

# **The ethics of antibiotic stewardship**

## **Delaying the imminent end of the antibiotic area**

**Adrian Brink**

**Clinical Microbiologist, Ampath National  
Laboratory Services, Milpark Hospital,  
Johannesburg**





### **Emergence of extensive drug resistance (XDR) among Gram-negative bacilli in South Africa looms nearer**

**“The fact that the antibiotic prescribing fraternity has not yet accepted stewardship of the emerging problem of XDR Gram-negative bacilli has given rise to an ethical dilemma both in South Africa and internationally. To delay the imminent end of the antibiotic era, it may well be time now to challenge the right of doctors to prescribe whichever antibiotic they wish, including the dosage and duration”**

# Scope of presentation

- Current status of resistance
- Strategies for antibiotic stewardship
- Using the care bundle approach in antibiotic prescribing
- Antibiotic optimization



# Current status of resistance

## % antibiotic resistance of bacteraemic strains of Gram-negative pathogens in private practice in South Africa: January - June 2006

Antibiotic	<i>A.baumannii</i> (n=190)		
	n	% Overall	Range
Ceftazidime	82	43	21-81
Cefepime	82	43	10-83
Piperacillin-tazobactam	80	42	14-83
Ciprofloxacin	68	36	10-75
Levofloxacin	59	31	10-75
Amikacin	55	29	7-70
Tobramycin	36	19	7-40
Imipenem	63	33	3-72
Meropenem	61	32	3-72

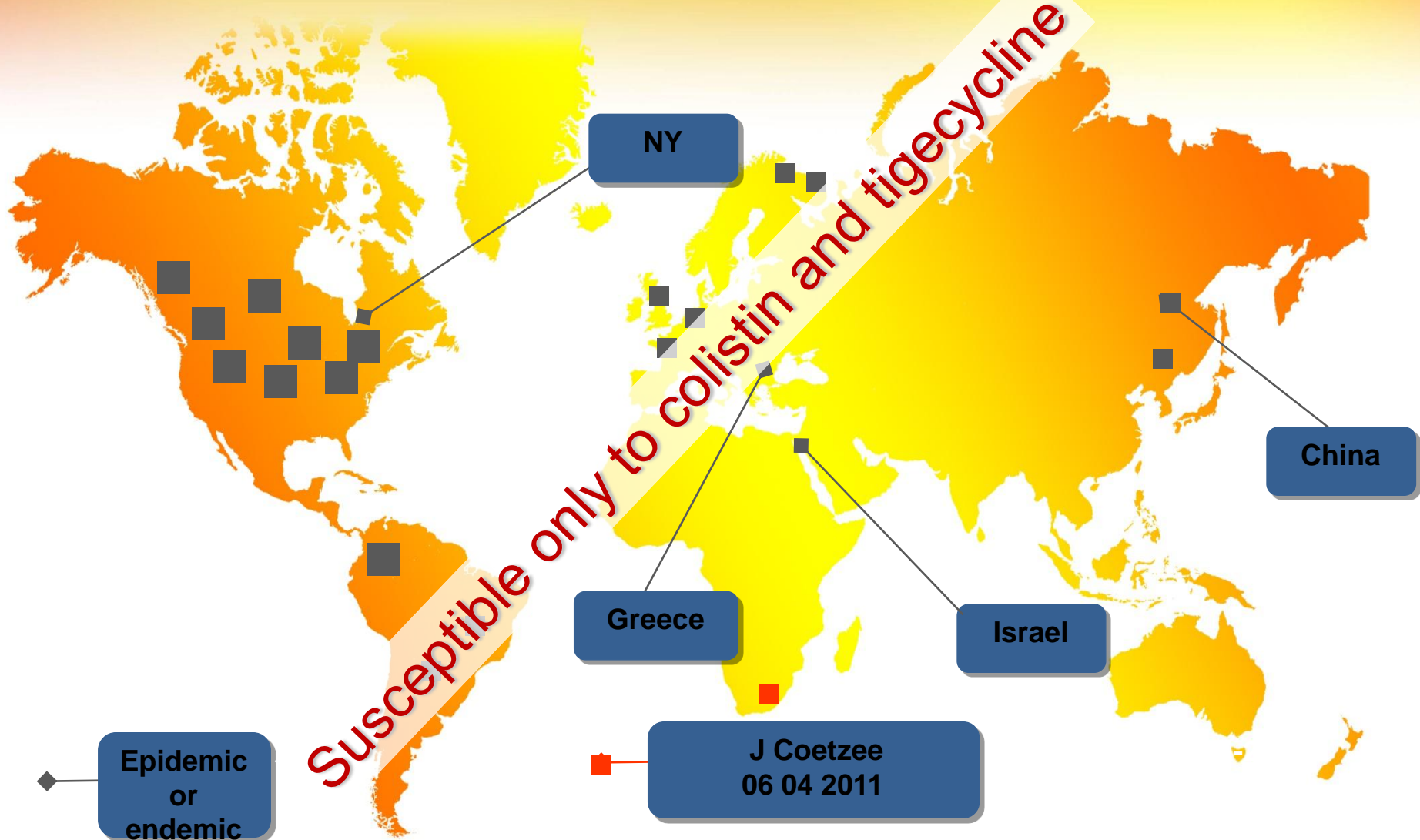
## % antibiotic resistance of bacteraemic strains of Gram-negative pathogens in private practice in South Africa: January - June 2006

