Developing new strategies in bacterial infections

Reviving old antibiotics

MG Vossen
Universitätsklinik für Innere Medizin I
Klinische Abteilung für Infektionen und Tropenmedizin
Medizinische Universität Wien / AKH Wien
Währinger Gürtel 18-20
1090 Wien

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Conflict of Interest

No potential or actual conflicts of interest to declare

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Do you agree?

1. There is no need for old antimicrobials. The new drugs are more potent, developed to a larger extent and fill any gaps in the spectrum.

2. Fosfomycin – that's a drug for UTIs!

3. Old antibiotics are well researched, the needed dosage has been evaluated and used for many decades – there is no need to change anything!

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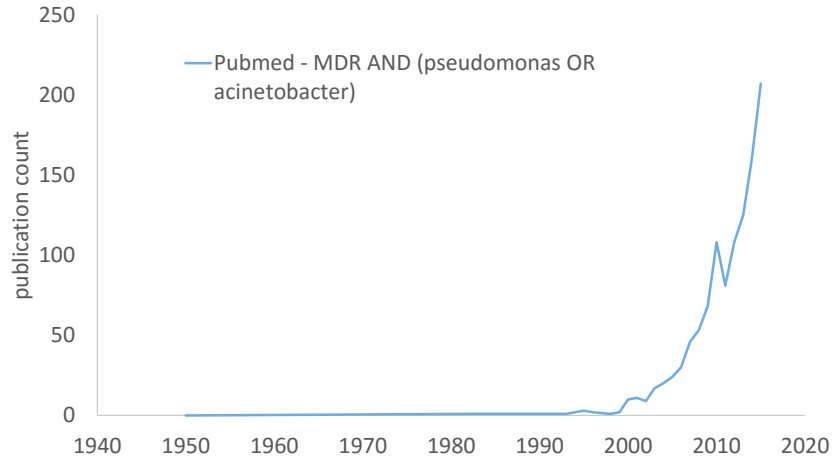
Old?

- Developed 1900 – 1980
- Abandoned after initial use due to disadvantages in
  - Tolerability
  - Efficacy
  - Administration route
- Used for a single indication
- Used in selected countries

Chloramphenicol
Colistin
Fosfomycin
Fusidic acid
Pristinamycin
Mecillinam
Minozyklin
Nitrofurantoin
Nitroxolin
Temocillin

para-Aminosalicylic acid (PAS)
Clofazimine

Why bother?



Medline citation report for keywords "MDR" and "pseudomonas OR acinetobacter", accessed 03/13/2016

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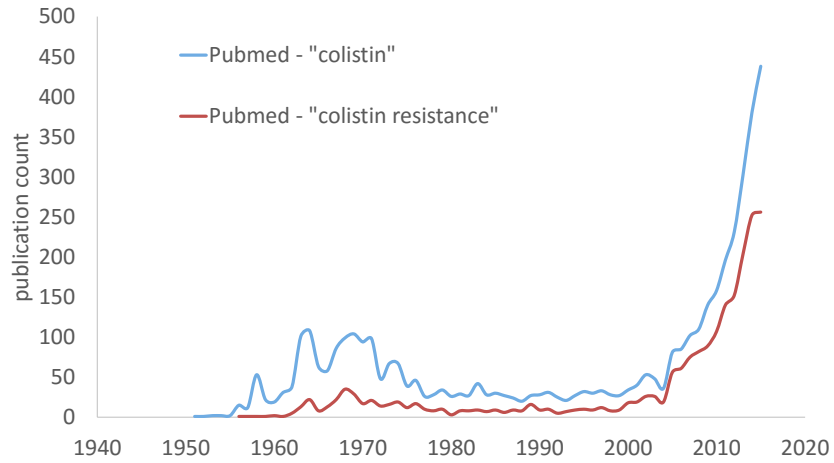
Why bother?



