PK-PD Controversies of New Antibiotics: Room for Individualisation?

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Consultant/Advisory Board/Speaker fees

- Pfizer, MSD, Angelini
- Thermo Fisher, Shionogi
- BioTest, Nordic Pharma, InfectoPharma
- Gilead Sciences, GSK
- Hikma, Advanz

- **Research grant**
  - Pfizer, MSD, Shionogi

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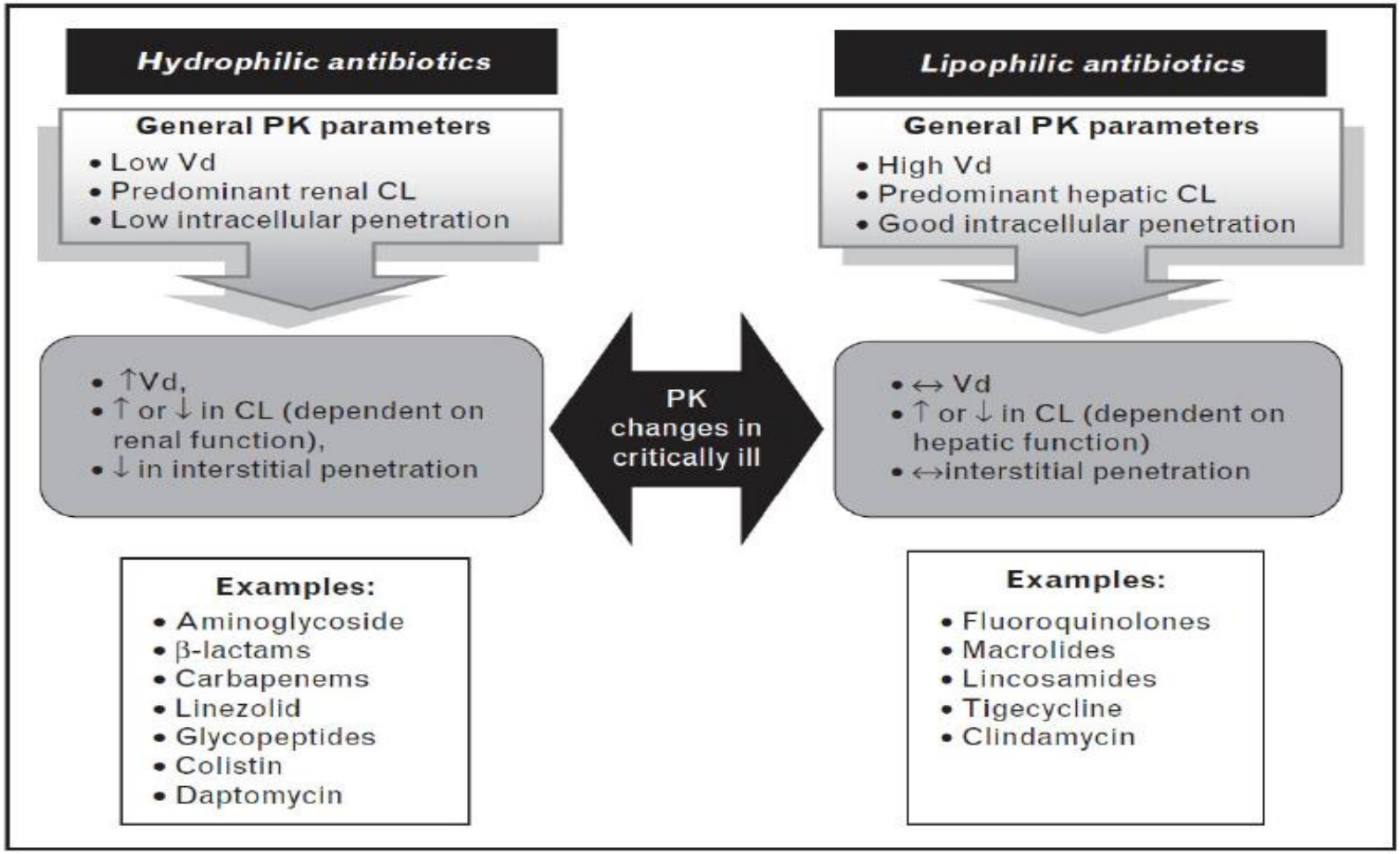
REVIEW

The management of anti-infective agents in intensive care units: the potential role of a 'fast' pharmacology

Dario Cattaneo [a,b], Alberto Corona[c], Francesco Giuseppe De Rosa[d], Cristina Gervasoni[b,e], Danijela Kocic[f] and Deborah Je Marriott[g]



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The management of anti-infective agents in intensive care units: the potential role of a 'fast' pharmacology

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Table 1. Pathophysiological changes in critically ill patients and their effects on the pharmacokinetics of antimicrobial agents.