Antibiotic	<i>P.aeruginosa</i> (n=382)		
	n	% Overall	Range
Ceftazidime	172	45	11-90
Cefepime	202	53	21-70
Piperacillin-tazobactam	183	48	21-61
Ciprofloxacin	176	46	30-67
Levofloxacin	176	46	21-67
Amikacin	183	48	11-67
Tobramycin	202	53	11-100
Imipenem	172	45	23-63
Meropenem	160	42	15-64

## % Resistance bacteraemic strains of Gram-negative pathogens in private practice in South Africa: Jul - Dec 2007

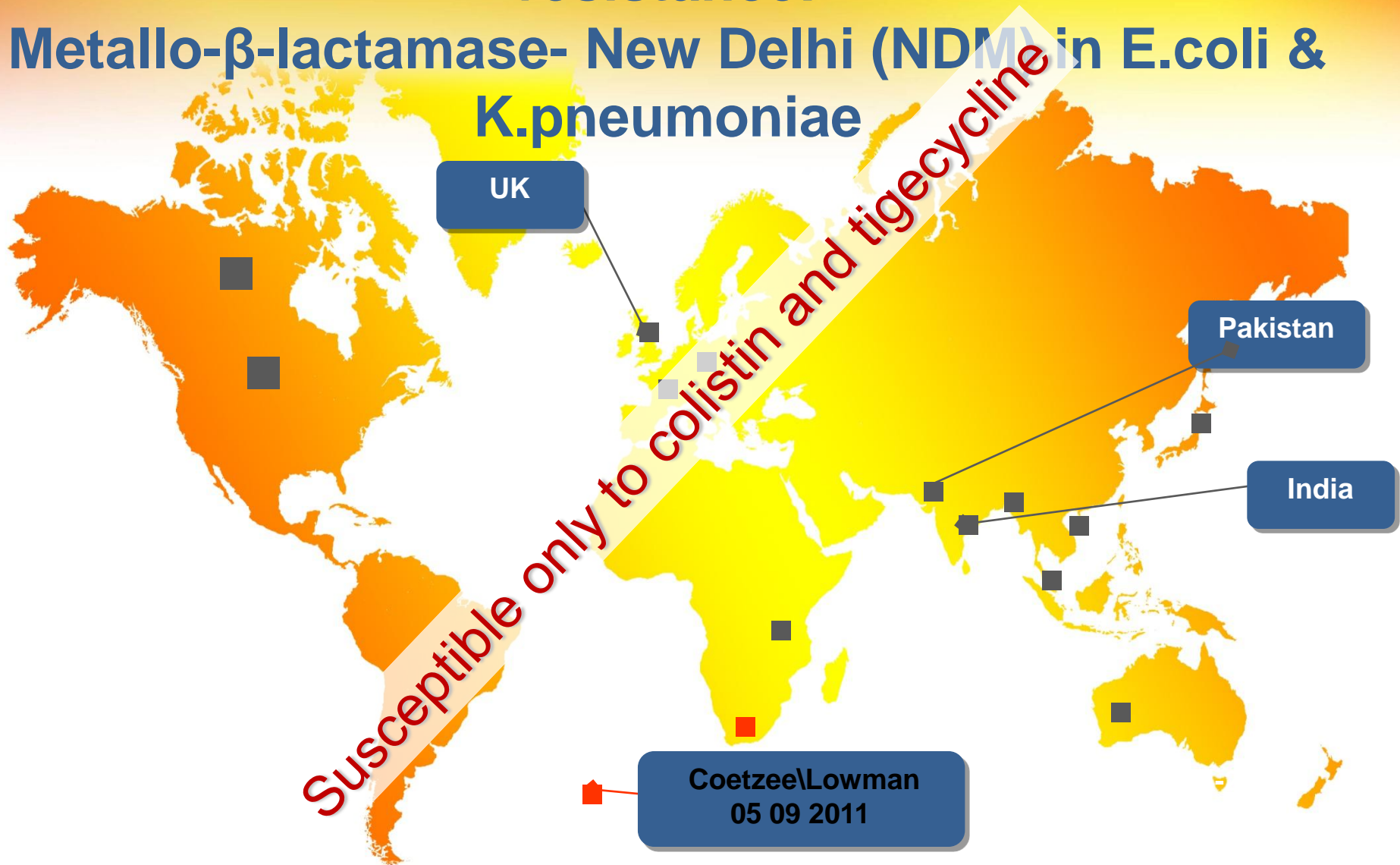
	<i>E.coli</i> (n=503)	<i>K.pneumoniae</i> (n=548)	<i>Enterobacter</i> spp (n=190)
Antibiotic	Overall (Range)	Overall (Range)	Overall (Range)
Ampicillin	82 (65-90)	100 ( - )	100 ( - )
Co-amoxiclav	39 (0-57)	62 (31-73)	99 (91-100)
Cefuroxime	18 (0-33)	62 (31-72)	83 (0-96)
Ceftriaxone/Cefotaxime	7 (0-15)	57 (43-66)	62 (44-91)
Cefepime	5 (0-14)	54 (50-64)	26 (10-46)
Piperacillin-tazobactam	9 (0-23)	49 (26-67)	38 (17-66)
Ciprofloxacin	16 (0-36)	39 (18-64)	16 (0-40)
Levofloxacin	16 (0-36)	39 (28-64)	16 (0-40)
Gentamicin	14 (0-32)	31 (0-43)	25 (10-52)
Amikacin	6 (0-15)	25 (8-50)	6 (0-16)
Ertapenem	2 (0-8)	2 (0-8)	5 (0-17)
Imipenem	1 (0-6)	1 (0-1)	1 (0-5)
Meropenem	1 (0-6)	1 (0-1)	1 (0-5)
<b>% ESBL production</b>	<b>5 (0-11)</b>	<b>50 (33-59)</b>	<b>23 (9-37)</b>