Medline citation report for keywords "colistin" and "colistin resistance", accessed 02/21/2016

Possible benefits

- Old antimicrobials may prove valuable in the treatment of extended and multi drug resistant strains
  - ESBL / MRGN
  - NDM1 and other carbapenemase producing strains
  - MRSA
  - VRE
- The increased use of old antimicrobials might alleviate the burden of resistance selection for new antimicrobials

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Reviving? Why not just use it?

- Old antibiotics have not been developed with modern standards
- Pharmacokinetic / pharmacodynamic data is often missing
  - Insufficient or too high dose / frequency regimen
    - Leading to toxicity, resistance or treatment failure
  - Disposition in extracorporeal organ replacement unknown
- No randomized controlled trials or insufficient quality
  - Efficacy data from old trials may be misleading
  - Potentially unknown adverse drug reactions

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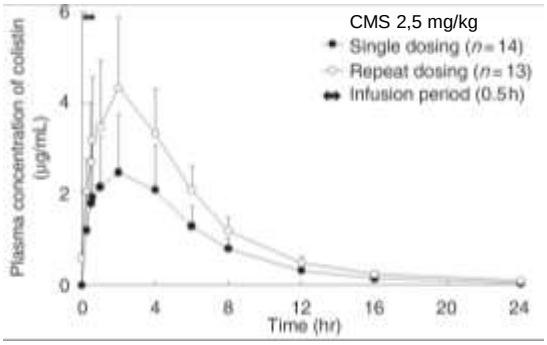
Reviving? Why not just use it?

- Colistin dosing 1969: 2.625 – 4.375 MIU q24
- Colistin dosing 2009: 12 MIU loading dose, 4.5 MIU q12
- Colistin dosing 2016: …?



Parker RH, J Chronic Dis 1969; 21: 719–36.
Mizuyachi K, Current Medical Research and Opinion 2011; 27: 2261–70.

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Challenges

- Companies have no financial interest in old compounds
  - No patent protection
  - Any research will benefit all competitors equally
  - Potential competition for newly developed compounds
- > Research funding by authorities / governments necessary
- AIDA
  - EU (FP7) funded project to provide clinical efficacy data and optimal dosing recommendations for
    - Colistin
    - Fosfomycin
    - Nitrofurantoin
    - Minocyclin
    - Rifampicin

AIDA

Vienna MG

Chloramphenicol

- Isolated from Streptomyces venezuelae 1947
- US production of oral drug stopped 1991
- Binding to bacterial 50S ribosomal subunit
- Bactericidal against *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae.*
- Bacteriostatic against a broad variety of gram positive (incl. MRSA and VRE) and negative bacteria, especially *Yersinia* and *Ricketsia spp*.
- Backup agent for *Bacillus anthraxis, Salmonella typhi and paratyphi*

Eliakim-Raz N, J Antimicrob Chemother 2015; 70: 979–96, Livermore DM, International Journal of Antimicrobial Agents 2011; 37: 415–9; Lautenbach E, Clin Infect Dis 1998; 27: 1259–65.

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Chloramphenicol

- Acquired resistance in many strains, Carbapenemase producing Enterobacteriaceae have been shown to be resistant in > 75%
- Higher mortality in chloramphenicol arms for respiratory tract infections, meningitis and enteric fever
- Favourable (ns) outcome in retrospective analysis compared to rifampicin, penicillin, ampicillin or ciprofloxacin in VRE bacteremia
- RCTs of chloramphenicol against MRSA, VRE and MRGN are needed

Eliakim-Raz N, J Antimicrob Chemother 2015; 70: 979–96, Livermore DM, International Journal of Antimicrobial Agents 2011; 37: 415–9; Lautenbach E, Clin Infect Dis 1998; 27: 1259–65.