Changes	Effect on drug pharmacokinetics
Impaired drug absorption	Reduced bioavailability of orally administered antimicrobials (not frequent in critically ill patients)
Hypoalbuminemia	Increased drug clearance and higher risk to fail PK/PD target attainment (most relevant for renally excreted antimicrobials with protein binding >80%)
Obesity	Changes in the Vd, hepatic drug metabolism and renal excretion for hydrophilic antimicrobials (i.e. beta-lactams, vancomycin)
Renal insufficiency	Reduced clearance of hydrophilic drugs with increased risk to reach supra-therapeutic plasma concentrations and to develop drug-related toxicity (i.e. beta-lactams, aminoglycosides; glycopeptides)
Hepatic insufficiency	Increased risk of accumulation of antimicrobials with high hepatic extraction rate. For the remaining, the effects on drug pharmacokinetics are less predictable
Augmented renal clearance (acute hyperdynamic phase)	Increased clearance of hydrophilic antimicrobials with increased risk of sub-therapeutic plasma concentrations (i.e. beta-lactams, linezolid, fluconazole)
Altered fluid balance (increased capillary permeability)	Expansion of extracellular fluid volume leading to increased drug Vd and lower plasma drug concentrations. This effect is particularly relevant for hydrophilic antibiotics with low Vd (i.e. aminoglycosides, beta-lactams)
Extracorporeal clearance for organ support (RRT, ECMO)	increased Vd and clearance of hydrophilic antimicrobials with increased risk of drug underexposure

Vd: volume of distribution; RRT: renal replacement therapy; ECMO: extracorporeal membrane oxygenation.

New Antibiotics
Room for Individualization

- **Long acting "lineless antibiotics"**
  - Dalbavancin
  - Oritavancin
- **New BL / BLI**
  - Ceftolozane/tazobactam & ceftazidime/avibactam
  - Meropenem/vaborbactam
  - Cefiderocol
  - Imipenem/relebactam
  - Cefepime-zidebactam
- **New tetracyclines**
  - Omadacycline
  - Eravacycline
- **Pleuromutilin**

Room for Individualization

- Clinical
- Pharmacological
- Microbiological

The Example of Cytochrome CYPA4

Pea F *Current Opinion in Pharmacology* 2015, 24:18–22

- **Major biotransformation of several therapeutic drugs**
- **CYPA4, Statins & Macrolides**
  - Clarithro and erythro, but not azithro, inhibit CYP3A4
  - → Expected increased plasma exposure
    - Atorvastatin, lovastatin and simvastatin
  - → Possible rhabdomiolisis and acute renal failure

Other Patients / Chronic Treatments

Warfarin
Oral Antidiabetics
Kidney failure

Bacterial Meningitis: Dose Optimization

Heffernan AJ, Roberts, JA Curr Op Infect Dis 2021; 34(6): 581-590

- **Limited data for BL / BLI inhibitors**
- **Further evidence for**
  - Improved outcomes with intraventricular administration
- **Ongoing paucity of PK Studies guiding dosing recomendations**
- **Historical examples and bias:**
  - Vancomycin and steroids
  - Beta-lactams and meningeal inflammation
  - Tetracycline and bacteriostasis

Loading Dose & Continuous / Extended Infusion (CEI) in Critically Ill Patients treated with Beta-Lactams

Wu CC et al J Clin Pharm Ther 2021

- **For CEI Vs. intermittent administration (IA)**
  - Overall mortality 0.82 (95% CI: 0.72-0.94)
  - Clinical cure 1.31 (95% CI: 1.15-1.49)
- **Subgroup and meta-regression analyses**
  - Loading dose → significantly increased clinical cure rate
    - RR: 1.44, 95% CI: 1.22-1.69
  - Also significant after adjustments for beta-lactam type
- **Subgroup analysis of administration**
  - Both groups had low mortality and high clinical cure rates

Meropenem TDM Review

Steffens NA et al J Clin Pharm Ther 2021

- **35 studies included**
- **TDM can be beneficial**
  - Adjusts the treatment
  - Aids clinical outcomes
  - Indicates the appropriate dosage
  - Prevents failure, toxicity and possibly antimicrobial resistance
- **Essential:**
  - Multidisciplinary effort
  - Basic pharmacological knowledge
  - Communication among the medical team

Lower dosages in patients with low Cr Cl or high uric acid level dosages
Prolonged infusion beneficial with MIC <4mg/L