# The emergence of KPC (*K.pneumoniae* carbapenemases) is a cause of great concern



# The latest threat in the war on antibiotic resistance:

## Metallo- $\beta$ -lactamase- New Delhi (NDM) in E.coli & K.pneumoniae



.....emergence and outbreaks due to colistin resistant KPC- producing *K.pneumoniae*



Zarkotou et al. *J Clin Microbiol* 2010;48: 2271–74  
Kontopoulou et al. *J Hosp Infect* 2010;76:70-73

# Antibacterial Compounds Undergoing Clinical Development in Phase 2 or Later Studies

Spectrum and product	Class (MOA)	Novel MOA	Formulation
<b>Gram-positive</b>			
Ceftobiprole	Cephalosporin	No	IV
Ceftaroline	Cephalosporin	No	IV
Telavancin	Lipoglycopeptide	Yes	IV
Dalbavancin	Lipoglycopeptide	No	IV
Oritavancin	Glycopeptide	No	IV
Iclaprim	Diaminopyrimidine (dihydrofolate reductase inhibitor)	No	IV, oral
TD-1792	Multivalent vanco-cephalosporin	Unknown	IV
RX-1741	Oxazolidinone	No	Oral

# Antibacterial Compounds Undergoing Clinical Development in Phase 2 or Later Studies (cont)

Spectrum and product	Class (MOA)	Novel MOA	Formulation
Gram-positive + Gram negative			
Faropenem	Penem	No	Oral
PZ-601	Carbapenem with MRSA activity	No	IV
Tomopenem	Carbapenem with MRSA activity	No	IV
Cethromycin	Macrolide	No	Oral
EDP-420	Bicyclolide; bridged macrolide structure	No	Oral
PTK-0796	Aminomethylcycline	No	IV, oral
NXL-103	Streptogramin	No	Oral
RX-3341	Quinolone with MRSA activity	No	IV

**What can be done about it?**



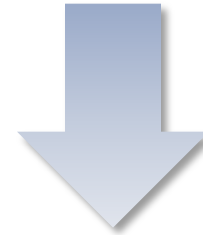
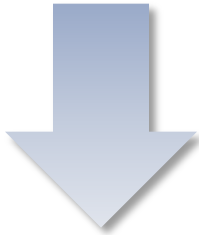
# Antimicrobial stewardship

# Consequences of Inappropriate Rx: Collateral Damage

Excessive use

Inappropriate drug administration

Suboptimal dosing



- **Collateral damage**
  - Selection of drug-resistant organisms
  - Infection with MDR pathogens
  - Super-infection with fungal pathogens
  - CDI