Chloramphenicol

- Parenteral, oral and topical formulations available
  - 80% oral bioavailability
  - 3x1g typical regimen
- Penetrates well into tissues including CNS (50% of plasma concentration)
- Bone marrow toxicity
  - Dose dependent suppression of bone marrow after >7 days therapy
  - Non dose depenent, non predictable fatal aplastic anemia (1 in 30.000-40.000) after a latency period of 2-8 weeks
- Neurotoxicity

- Use only as measure of last resort after microbiological testing

Eliakim-Raz N, J Antimicrob Chemother 2015; 70: 979–96, Livermore DM, International Journal of Antimicrobial Agents 2011; 37: 415–9; Lautenbach E, Clin Infect Dis 1998; 27: 1259–65.

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Polymyxins

- Colistin (Polymyxin E) and Polymyxin B
- Initially discovered 1949, market introduction 1959, broad clinical use until late 1970s.
- Cationic polypeptide, destabilizing the Gram negative cell membrane
- Rapidly bactericidal in high concentrations
- Active against almost all Gram negative bacteria
  - *Enterobacteriaceae,* ***Pseudomonas spp, Acinetobacter spp****. Haemophilus influenza, Salmonella, Shigella,* ***Klebsiella****, Legionella, Aeromonas, Citrobacter, Bordetella pertussis, Campylobacter spp.*
- Polymyxin B may be less nephrotoxic compared to Colistin
  - Only limited data available, more polymyxin B trials needed

Kassamali Z, Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2015; 35: 17–21.2. Pike M, Journal of Pharmacy Practice 2014; 27: 554–61.

Colistin

- Administered parenteral as colistimethate sodium (CMS)
  - In-vivo conversion to colistin, unmetabolized CMS excreted renally
  - Colistin halflife time >> CMS
  - High interpatient variability of plasma concentrations
  - Colistin metabolism not fully understood
- For highly resistant germs combination with second active compound advisable
- Target serum concentration: 2 – 2.5 mg/L

Eliakim-Raz N, J Antimicrob Chemother 2015; 70: 979–96, Livermore DM, International Journal of Antimicrobial Agents 2011; 37: 415–9; Lautenbach E, Clin Infect Dis 1998; 27: 1259–65. Pogue JM, Clinical Infectious Diseases 2015; 61: 1778–80.

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Colistin

- Marked nephrotoxicity (up to 44% AKI), especially if combined with multiple possibly nephrotoxic substances
  - Especially diuretics, NSAIDs, contrast agents
  - No added toxicity with aminoglycosides or vancomycin
- Small therapeutic window – increased nephrotoxicity if…
  - dose > 5 mg/kg/d colistin base = 12 mg/kg/d CMS (ideal body weight)
  - serum concentration > 2.5 mg/L
- Protective action of ascorbic acid debated
  - Yes: 2x2-4g ascorbic acid, 43 vs. 27 pat. HR 0.27 (.13–.57) p<.001[Ref1]
    - Small, not randomized, not powered for ascorbic acid
  - No: 2x2g ascorb acid, 13 vs. 15 pat. RR 0,9 (.47–1.72) p=0.956[Ref2]
    - Even smaller, but randomized and powered for ascorbic acid

1. Dalfino L, Clin Infect Dis 2015; 61: 1771–7.
2. Sirijatuphat R, Antimicrobial Agents and Chemotherapy 2015; 59: 3224–32.3.
3. Pike M, Journal of Pharmacy Practice 2014; 27: 554–61.

Colistin

- Current standard dosing regimen for CMS: 3-5 mg/kg q12 plus loading dose between 9-12 MIU
- Garonzik/Nation formula for CBA dose calculation
  - Based on population PK model for CMS and colistin in critically ill pat.
  - MIC, bodyweight and renal function adapted dosing
  - Loading dose: target $C_{ss,avg}$ x 2.0 x body weight (kg)
  - Maintenance dose: target $C_{ss,avg}$ x (1.50 x CrCL + 30)
  - Only suitable for Pat. with a CrCl < 70 ml/min
  - Use ideal body weight in overweight patients
  - Avoid LD larger than 300 mg CBA (=690 mg CMS)
- PK Models predict universal 9 MIU LD plus 4.5 MIU q12 MD
- Cave: High clearance during renal replacement therapy

Eliakim-Raz N, J Antimicrob Chemother 2015; 70: 979–96, Livermore DM, International Journal of Antimicrobial Agents 2011; 37: 415–9; Lautenbach E, Clin Infect Dis 1998; 27: 1259–65, Garonzik SM, Antimicrob Agents Chemother 2011; 55: 3284–94, Mohamed AF, J Antimicrob Chemother 2014; 69: 1350–61.