Zhao Y-C Infect Dis Ther 2021

Cefiderocol PK & PD

Bilal M et al Clin pharmacokinetic 2021

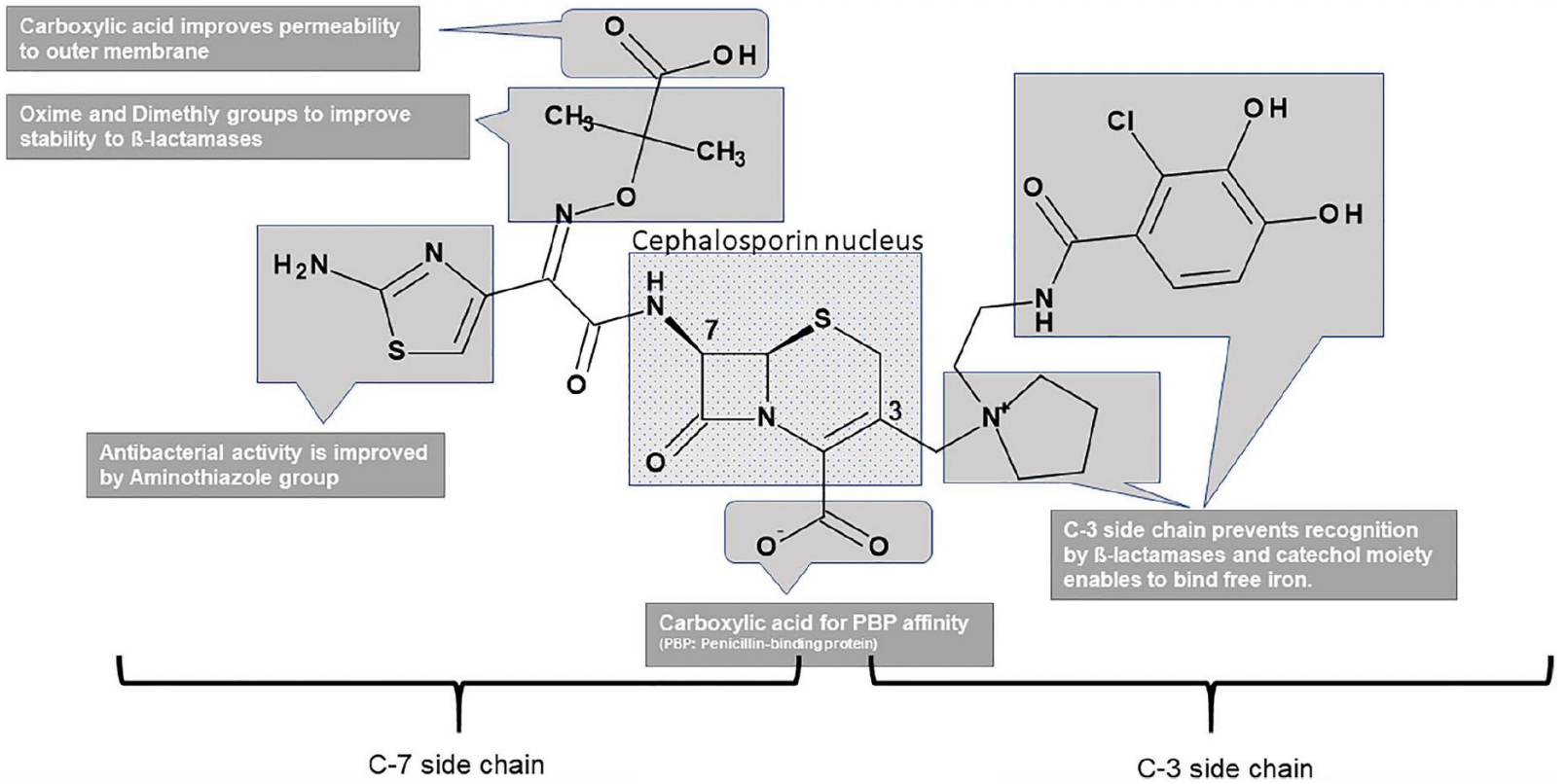

Fig. 1 Illustration of important functional groups in the cefiderocol molecule [1]. The cephalosporin nucleus is complemented by five functional groups in the C-3 and C-7 side chains, resulting in an improved outer membrane permeability, antibacterial activity, beta-lactamase stability, and the capability to bind free iron. Based on [1]

Cefiderocol Compassionate use: Burn patient with *A. baumannii* XDR BSI

Corcione S, D'Avolio A, De Rosa FG

- On December 2018, the patient was admitted to our Burn Unit Center with an extensive deep burn on chest, legs, arms and back (TBSA 85%)
- She was intubated and the debridement of skin necrosis and coverage of allograft was performed in the early days after admission.
- During her hospital stay she developed BSI due to vancomycin resistant *E. faecium* and candidemia due to *C. parapsilosis*
- On day 160, the patient reported a clinical worsening with persistent fever, leukocytosis and hypotension. Blood cultures from peripheral and central line were positive for XDR-AB, only susceptible to amikacin (MIC<1 mg/L). On day 165 the skin and rectal swabs resulted positive to XDR-AB (with the same pattern of resistance) and carbapenem resistant *Pseudomonas aeruginosa*.
- Compassionate program use conducted by drug manufactory (Shionogi, Rome, Italy). Cefiderocol 2 gr q6h (3 hours infusion) was started in combination with amikacin 1 gr q24h i.v, according to the manufacturer manual for a creatinine clearance >120 mL/min (creatine clearance at time of analysis 240 mL/min)

Cefiderocol in a Burn Patient with *A. baumannii* XDR BSI

Personal data: Corcione S & De Rosa FG

Materiale: T. rettale

Esame/Ricerca **Ceppi resistenti ai carbapenemi**

Ceppi isolati/identificati *Carica Microbica*

Ceppo 1 **Pseudomonas aeruginosa**

Antibiotici	*MIC*	*MIC Breakpoint*	*S<=*	*R>*	*Note*
Imipenem		*R*	*4*	*4*	*Breakpoint validi per terapia a dosaggio elevato*
Meropenem		*R*	*2*	*8*	

Antibiogramma interpretato secondo i **criteri ed i dosaggi terapeutici** indicati da EUCAST 2019 (European Committee on Antimicrobial Susceptibility Testing – http://www.eucast.org/clinical_breakpoints/)-ove non altrimenti specificato
MIC = Concentrazione minima inibente (ug/mL)
S = efficacia terapeutica a dosaggio standard, **I** = efficacia terapeutica a dosaggio elevato, **R** = inefficacia terapeutica anche a dosaggio elevato, **IE** = Evidenze insufficienti per definire l'attività della molecola su questo microrganismo
L'interpretazione indicata in referto deriva dal valore di MIC e dall'applicazione di regole del Sistema Esperto

****CEPPO MULTIRESISTENTE***:
Attivare, in aggiunta alle precauzioni standard, le PRECAUZIONI DI ISOLAMENTO PER le INFEZIONI TRASMESSE PER CONTATTO (se previsto dal CIO di Presidio)
Vedere referti precedenti