CDI, *Clostridium difficile* infection

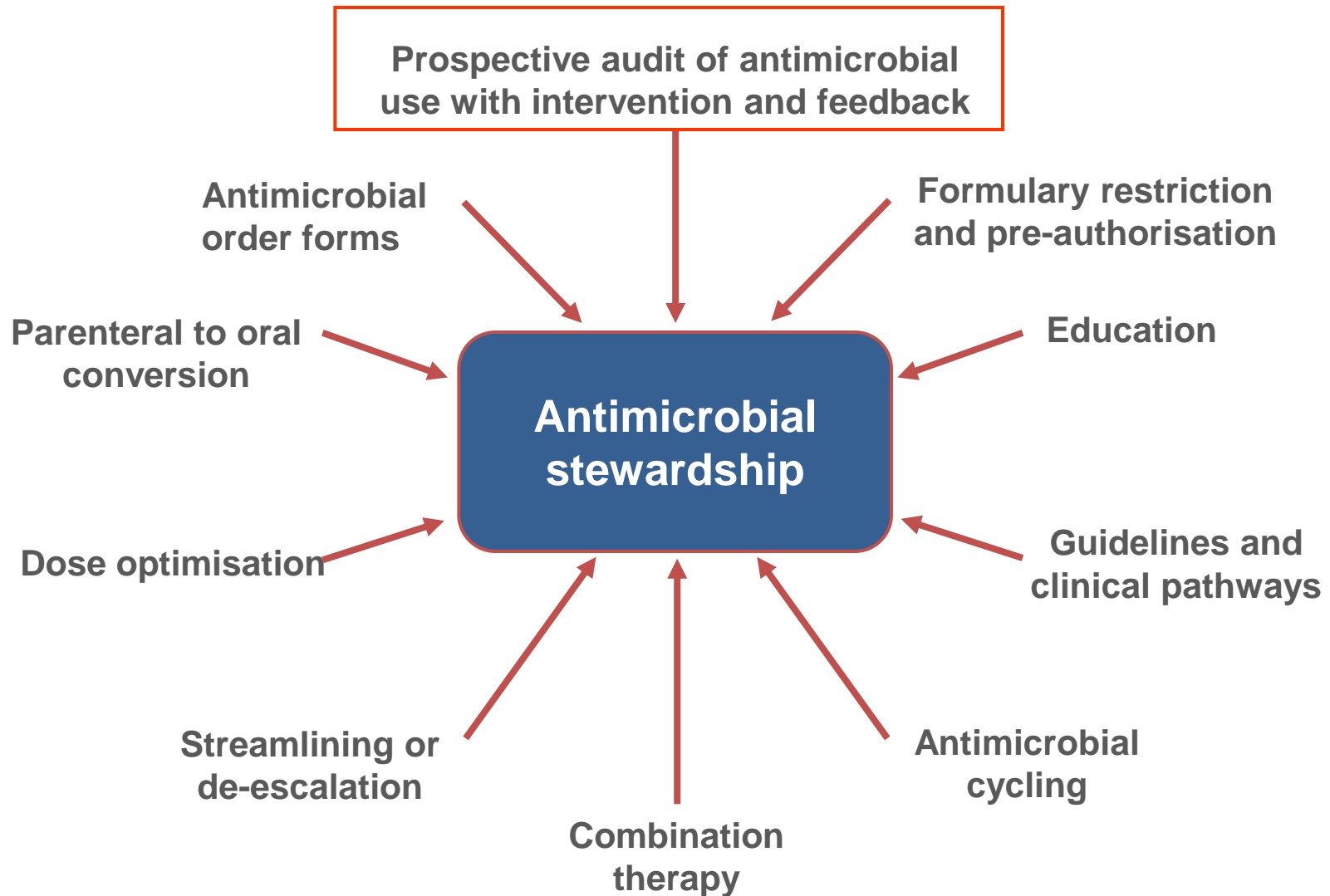
# Some of the core values that commonly apply to medical ethics, might apply to inappropriate antibiotic treatment

- Non-Maleficence
  - *Primum non nocere*: "first, do no harm"
  - Many feel it is more important not to harm your patient, than to do them good
- Beneficence
  - *Salus aegroti suprema lex*
  - In the medical context, this means taking actions that serve the best interests of patients
- Doctrine of double effect (DDE)
  - Thomas Aquinas, [O.P.](#) ( [/ə'kwainəs/ ə-KWY-nəs](#); Aquino, 1225 – Fossanova, 7 March 1274
  - Refers to two types of consequences which may be produced by a single action, and in medical ethics it is usually regarded as the combined effect of beneficence and non-maleficence
  - Empirical antibiotic treatment vizaviz inappropriate use and collateral damage

# What is antibiotic stewardship

- Stewardship is an ethic that embodies **responsible planning and management of resources.**
- The concept of stewardship has been applied in diverse realms, including with respect to environment, economics, health, property, information, and religion, and is **linked to the concept of sustainability.**
- Historically, stewardship was the responsibility given to household servants to bring food and drinks to a castle dining hall.
- The term continues to be used in many specific ways, but it is also used in a more general way to refer to a **responsibility to take care of something belonging to someone else.**
- To be a steward, and or act in steward to something, is known as stewardship.

