chetna N. Govind[15,16]
Natalie Schellack[17]
Marc Mendelson[11]

Stewardship of BLICs in SA

- Ceftazidime-avibactam (CA) and ceftolozane-tazobactam (CT) are the first of the new generation BLICs registered in SA.
- In this regard, it is evident that new molecules and novel BLICs with in vitro activity against DTR-GNB, only partially address the currently prevalent mechanisms of resistance
- As such, effective therapy is dependent on accurate and prompt identification of the organism, and on phenotypic and genotypic antimicrobial susceptibility and mechanisms of resistance testing, respectively.
- Their potential uncontrolled use as a “one-size fits all” treatment for DTR GNBs could prove catastrophic for their future preservation as viable therapeutic options
- However, this would warrant a paradigm shift in management of serious GNB infections

Brink et al. Curr Opin Crit Care 2020; 26: 478-488. doi: 10.1097/MCC.0000000000000752.
Brink AJ. Curr Opin Infect Dis 2019;32:609-16.

The beta-lactamase landscape



Conceptual approach to β-lactamase inhibition-based stratification

- The available evidence regarding the use of currently available β-lactam/β-lactamase inhibitor combinations (BLICs) as well as an emerging body of data on novel agents in the antibiotic development pipeline requires a paradigm shift as to how we recommend the use of both current and new antibiotics

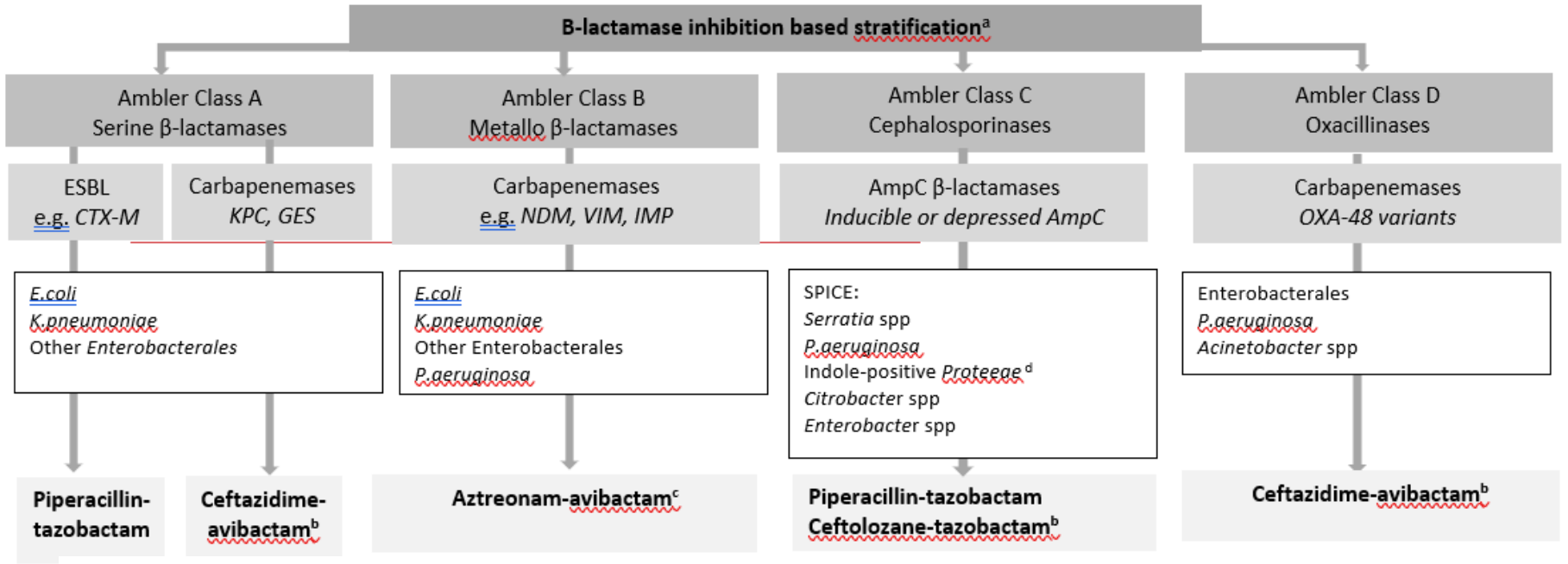
- Therefore, recommendations for use should be strategic and should perhaps rely on categorization of mechanism-based inhibition of β-lactamases.

- In this regard, in order to minimize antibiotic selective pressure a conceptual approach to BLIC therapy is proposed

Brink et al. *S Afr J Infect Dis*. 2022;37(1)

Conceptual approach to β-lactamase inhibition-based stratification

Figure 1. Conceptual approach to B-lactamase inhibitor therapy for severe infections



[a] Any novel β-lactamase inhibitor combination (BLIC) in the pipeline to be stratified pending spectrum of activity or β-lactamase inhibition

[b] As per Table 2-4, ceftazidime-avibactam and ceftolozane-tazobactam only recommended as alternative treatment, when preferred 1st line antibiotics are not susceptible, not available or tolerated or in cases of confirmed bacteriological and clinical failure

[c] Currently in Phase IIIb trials

[d] *Proteus vulgaris, Morganella morganii, Providencia stuartii, Providencia rettgeri*

Brink et al. *S Afr J Infect Dis*. 2022;37(1)

New drugs approved or in clinical development with activity against multi-drug resistant Gram-negatives