Ceppi isolati/identificati *Concentrazione*

Ceppo 1 **A. baumannii/haemolyticus**

Antibiotici	*MIC*		*MIC Breakpoint* *S<=*	*R>*	*Note*
Meropenem	>8	*R*	*2*	*8*	
Levofloxacina	>1	*R*	*0.5*	*1*	
Gentamicina	>4	*R*	*4*	*4*	*Breakpoint validi per terapia a dosaggio elevato*
Tobramicina	>4	*R*	*4*	*4*	*Breakpoint validi per terapia a dosaggio elevato*
Trimetoprim-sulfametossazolo	>4/76	*R*			
Colistina	8	*R*	*2*	*2*	*I test di sensibilità a Colistina non evidenziano la pr ceppi eteroresistenti che possono ridurre l'efficacia*
Tigeciclina	12	*IE*	*0.5*	*0.5*	
Ciprofloxacina	>32	*R*	*0.06*	*1*	
Imipenem	>32	*R*	*2*	*4*	

Antibiogramma interpretato secondo i **criteri ed i dosaggi terapeutici** indicati da EUCAST 2019 (European Committee on Antimicrobial Susceptibility Testing – http://www.eucast.org/clinical_breakpoints/)-ove non altrimenti specificato
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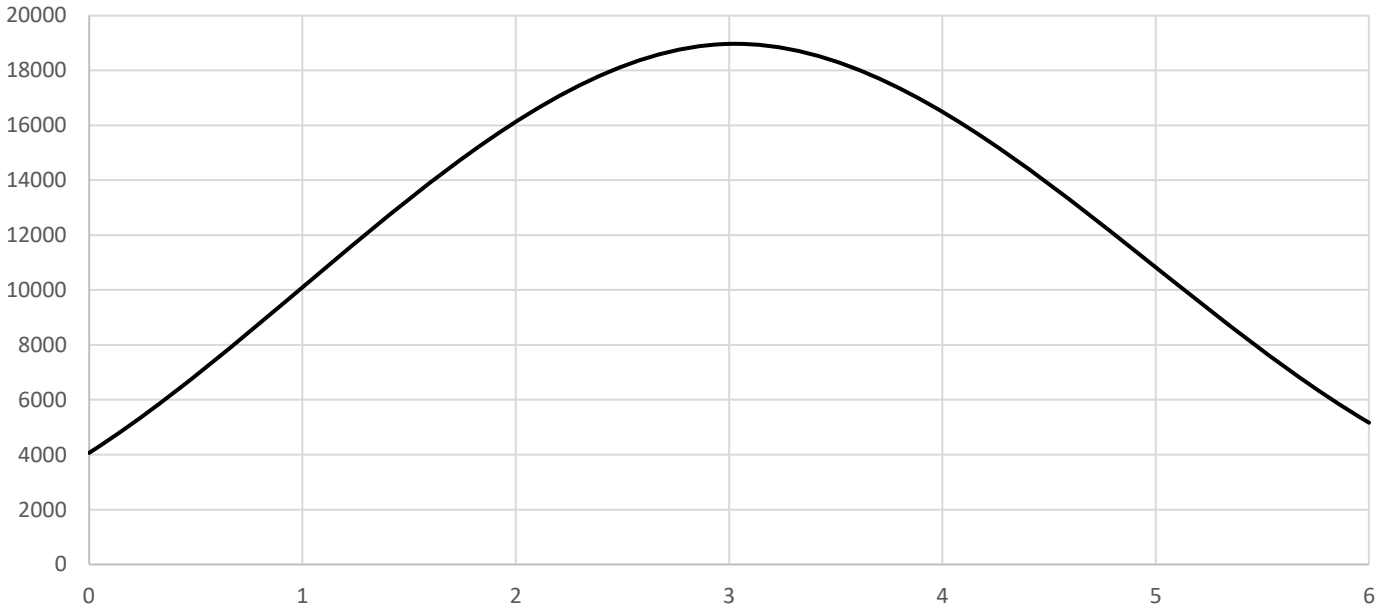
****CEPPO MULTIRESISTENTE***:
Attivare, in aggiunta alle precauzioni standard, le PRECAUZIONI DI ISOLAMENTO PER le IN
TRASMESSE PER CONTATTO (se previsto dal CIO di Presidio)

Treatment for 14 days: Progressive improvement and negative blood cultures after one week of treatment.

Side effects: Hyperchromic urine and possibly anemia. Patients survived up to day 253,

when death occurred mainly because of acute kidney failure.