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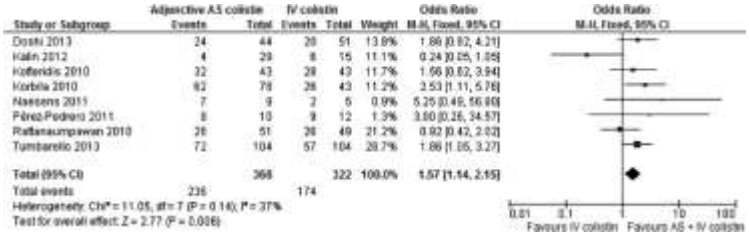
Colistin

- Sputum concentration << serum concentrations
- Inhalative colistin as add-on therapy enhances clinical response and reduces infection associated mortality



- No reduction of overall mortality (OR, 0.74; 95% CI, 0.54–1.01; $p = 0.06$)
- Very low quality of evidence

Valachis A, Crit Care Med 2015; 43: 527–33.

Vinsen MG

Fosfomycin

- Isolated from streptomyces spp in 1968, clinical use since 1971
- Targeting peptidoglycan synthesis
- Very low molecular weight, hydrophilic, no protein binding
- Very good tissue penetration
  - Brain, eye, lung, muscle; abscess fluid, ascites, sputum
  - Accumulation in the bone (high affinity to hydroxylapatite)
  - "add-on" therapy in abscesses, soft tissue and bone infections
- Intravenous formulation is dosed with 4-8g q8

Kaase M, Journal of Clinical Microbiology 2014; 52: 1893–7.2. Raz R, Clinical Microbiology and Infection 2012; 18: 4–7.

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Fosfomycin

- No cross-resistance to other antimicrobials
- Rapidly bactericidal against *Streptococcus spp., S. aureus (incl. MRSA), E.coli, Haemophilus, Neisseria spp.* and *Proteus mirabilis.*
- Higher MICs in *Enterobacter*, *Klebsiella and Serratia spp.*
- *Pseudomonas spp.* often resistant
- Active in otherwise highly resistant strains
  - 78% of 107 carbapenem resistant strains from Germany showed fosfomycin susceptibility
  - 54.2% successful clinical outcome on day 14 in a case series of critically ill patients with Gram negative XDR infections

Kaase M, Journal of Clinical Microbiology 2014; 52: 1893–7.2. Raz R, Clinical Microbiology and Infection 2012; 18: 4–7. Pontikis K, International Journal of Antimicrobial Agents 2014; 43: 52–9.

Fosfomycin

- Oral formulation: Fosfomycin-trometamol
  - Oral bioavailability of Fosfomycin-trometamol 40%
  - Recommended as first-line treatment in UTI by ESCMID and IDSA
  - Clinical success rate at 48 hours, 1-3 doses: 74.8% of 119 retrospectively analysed patients (Ref[1])
  - Success rate day 7-9, 3 doses 3g q24: clinical 94.3%, mibi 78.5% (Ref[2])
  - AIDA project: Nitrofurantoin 100mg q8/5 days vs Fosfomycin 3g single dose in 600 women with uncomplicated UTI – estimated completion date: December 2016
- Monotherapy in-vitro: fast induction of resistance
- Low resistance rates despite increased use
- Should restriction to i.v. use be discussed to "conserve" the substance for use in MDR and XDR bacteria?