# Strategies for Antimicrobial Stewardship



# Antimicrobial stewardship

## Cycling vs. Diversity

# Cycling vs. Diversity

Heterogeneous AB use is a potential way of ↓ the selection pressure that leads to AB resistance

- Cycling (Rotation)
  - Scheduled substitution of a class (or a member of that class) not sharing a common mechanism of action that exhibits a comparable spectrum of activity
  - May be followed by a 3rd, 4th, or any number of substitutions, but cycle must be repeated
- Diversity
  - Simultaneous mixed use of different AB classes for different pts in a unit
  - Allows for greater AB heterogeneity

**Brown EM. *J Antimicrob Chemother.* 2005;55:6-9**

**Fridkin SK. *Clin Infect Dis.* 2003;36:1438-1444**

**Bergstrom CT. *Proc Natl Acad Sci USA.* 2004;101:13285-13290**

**Sandiumenge A. *J Antimicrob Chemother.* 2006;57:1197-1204**

# Cycling vs. Diversity – A Case Study for VAP

Length and Periods of Usage						
Months 1-10 Patient Specific	Months 11-22 Prioritization			Months 23-34 Restriction		Months 35-44 Mixing
<p>Therapy determined by a patient-specific strategy</p> <ul style="list-style-type: none"> <li>•Multiple choices</li> <li>•LOS</li> <li>•Prior abx exposure</li> </ul>	Carbapenem	Cephalosporin	Pip/tazo	No Pip/tazo	No Cephalosporin	No Carbapenem
						<p>Changed in consecutive pts following a pre-established schedule</p> <p>APCarb → Cip → Clin + APCeph → P/T</p>

APCarb, anti-pseudomonal carbapenem; Cip, ciprofloxacin; Clin, clindamycin, APCeph, anti-pseudomonal cephalosporin; P/T, piperacillin/tazobactam.

# Cycling vs. Diversity – A Case Study

- Guideline-driven strategies of empirical AB prescription for pneumonia were not associated with any benefit
- Prioritization and restriction determined high homogeneity
  - Facilitated colonization by Enterobacteriaceae and non-fermentative gram-negative bacilli
  - Outbreaks of CR-Ab during carbapenem prioritization
  - ESBL-producing Enterobacteriaceae during cephalosporin prioritization
- Patterns favoring balanced use of different antimicrobials should be preferred

# What Does This Suggest?

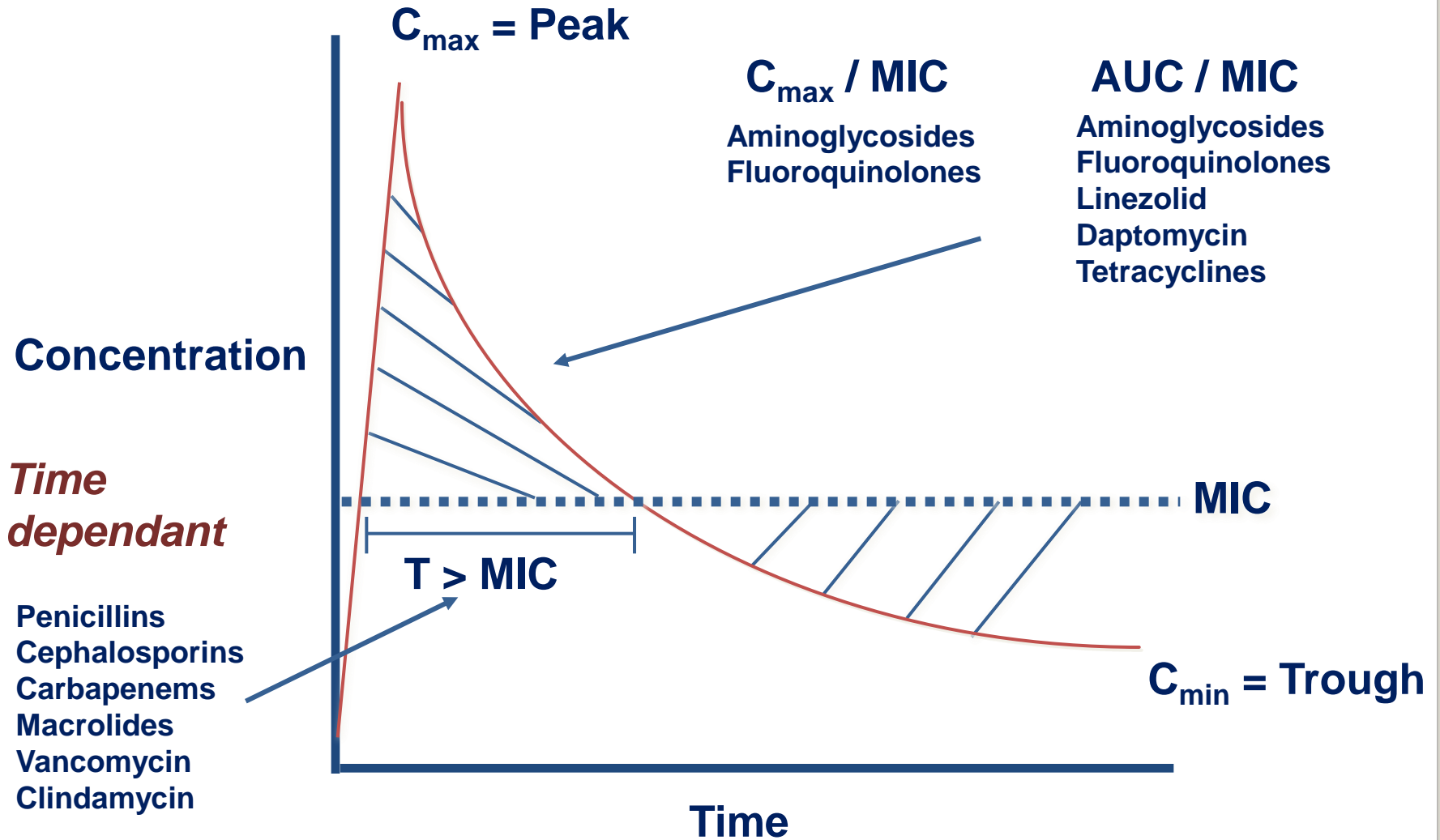
- A new approach to antibiotic choice that is patient specific with a focus on using multiple agents appropriately can lead to prescribing diversity
- Structured programs of restriction or prioritization can lead to high use of a limited number of drugs that help drive the development and spread of resistance