PK Lab
D'Avolio A, Torino

C_{max} and C_{min}: 18968 ng/mL, 4063 ng/mL

Beyond Vancomycin: The Tail of the Lipoglycopeptides

Klinker KP, Borgert SJ. Clin Ther. 2015;37(12):2619-36

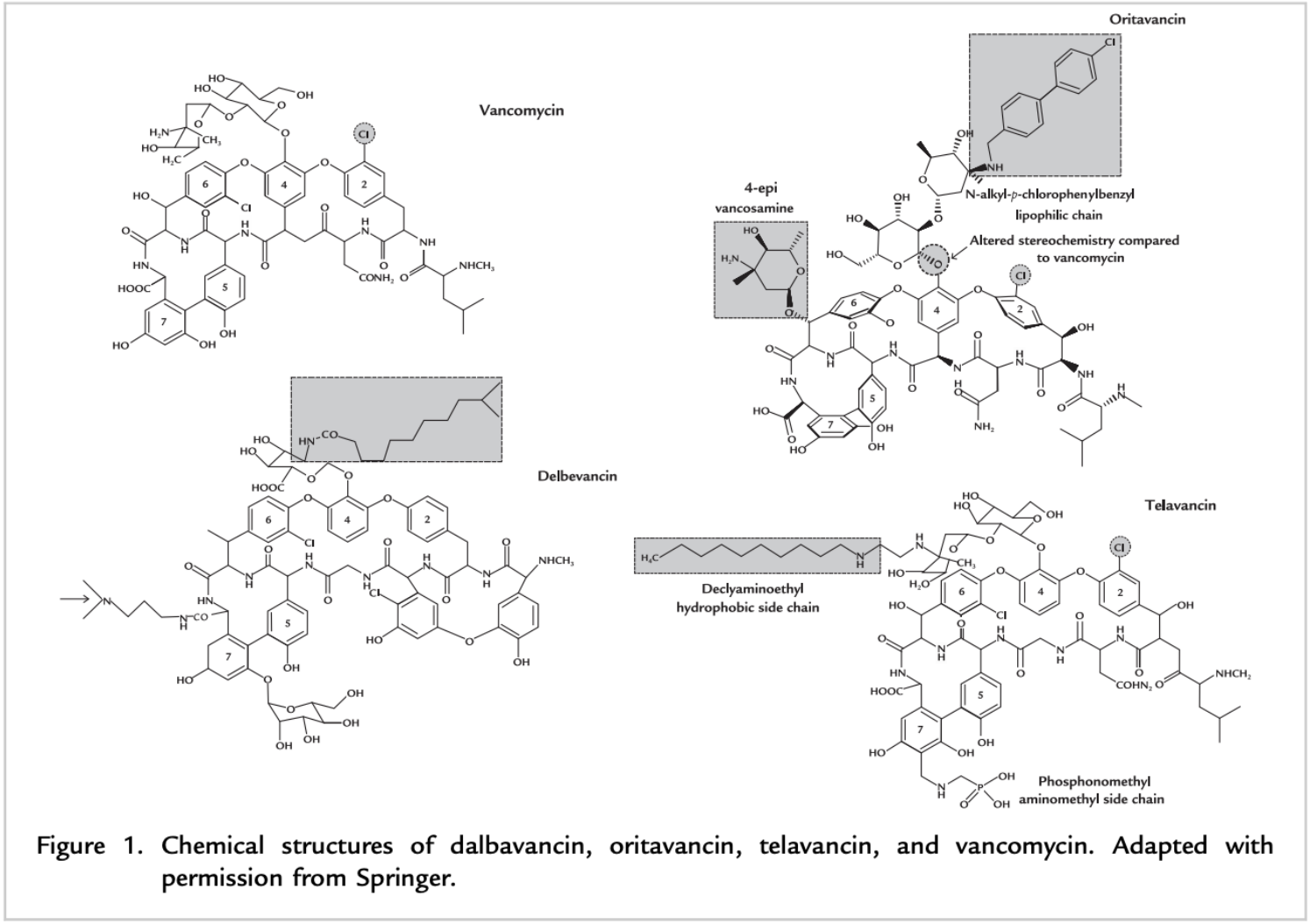


Figure 1. Chemical structures of dalbavancin, oritavancin, telavancin, and vancomycin. Adapted with permission from Springer.

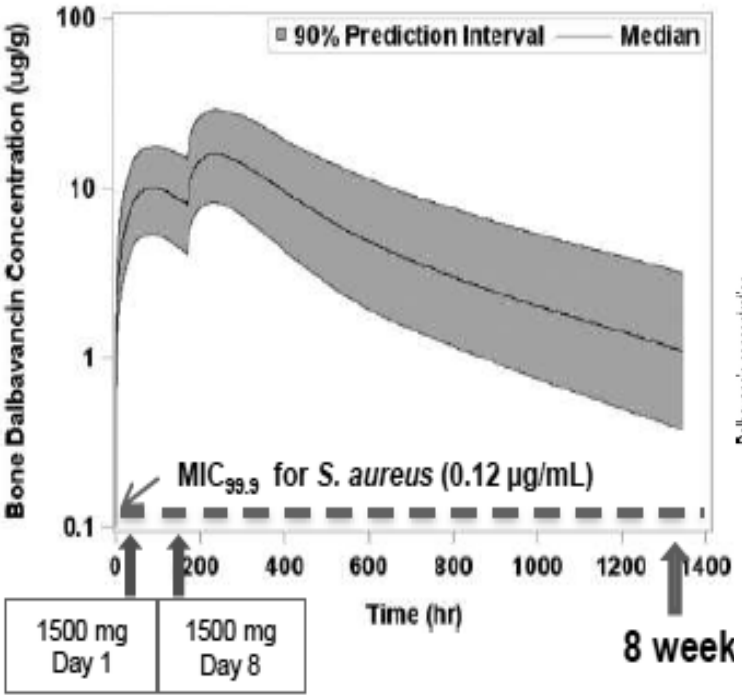
Beyond Vancomycin: The Tail of the Lipoglycopeptides