	ESBL	KPC	OXA-48	MBL	CRPA	CRAB	Phase
β-lactam/β-lactamase inhibitors							
Meropenem/vaborbactam	✓	✓	–	–	–	–	Postmarket
Meropenem/nacubactam	✓	✓	✓	–	–	–	Phase I
Meropenem/QPX7728	✓	✓	✓	✓	±	✓	Preclinical
Imipenem/relebactam	✓	✓	–	–	✓	–	Postmarket
Ceftazidime/avibactam	✓	✓	✓	–	✓	–	Postmarket
Ceftolozane/tazobactam	✓	–	–	–	✓	–	Postmarket
Cefepime/tazobactam (2 g/2 g)	✓	–	✓	–	–	–	Phase III[a]
Cefepime/enmetazobactam	✓	–	–	–	–	–	Phase III
Cefepime/zidebactam	✓	✓	✓	✓	±	±	Phase I
Cefepime/VNRX5133	✓	✓	✓	±	±	–	Phase III
Cefepime/QPX7728	✓	✓	✓	✓	±	–	Preclinical
Ceftibuten/VNRX-7145	✓	–	–	–	–	–	Phase I
Ceftibuten/QPX7728	✓	✓	✓	–	–	–	Preclinical
Cefpodoxime/ETX-0282	✓	–	–	–	–	–	Phase I
Aztreonam/avibactam	✓	✓	✓	✓	–	–	Phase III[b]
Sulbactam/durlobactam	✓	✓	✓	✓	–	✓	Phase III
β-lactams							
Cefiderocol	✓	✓	✓	±	✓	±	Phase III
Tebipenem	✓	–	–	–	–	–	Phase III
Sulopenem	✓	–	–	–	–	–	Phase III
Aminoglycosides							
Plazomicin	✓	✓	✓	±	–	–	Postmarket
Tetracyclines							
Eravacycline	✓	✓	✓	✓	–	±	Postmarket
Polymyxins							
SPR741 plus beta-lactams	✓	±[c]	±[c]	–	–	✓	Phase I
SPR206	✓	✓	✓	✓	✓	✓	Phase I
QPX9003	✓	✓	✓	✓	✓	✓	Preclinical

[a]Not yet recruiting.
[b]Suspended because of a delay in drug availability.
[c]Active against *Eschrichia coli*, inactive against *Klebsiella pneumoniae*.

Paterson et al. Curr Opin Infect Dis 2020;33:214-223.

Conceptual approach to β-lactamase inhibition-based stratification

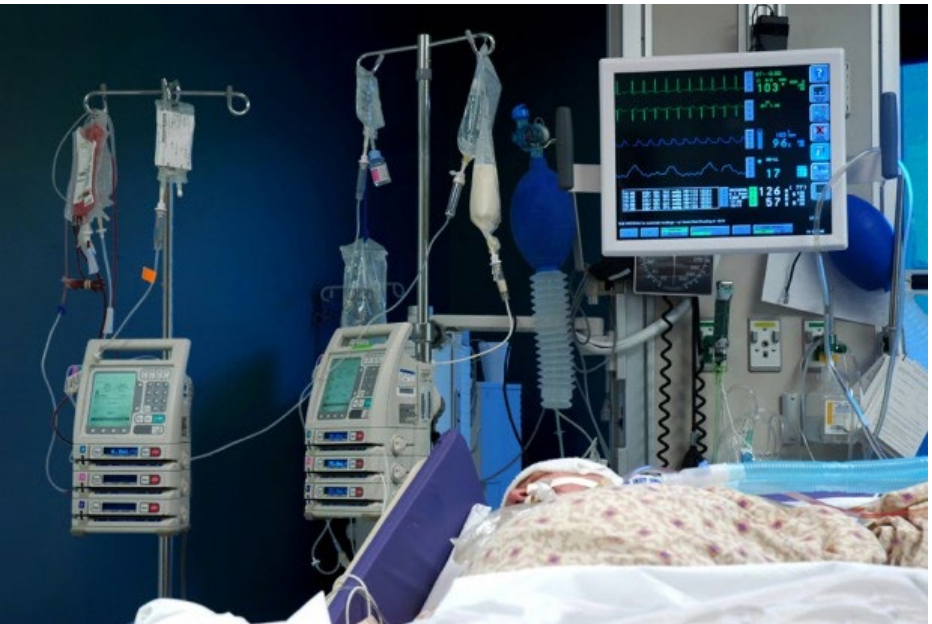
- The objectives of our recommended approach to management of MDR- and DTR-GNB (i.e., mechanism-based inhibition therapy) are to:
  - Optimise patient outcomes in settings where there has been increasing dependence on colistin as salvage monotherapy.
  - Avoid redundant and inappropriate use of CA and CT, from an antibiotic stewardship and cost-containment point-of-view.
  - Ensure the longevity of existing broad-spectrum agents (i.e., carbapenems, ceftazidime, cefepime, tigecycline, piperacillin-tazobactam and colistin) and the new antibiotics (i.e., CT and CA and those that follow).

Moving away from empiricism to directed therapy

- The proposed β-lactamase inhibition-based stratification implies or signifies less empirical use and directed therapy based on genealogy i.e. genotyping β-lactamases genes
- With current and novel rapid-diagnostic tests it would be possible within a few hours to direct and tailor therapy
- This would require translational stewardship interventions to optimize patient-level outcomes

Brink et al. *Semin Respir Crit Care Med* 2022;43:75–96

Conclusions



Conclusions

- Reserve antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable.

- These medicines should be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

- A case in point, is the successful one-health intervention of colistin and the proposed conceptual approach to β-lactamase inhibition-based stratification of new BLICs in South Africa

“An antibiotic steward knows how to use an antibiotic,

a good antibiotic steward knows when to use an antibiotic,

and a great antibiotic steward knows when not to use an antibiotic”

(Adapted from a quote regarding surgeons)