1. Sastry S Antimicrobial Agents and Chemotherapy 2015; 59: 7355–61.2.
2. Pullukcu H, Int J Antimicrob Agents 2007; 29: 62–5.
3. Kaase M, Journal of Clinical Microbiology 2014; 52: 1893–7.2.
4. Raz R, Clinical Microbiology and Infection 2012; 18: 4–7.

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Fusidic acid

- Isolated from Fusidium coccineum and first clinical use 1962
- Steroid like antimicrobial, specific inhibitor of elongation factor G
- Potent bacteriostatic against *Staph. aureus*, incl. MRSA (MIC_{90} 0.25 mg/L)
- Moderate bacteriostatic activity against CoNS (MIC_{90} 0.25 mg/L in susceptible strains, 19-21% MIC > 1 mg/L), *Proprionibacterium* and *Neisseria spp.* (MIC_{90} 1 mg/L) and C. difficile (MIC_{90} 2 mg/L)
- Limited bactericidal activity against *S.pyogenes* (MIC_{90} 8 mg/L)
- Synergistic action with colistin against XDR *Acinetobacter baumanii* reported
- Moderate tuberculostatic activity

O'Neill AJ, J Antimicrob Chemother 2002; 50: 839–48.2. Verbist L, Journal of Antimicrobial Chemotherapy 1990; 25: 1–5. Fernandes P, Cold Spring Harbor Perspectives in Medicine 2016; 6 1. Phee LM, Antimicrob Agents Chemother 2015; 59: 4544–50.

Vervoort MG

Fusidic acid

- Increased activity in acidic pH
- High tissue penetration, even as topical ointment (not recommended due to resistance selection)
- Inhibits intracellular growth of staphylococci (long term persisters)
- > 95% protein bound, > 90% oral bioavailability
  - Food intake reduces oral bioavailability by 18%, AUCDose by 16.7%
- Despite prolonged use in Europe <10% *S. aureus* resistant
- High frequency of mutation selection (for *S.aureus* $7.6x10^{-7}$)
  - Combination therapy essential – especially in high inocula
  - Markedly reduced serum levels if co-administered with Rifampicin

Oldach D, 25th European Congress of Clinical Microbiology and Infectious Diseases, Poster 2352. Bulitta JB, Antimicrob Agents Chemother 2013; 57: 498–507. O'Neill AJ, J Antimicrob Chemother 2002; 50: 839–48.2. Verbist L, Journal of Antimicrobial Chemotherapy 1990; 25: 1–5. Fernandes P, Cold Spring Harbor Perspectives in Medicine 2016; 6: a025437.

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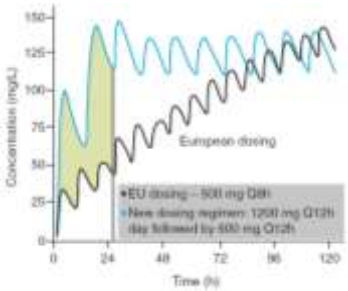
Fusidic acid

Type of therapy and indication	No. of cases treated	cases with FA resistance	Resistance, %	Drugs used in combination with FA
Monotherapy				
Burns	13	6	…	…
Mainly skin/soft tissue infection	721	30	…	…
Surgical infection	102	4	…	…
Chronic osteomyelitis	13	2	…	…
Colonization	6	2	…	…
Total	855	44	5.1	…
Combination therapy				
Acute bone/joint infection	76	0	…	Clox or Ery
Severe staphylococcal sepsis and bacteremia	455	3	…	β-lactam, Ery, Rif, and Nov
MSSA infection	244	1	…	β-lactam
MRSA infection	48	0	…	Rif and Nov
Chronic osteomyelitis	29	1	…	β-lactam
Cystic fibrosis	25	2	…	β-lactam, Chl, Lm, and Nov
hVISA infection	9	0	…	Rif and Chl
Total	886	7	0.8	…

Howden BP, Clin Infect Dis 2006; 42: 394–400.