Klinker KP, Borgert SJ. Clin Ther. 2015;37(12):2619-36

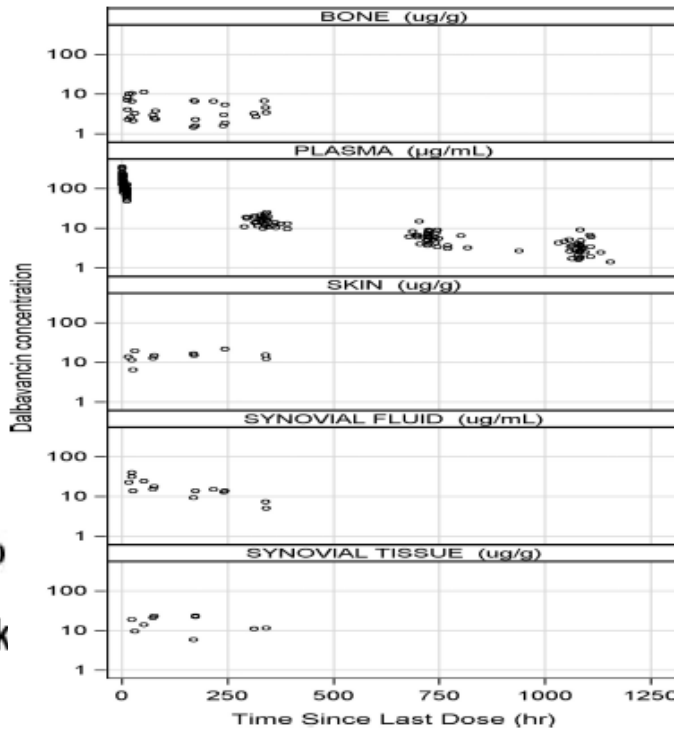
- **Approximately 4- to 8-fold more potent than vancomycin**
  - Against Gram-positive organisms
  - Including activity against vancomycin-intermediate or vancomycin-resistant strains of Staphylococcus and Enterococcus species
- **Oritavancin**
  - Maintains activity against Enterococcus species harboring vanA operon
- **These agents serve to fill different clinical roles in the management of gram-positive infections**

Dalbavancin: PK

Dunne, 2015, Marbury 2015



Simulated mean concentration time profile in bone with 1,5 g IV on days 1 and 8



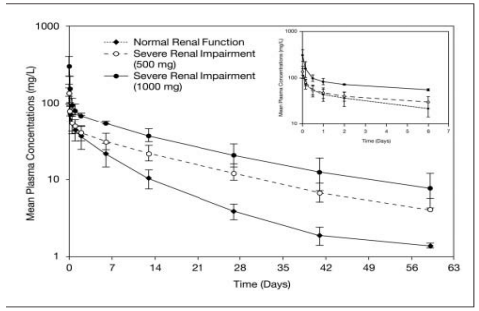


Figure 2. Mean plasma concentration-time profiles of dalbavancin in participants with normal renal function and in those with severe renal impairment after a single intravenous (IV) infusion dose of 500 mg or 1000 mg of dalbavancin in study 2. Insert indicates the concentration-time profile over 7 days after dosing.

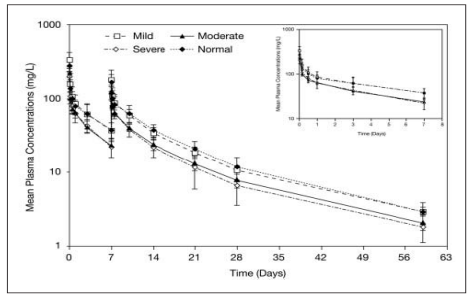


Figure 5. Mean plasma concentration-time profiles of dalbavancin in participants with normal hepatic function and in those with mild, moderate, or severe hepatic impairment after intravenous (IV) infusion dosing with 1000 mg on day 1 followed by 500 mg on day 8 of dalbavancin in study 3. Insert indicates the concentration-time profile over 7 days after dosing.

Advantages of Outpatient Treatment with Long-Acting Lipoglycopeptides (laLGP)
Krsak M et al. Pharmacotherapy. 2020;40(5):469-478

- **Possible utility in transitions to outpatient settings:**
  - People who use drugs, those who cannot reliably adhere to unsupervised treatment (poor mental or physical health)
  - People with complicating life circumstances
    - Homelessness, incarceration, rural location
  - Inadequate health insurance
- **Review of evidence and possible cost-effectiveness from patient, payer, and hospital perspectives**
- **Barriers to broader use of laLGPs:**
  - Relative lack of prospective data regarding efficacy in serious infections
  - Narrow US & FDA indications restricted to ABSSSI
  - Lack of reimbursement infrastructure

In vitro & *In vivo* Assessments of Cardiovascular Effects with Omadacycline

Tanaka SK & Villano S AAC 2016

- **First-in-class aminomethylcycline antibiotic**
- **Nonclinical studies explored the cardiovascular risk potential**
  - Exclusive binding to the muscarinic subtype 2 acetylcholine receptor (M2)
  - Concentration-dependent antagonism of a pan-muscarinic agonist (carbamylcholine) in the SA node model
  - No effect
    - hERG channel activity at 100 g/ml (179.5 M)
    - QTc in conscious monkeys at doses up to 40 mg/kg of body weight
- **Conclusions:**
  - Attenuates the parasympathetic influence on the heart rate
  - Low potential to induce cardiac arrhythmia
  - Low potential for significant cardiovascular toxicity