# Antimicrobial stewardship

## Optimizing Antimicrobial Exposure

# Dosing is Important

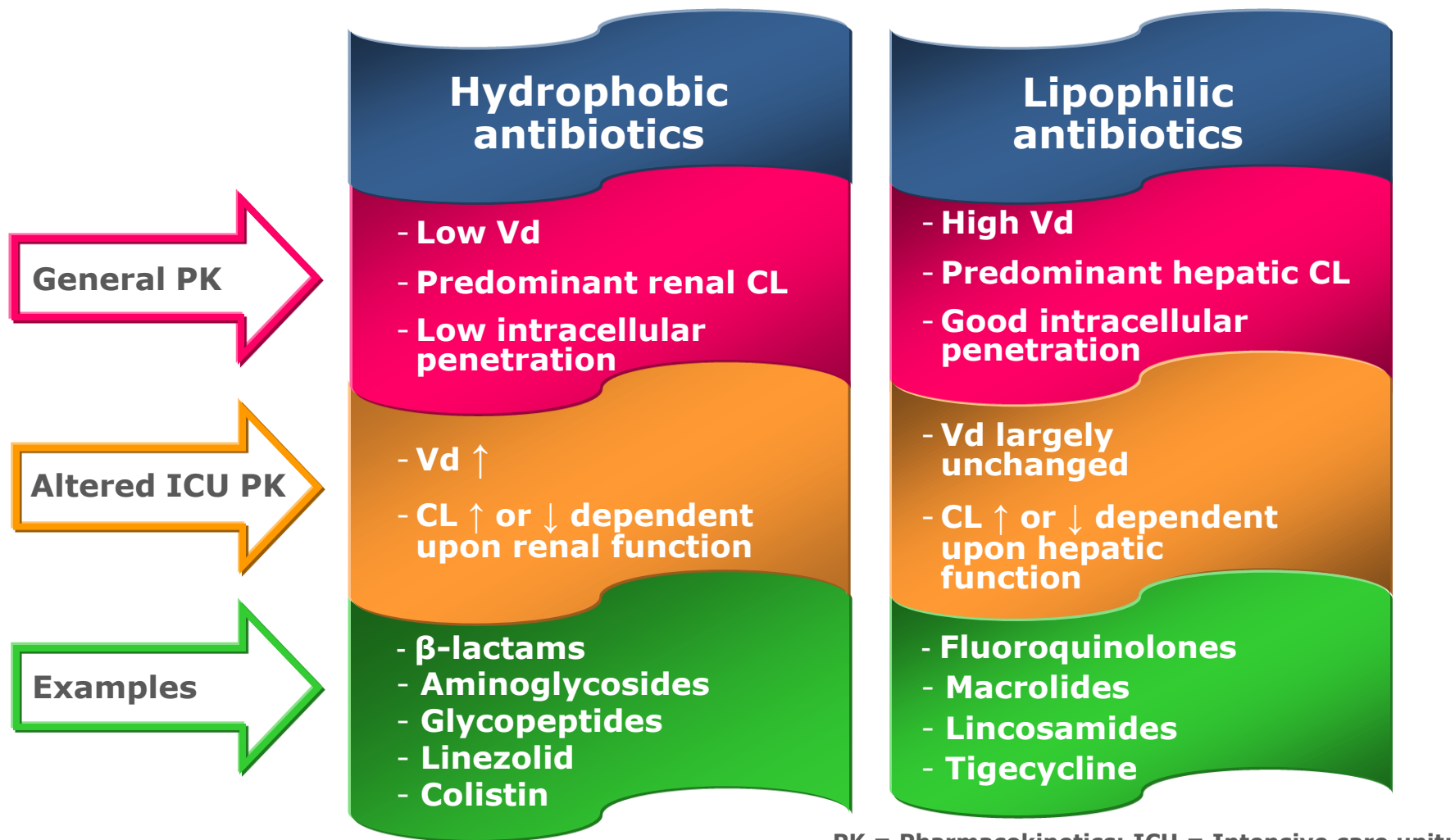
*Concentration dependant*



Nicolau DP. *J Infect Chemother.* 2003;9:292-296

Ambrose PG. *Clin Infect Dis.* 2007;44:79-86

# The Interrelationship of Hydrophilicity and Lipophilicity of Antibiotic Molecules on Pharmacokinetic Characteristics



PK = Pharmacokinetics; ICU = Intensive care unit; Vd = Volume of distribution; CL = Clearance

# Practically: Optimizing Antimicrobial Exposure

- Increase dose
  - Aminoglycosides, fluoroquinolones, beta-lactams
- Increase frequency
  - Beta-lactams, vancomycin
- Increase infusion duration
  - Beta-lactams via
    - Prolonged IV infusion (0.5 hr → 3hr)
    - Continuous IV infusion -loading dose followed by total daily dose  
24 h
- Loading doses for highly protein bound drugs (and/or hypoalbuminaemia)  
Tigecycline, teicoplanin

# Antimicrobial stewardship

Combination therapy  
( $\beta$ -lactam  $\pm$  aminoglycoside)

# What are the Reasons for Combination Rx?

- A. Synergy needed for cure
- B. Improve outcome in very sick pts
- C. Prevent development of resistance
- D. Expanded spectrum to cover gaps in empiric Rx

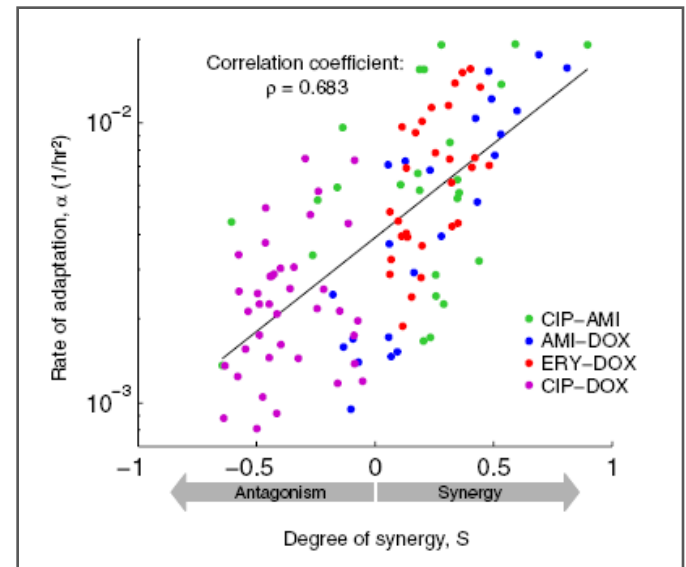
# Mono- vs Combination Rx What is the Evidence? ( $\beta$ -lactam $\pm$ aminoglycoside)

- Combination no benefit for sepsis  