Fusidic acid

- Auto inhibition of clearance
  - 500 mg q12 results in steady state in 3 weeks
  - 750 mg q12 results in steady state in 8 days
  - Front loading with 1,5g q12 (MD: 600 mg q12) achieves therapeutic levels on day1 delaying emergence of resistant clones



Fernandes P, Cold Spring Harbor Perspectives in Medicine 2016; 6: a025437.

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Fusidic acid

- RCT Fucidic acid (CEM-102) vs. Linezolid in ABSSSI
  - FA: FLD 1500 mg q12, MD 600 mg q12 vs. LIN: 600 mg q12
  - 1 FA isolate rose from 0.12 µg/mL to 8 µg/mL on Day 11 - with reduced fittness

	Treatment group			
	CEM-102 loading dose		Linezolid	
Population	Proportion of patients	Success rate, % (95% CI)	Proportion of patients	Success rate, % (95% CI)
Intent-to-treat	83/89	95 (76.2–92.7)	72/77	96 (87.2–98.6)
Microbiological intent-to-treat	52/59	88 (78.9–95.1)	54/58	93 (83.3–98.1)
Clinically evaluable	60/65	92 (83.0–97.5)	67/68	99 (92.1–100)
Microbiologically evaluable	48/50	96 (86.3–99.5)	48/49	98 (89.2–100)
Staphylococcus aureus (microbiologically evaluable population)	46/48	96 (85.9–99.5)	47/48	98 (88.9–100)
MRSA (microbiologically evaluable population)	30/31	97 (83.3–99.9)	37/37	100 (90.5–100)
Streptococcus pyogenes (microbiologically evaluable population)	1/1	100	2/2	100
Streptococcus agalactiae (microbiologically evaluable population)	1/2	50	0	N/A
Other (haemolytic streptococcus (microbiologically evaluable population)	1/1	100	0	N/A
Early response[a] (intent-to-treat population)	60/63	95 (86.7–99.0)	63/65	97 (89.3–99.6)

Craft JC, Clin Infect Dis 2011; 52: S520–6.

Temocillin

- Developed and marketed in the 1980s, currently only available in Belgium and Great Britian
- Carboxypenicillin (carbenicillin, ticarcillin) – inherits good tolerability profile of the beta-lactames
- Activity against Gram negative organisms
  - Excluding *Pseudomonas spp.* (MIC 128–256 mg/L) and anaerobes
  - MICs against *Enterobacteriacea* range 2-32 mg/L, >90% <16 mg/L
- Remarkable stability against TEM, SHV, CTX-M and AmpC
  - Similar stability as carbapenems
  - Potential carbapenem-sparing agent
- No activity against Gram positive bacteria
- Minimal risk for C.difficile associated diarrhoea

Livermore DM, J Antimicrob Chemother 2009; 63: 243–5. Balakrishnan I, J Antimicrob Chemother 2011; 66: 2628–31.

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Temocillin

- Protein binding 70-85%, resulting in low renal clearance
  - 2g q12 -> 15-30 mg/L trough level
  - 8 mg/L breakpoint in critically ill patients
- 2g q12 regimen superior to 1g q12
  - CCR 91% vs 73% p<0.05 in a retrospective analysis of 92 patients
    - 42 UTI, 42 blood stream infections, 8 HAP by enterobacteriaceae
- 2g q8 has been reported to be safe
  - Time above MIC: 80% of dosing interval for 16 mg/L isolate
  - 6g continuous infusion for higher MICs / critically ill patients
- Post HD dosing in iRRT available (2g postHD, 3g pre weekend)
- Valuable alternative to carbapenems in multi resistant Gram-negative infections

Livermore DM, J Antimicrob Chemother 2009; 63: 243–5. Balakrishnan I, J Antimicrob Chemother 2011; 66: 2628–31.
Vandecasteele SJ, International Journal of Antimicrobial Agents 2015; 46: 660–5, Laterre P-F, J Antimicrob Chemother 2015; 70: 891–8.