Lefamulin: Promising Novel Pleuromutilin Antibiotic

Veve MP & Wagner JL Pharmacotherapy 2018 Sep;38(9):935-946

- **Pleuromutilin developed in 1950**
- **Time-dependent killing**
- **Microbiological activity**
  - Gram-positive and atypical organisms associated with CABP
    - *S. pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*
    - *Legionella pneumophila*, *Chlamydophila pneumoniae*
  - *Staphylococcus aureus*
    - MRSA, VISA, heterogeneous strains
  - Vancomycin-resistant *E. faecium*
  - Activity against
    - MDR *Neisseria gonorrhoeae*
    - *Mycoplasma genitalium*

Lefamulin
ID Exchange 21 August 2019

- **FDA Approves Lefamulin For CAP**
  - Two studies Vs. moxifloxacin (+/- Linezolid) com
    - Clintrialsgov → trials completed
  - Interference with the bacteria's ability to replicate
  - Available in both injectable (IV) and oral forms
- Reuters (8/19, Joseph, Sarkar)
  - FDA approved Nabriva Therapeutics Plc's Xenleta (lefamulin) "for treating patients with CAP
- MedPage Today (8/19, Walker) also covers the story

Current Drug Metabolism, 2014, *15*, 581-598

A 30-years Review on Pharmacokinetics of Antibiotics: Is the Right Time for Pharmacogenetics?

Lorena Baietto[1*], Silvia Corcione[1*], Giovanni Pacini[2], Giovanni Di Perri[1], Antonio D'Avolio[1#†] and Francesco Giuseppe De Rosa[1†]

- **Pharmacogenetics → Different degree of diffusion**
- **HIV treatment:**
  - Abacavir and screening for HLA-B*5701 before starting treatment is standard of care
  - Efavirenz plasma levels influenced by single nucleotide polymorphism (SNP) CYP2B6-516G>T (rs3745274)
- **Antibiotics:**
  - Drug transporters involved in antibiotic bioavailability, especially for fluoroquinolones, cephalosporins, and antituberculars
- **Few data available for recently developed antibiotics**

Specific Transporters of Aminoglycosides, Tetracyclines, Macrolides, Daptomycin and Type of ADME Processes Involved

Baietto L et al Curr Druf Metabolism 2014

Other antibiotics	Transporter	Coding gene	*In-vitro* model	ADME process involved	Reference
Aminoglycosides					
Tobramycin	P-pg	*ABCB1*	Mice	Oral delivery	Banerjee *et al*. 2000 [25]
Tetracyclines					
Minocycline	P-pg	*ABCB1*	Mice	BBB transport	Milane *et al*. 2007 [32]
Riluzole					
Macrolides					
Azithromycin	P-pg	*ABCB1*	Rats	Biliary and intestinal excretion	Sugie *et al*. 2004 [33]
Azytromycin	OATP1A5	*SLCO1A5*	MDCKII cells and rats	Intestinal absorption	Garver *et al*. 2008 [34]
Claritromycin					
Daptomycin	P-pg	*ABCB1*	MDCKII cells and THP-1 macrophages	Intracellular activity against phagocytized *S. Aureous*	Lemaire *et al*. 2007 [35]
Rifampicin	P-pg	*ABCB1*	Mice	Intracellular accumulation	Schiuetz *et al*. 1996 [36]

ADME, absorption distribution metabolism elimination; P-gp, P-glycoprotein; OAT, organic anion transporter; ABC, ATP binding cassette; SLC, solute carrier; BBB, blood brain barrier.

Tedizolid

Salavert Lletí M et al Rev Esp Quimioter 2021;34 S1:22-25

Table 1 Summary of new evidence for long-term treatments with tedizolid

Author (year, N)	Age (median, in years)	Linezolid (previous use,%)	BJI (%)	Duration of tedizolid therapy (days, interval)	Adverse events (%)	Discontinuation (%)	Cure or improvement (%)
Mensa et al., 2020; N=81	66	44%	47%	28 (14-59)	11%	5%	80%
York et al., 2020; N=60	62	82%	85%	27 (22-32)	GI: 15% fatigue: 12% anaemia: 2%	18%	72%
Benavent et al., 2021; N=51	65	16%	100%	29 (15-44)	5.8% (only GI)	0	83%
Senneville et al., 2020; N=33	73	9%	100% (PJI)	56 (42-84)	60% anaemia: 12% pruritus:12%	12%	82%

BJI: bone and joint infections; GI: gastrointestinal; N: number of patients /cases; PJI: prosthetic joint infections

Long-Term Tedizolid in Ostearticular Infections

Salavert Lletí M et al Rev Esp Quimioter 2021;34 S1:22-25

- **Multicenter retrospective study from Spain**
  - Long-term use effective
  - Better safety profile
  - Less myelotoxicity and lower drug-drug interactions than linezolid
- **Cases (n = 51)**
  - Osteoarthritis 53%
  - Prosthetic joint infection 33%
  - Diabetic foot infections 18%
- **65% of the isolates: Staphylococci**
  - *S. aureus* 48%
- **Reasons for choosing tedizolid**
  - Potential drug-drug interactions 63%
  - Cytopenia 55%
- **Median treatment duration** 29 days
- **Concomitant rifampin** 24%

Benavent E et al. Antibiotics (Basel) 2021; 101(1):5

Time-Kill Evaluation of Antibiotic Combinations Containing Ceftazidime-Avibactam against XDR *P. aeruginosa*

Montero MM et al 2021

1. CZA-susceptible isolates:

- Bactericidal effect in 100% (14/14)