Paul M. *Cochrane Data Sys Rev* 2006  
Paul M. *Brit Med J* 2004
- Combination no benefit for endocarditis  
Falagas ME. *J Antimicrob Chemo* 2006;57:659-67  
Cosgrove SE, et al. *Clin Infect Dis* 2009;48:713-721
- Monotherapy preferred for neutropenia  
Schlesinger P. *Cochrane Data Sys Rev* 2003  
Paul M, et al. *Brit Med J* (2003) *bmj* 2003;326:1111
- Combination no benefit to avoid resistance or superinfection  
Bliziotis IA, et al. *Clin Infect Dis* 2005;41:149-158

More renal toxicity for  
combination in all settings

# Drug Combinations and Development of Resistance

- Studied synergistic and antagonistic antibiotic combinations against *E. coli*
- Synergistic combinations facilitated development of resistance to both agents
- Found a high correlation between synergy and the rate of resistance adaptation



# Using the Care Bundle Approach in Antibiotic Prescribing

# Using the Care Bundle Approach in Antibiotic Prescribing in Hospitals

- Care bundle approach being widely adopted to optimize delivery in health care
- Elements consist of
  - Group of key evidence-based or logical actions
  - Instituted over a specific time frame
- If delivered together (in conjunction with infection control bundles), have a greater clinical impact than if delivered individually
- Could serve as the pillars of any antibiotic stewardship program