Vanessen MG

Nitrofurantoin

- Developed in the 1940s, clinical use since 1953
- Active against *E. faecalis, S. aureus and saprophyticus, E.coli, K. pneumonia* and *Citrobacter spp.*
- First line treatment for UTI in most current guidelines
- Good oral bioavailability around 80%, therapeutic drug levels only in lower urinary tract
- 3x 50-100 mg for 5 to 7 days (3 days high dose is inferior)
- Clinical cure rates between 79% and 92%
  - No difference to (co-)trimethoprim, ciprofloxacin or amoxicillin
  - Microbiological cure rate analysis favors comparators
- Emergence of resistant strains rare

Syed H, BMJ Case Rep 2016; 2016.2. Huttner A, J Antimicrob Chemother 2015; 70: 2456–64.

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Nitrofurantoin

- Many PK/PD details unclear –> AIDA
  - Superiority RCT in UTI: Nitrofurantoin 100 mg q8 vs. Fosfomycin-trometamol 3g single dose
  - PK/PD target identification
- Contraindicated in renal insufficiency, GFR down to 40 ml/min safe?
- Possible development of pulmonary fibrosis in long term use
  - Frequency of all pulmonary reactions: 0.001%
- Side effects in short term use negligible
  - Nausea, headaches, GI symptoms

Syed H, BMJ Case Rep 2016; 2016.2. Huttner A, J Antimicrob Chemother 2015; 70: 2456–64.

Vlassen MG

Nitroxolin

- Available since 1960s
- Broad spectrum bacteriostatic urinary antiseptic for UTI
  - *S. aureus, beta-hemolytic streptococci*
  - *E. coli, K. pneumonia, P. mirabilis, P. vulgaris, M. morganii, and S. saprophyticus, Citrobacter, Enterobacter*
  - *M. hominis, Ureaplasma urealyticum*
  - *Candida albicans, C. tropicalis, C. parapsilosis, C. krusei, C. glabrata*
- No cross resistance
- Only limited gastrointestinal adverse effects
- Reduces adhesin expression and thus bacterial attachment

Naber KG, BMC Infect Dis 2014. Kresken M, Antimicrob Agents Chemother 2014; 58: 7019–20.3. Wagenlehner FME, Antimicrob Agents Chemother 2014; 58: 713–21.

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Nitroxolin

- Therapeutic dose 250 mg q8, prophylactic 250 mg q12-24
- 99% of dose excreted in urine as active metabolites
- Urinary peak of metabolite activity equivalent to nitroxolin concentrations of 216 mg/L after a single dose of 200 mg
- Higher activity in acidic than basic pH
- Non-inferiority vs. norfloxacin and co-trimoxazole in meta-analysis with 466 patients
- No development of resistant strains during 20 years of use in Germany

Naber KG, BMC Infect Dis 2014. Kresken M, Antimicrob Agents Chemother 2014; 58: 7019–20.3. Wagenlehner FME, Antimicrob Agents Chemother 2014; 58: 713–21.

Vervoort MG

Clofazimine

- Synthesized in 1954, market introduction 1969, orphan drug status 1986
- Lipophilic iminophenazine dye
- 1x 100 mg q24 p.o. – expert opinion, no dose finding trials
- Anti(myco)bacterial and immunomodulating effect
- Anti Leprosy drug, also used for treatment of disseminated mycobacterium avium intracellulare infenctions
- Orange-pink skin pigmentation (75%), ichtyosis and pruritus, GI symptoms: nausea and emesis up to fatal enteropathy through crystal deposition in the mucosa

Arbiser JL, Journal of the American Academy of Dermatology 1995; 32: 241–7.