2. CZA-resistant isolates:

Combination therapies

- Greater overall reduction in bacterial load than monotherapy

CZA plus colistin

- Additive or synergistic in 100% (7/7) of the CZA-resistant isolates

CZA plus amikacin and CZA plus aztreonam

- Additive or synergistic in 85%

CZA combined with colistin, amikacin, or aztreonam

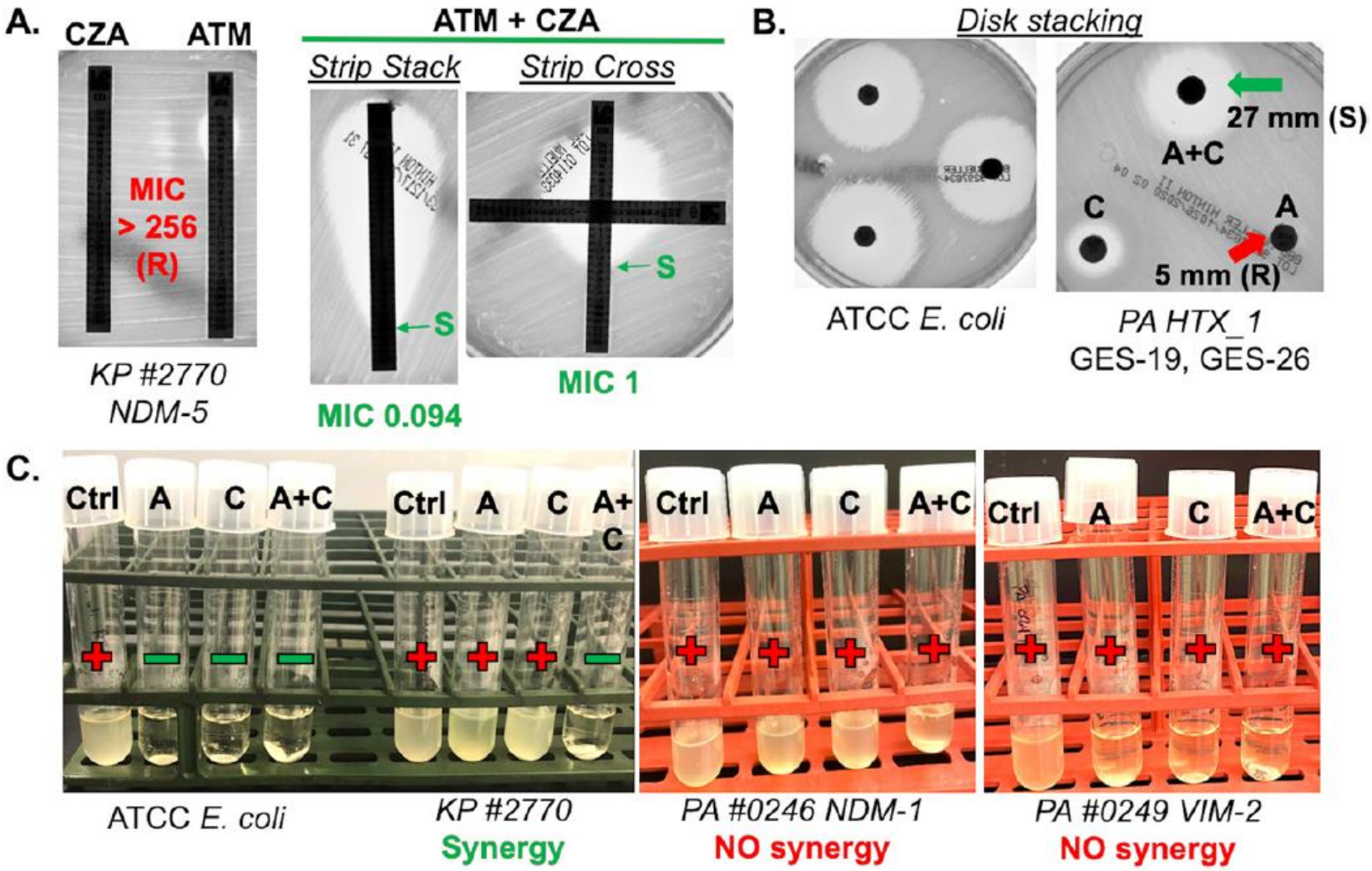
- More effective than monotherapy against XDR *P. aeruginosa* isolates

→ CZA combination useful for XDR *P. aeruginosa* infections

- Including those caused by CZA resistant isolates

Susceptibility Testing Methods for Aztreonam and Ceftazidime-Avibactam Combination Therapy on Extensively Drug-Resistant Gram-Negative Organisms

Khan A et al AAC 2021; 65(11):e00846-21



Alternative Vs. Traditional Approaches to MIC Determination for Carbapenem-Relebactam Combinations

Filimonova AV et al Antibiotics 2021

- **Standard MIC approach**
  - Does not consider the ratio of BL /BLI concentrations in humans
- **Study of carbapenem-to-relebactam concentration ratios (1,5-1) in time-kill assays**
  - (CLSI recommends varying imipenem concentrations at fixed relebactam concentrations)
- **→ Prediction of antibacterial effects**
  - With antibiotic/inhibitor MICs
- **→ Effects of imipenem or doripenem with relebactam**
  - Comparable in time-kill experiments

Conclusions

- PK Opportunities
- Microbiological definition
- Individualization
- Teamwork
- Excellence