# A Practical Approach to the AB Care Bundle

- Use the fewest number of agents as initial Rx that will treat the likely pathogens
  - **1 broad spectrum – monotherapy- agent** replacing 2 or 3 AB in combination exposes bacteria (normal flora) to 1/2 or 1/3 less antibiotic
- **Re-evaluate initial Rx** when cx results are available and no later than 3rd day of Rx
- **Use optimal dosing** plus route of administration and Rx for the shortest effective time to obtain a successful outcome

# Monotherapy Treatment Regimens

Early-onset HCAP	Late-onset HCAP/VAP	Skin and soft tissue infection*	Peritonitis of unknown origin
Ciprofloxacin Moxifloxacin Levofloxacin	Ceftobiprole (non-VAP)	Tigecycline	Tigecycline or piperacillin/tazobactam
Amp/sulbactam	P/T + FQ/AG + anti-MRSA	P/T ± anti-MRSA	P/T ± anti-MRSA
Ertapenem	Imi/Mero + FQ/AG + anti-MRSA	Ertapenem ± anti-MRSA	Carbapenem ± anti-MRSA
Ceftriaxone	Cefepime/ Ceftazidime + FQ/AMG + anti-MRSA	Cefepime ± anti-MRSA	Cefepime + MTZ ± anti-MRSA
		Ciprofloxacin ± anti-MRSA ± MTZ	Ciprofloxacin + anti-MRSA ± MTZ


## Day 3 Assessment of AB Care Bundle

- Was there an **antibiotic plan** (name, dose, route, interval of administration, and planned duration)?
- Was there a **review of the diagnosis**?
- If positive microbiological results available, any adaptation of antibiotic treatment?
  - **Streamlining**
  - **Discontinuation**
- If I.V. original therapy, **possibility of I.V.- oral switch** documented?

# **Antimicrobial stewardship**

**Prospective audit of antimicrobial use with intervention and feedback**

# But how is this managed?

- Clinical pharmacologist rounds in conjunction with clinical microbiologist focusing on antimicrobial prescribing
- Daily monitoring & feedback (friendly) of: 
  - Antibiotic agent choice
  - Antibiotic IV duration >7 , >10, >14 days
  - Antibiotic dosages (loading and maintenance)
  - Microbiology results vs. antibiotic appropriateness
  - Escalation and de-escalation
  - Duplicate antibiotic spectrums
  - Dosages taking into account co-morbidities and current drug therapy especially in liver and renal failure
  - Liaising with the treating Dr to assist with motivations or medical aid authorizations or unusual doses
  - Sorting out stock concerns regarding antimicrobials

## Milpark hospital: Trauma (n=35) & Burns ICU (N=10): Impact of prospective audit of antimicrobial use with intervention and feedback

	ADMISSIONS IN TICU	NO OF PAN/MDR ACINETOBACTER INFECTIONS	ADMISSIONS IN TICU	NO OF PAN/MDR ACINETOBACTER INFECTIONS
	2009	2009	2010	2010
JAN	-	-	-	-
FEB	81	6	***95	0
MARCH	80	6	77	0
APRIL	62	3	70	1
MAY	91	0	51	5
JUNE	76	8	62	0
TOTALS	390	23	355	6

- PDR A.baumannii & P.aeruginosa defined as susceptibility to colistin alone
- Daily clinical pharmacologist rounds
- Significantly less PDR infections 1.69% vs 5.89% after active intervention (P=0.0004)

# Conclusion

# Risk factors for inappropriate therapy

- Not using local data
- Use of broad-spectrum antibiotics (e.g. carbapenem) when not absolutely necessary
- Broad treatment of contamination, including surgical prophylaxis
- Treating colonization aggressively
- Excessive duration of antimicrobial treatment (i.e. continue antibiotics when infection is cured)

## Proposed 8-step plan

- 1<sup>st</sup>. Institute an antibiotic “**plan**”
- 2<sup>nd</sup>. Choose empiric therapy based on **site**, the most likely **pathogens**, **local S data**, **prior antibiotic use** and physician assessment of **severity of infection**
- 3<sup>rd</sup>. **Monotherapy** (Use the fewest number of agents as initial Rx that will treat the likely pathogens)
- 4<sup>th</sup>. **Optimize exposure** by adequate dosing incl loading doses where applicable consistent with PK/PD parameters
- 5<sup>th</sup>. **Review ID Dx**

## Last 3-Ts

- **6<sup>th</sup>. Timely start**

Any delay in initiation for serious Gram-negative sepsis is potentially lethal

- **7<sup>th</sup>. Timely tailoring/de-escalation/streamlining**

Based on clinical response and microbiological data

Re-evaluate initial Rx when cx results are available and no later than 3rd day of Rx

- **8<sup>th</sup>. Timely discontinuation when practical**

Monitor duration & Rx for the shortest effective time to obtain a successful outcome

# Always!

Best care

[www.bestcare.org.za](http://www.bestcare.org.za)