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Clofazimine

- Potentially useful for XDR Tb?
  - Initially developed as Tb drug
  - Inconsistent results in animal trials
  - Retrospective analysis showed no add-on benefit for clofazimin
  - Multicenter RCT, 105 Pt, individual anti Tb therapy, randomized for ± Clofazimin
    - Treatment success in CFZ arm 73.6% vs 53.8% in control arm, p=0.035
    - No difference in treatment discontinuation
    - But: not blinded, small number, no post treatment follow-up
- Promising anti XDR-Tb drug, further RCTs needed

Tang S, Clinical Infectious Diseases 2015; Chang K-C, Antimicrob Agents Chemother 2013; 57: 4097–104.

para-Aminosalicylic acid (PAS)

- Developed 1902, rediscovered 1943, clinical use since 1944
- Decomissioned ca. 1970 after introduction of rifampicin and pyrazinamide
- Gastro resistant (GR-PAS) granule formulation developed 1994
- Nanodelivery formulation developed 2013 (currently *in-vitro*)
- Backup medication for XDR tuberculosis
- Inhibiting mycobacterial dihydrofolate reductase
- Dose dependent intolerance reaction in up to 75% of all patients with PAS
  - Nausea, vomiting diarrhea
- 7% discontinuation with GR-PAS

Donald PR, Diacon AH. The Lancet Infectious Diseases 2015; 15: 1091–9. Pietersen E, The Lancet 2014; 383: 1230–9.3; Shean K, PLoS ONE 2013; 8: e63057; Zheng J, J Biol Chem 2013; 288: 23447–56.

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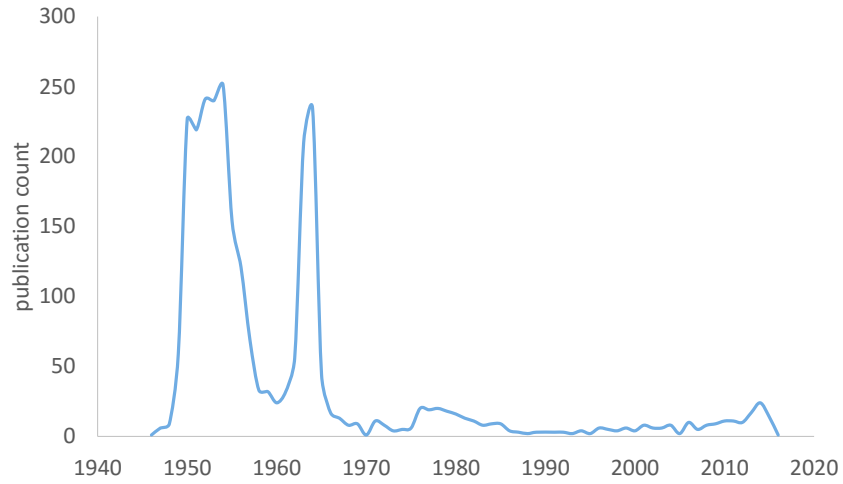
para-Aminosalicylic acid (PAS)



Medline citation report for keywords "para-aminosalicylic acid tuberculosis", accessed 02/21/2016

para-Aminosalicylic acid (PAS)

- Extensive first-pass metabolism – large doses required to saturate acetylation
- q24 regimen enhances exposure compared to q6 regimen
- NAT1*14B polymorphism reduces PAS acetylation capability
- Blocks INH acetylation by consumption of acetyl-CoA
- GR-PAS absorption enhanced by high-fat food
- 1960 dosing recommendation: 20 g PAS q24, current dosing recommendation for GR-PAS: 4g q12 – is this sufficient?
- Fast development of resistance if used extensively (6% PAS resistance in 107 South African XDR Tb Patients (2008-2012)

- Important drug for XDR-Tb, further RCTs needed (dose?)

Donald PR, Diacon AH. The Lancet Infectious Diseases 2015; 15: 1091–9. Pietersen E, The Lancet 2014; 383: 1230–9.3; Shean K, PLoS ONE 2013; 8: e63057.

What about now?

1. There is no need for old antimicrobials. The new drugs are more potent, developed to a larger extent and fill any gaps in the spectrum. Do you agree?

2. Fosfomycin – that‘s a drug for UTIs!

3. Old antibiotics are well researched, the needed dosage has been evaluated and used for many decades – there is no need to change anything!

Thank you!