Treatment of infections in an era of resistance: the return of the old antibiotics… temocillin – nitrofurantoin – minocycline – trimethoprim-sulfamethoxazole

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Certificat interuniversitaire de formation en maladies infectieuses
Liège, 4 juin 2015

The programme

- Temocillin
- Nitrofurantoine
- Minocycline
- Trimethoprim-sulfamétoxazole.

In a nutshell … Temocillin is an old antibiotic on the return

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doi:10.1093/jac/dkn511
Advance Access publication 18 December 2008

JAC

Temocillin revived

David M. Livermore[1]* and Paul M. Tulkens[2]

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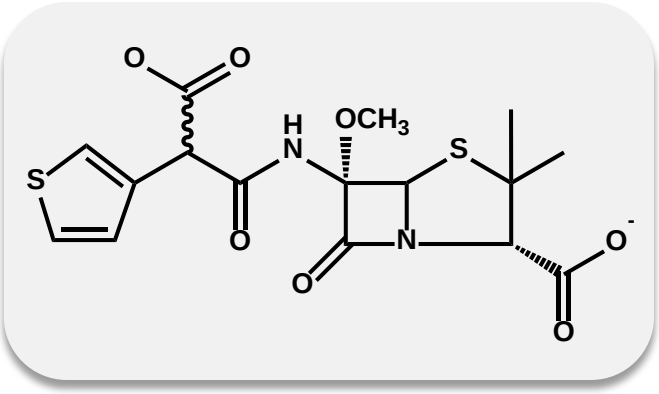
Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6-α-methoxy-ticarcillin) is resistant to most if not all classical and extended-spectrum β-lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion. Pharmacokinetic/pharmacodynamic analysis, aided by Monte-Carlo simulations, suggests a breakpoint of 8 mg/L for the registered maximum dosage of 4 g daily. Temocillin's weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*. In settings where these are unlikely or are covered by other agents, temocillin may be useful, potentially 'sparing' carbapenems and having little apparent potential to select for *Clostridium difficile*.

Keywords: ESBLs, AmpC, α-methoxy penicillins

In a nutshell … Temocillin identity card



- **Name:** temocillin ; 6-α-methoxy-ticarcillin
- **Passport number**: ATC code J01CA17
- **Birthdate:** 1984
- **Birthplace**: Beecham company, London, UK
- **Current address:** Eumedica, Manage, Belgium
- **VISA:** registered in Belgium; Luxembourg, UK

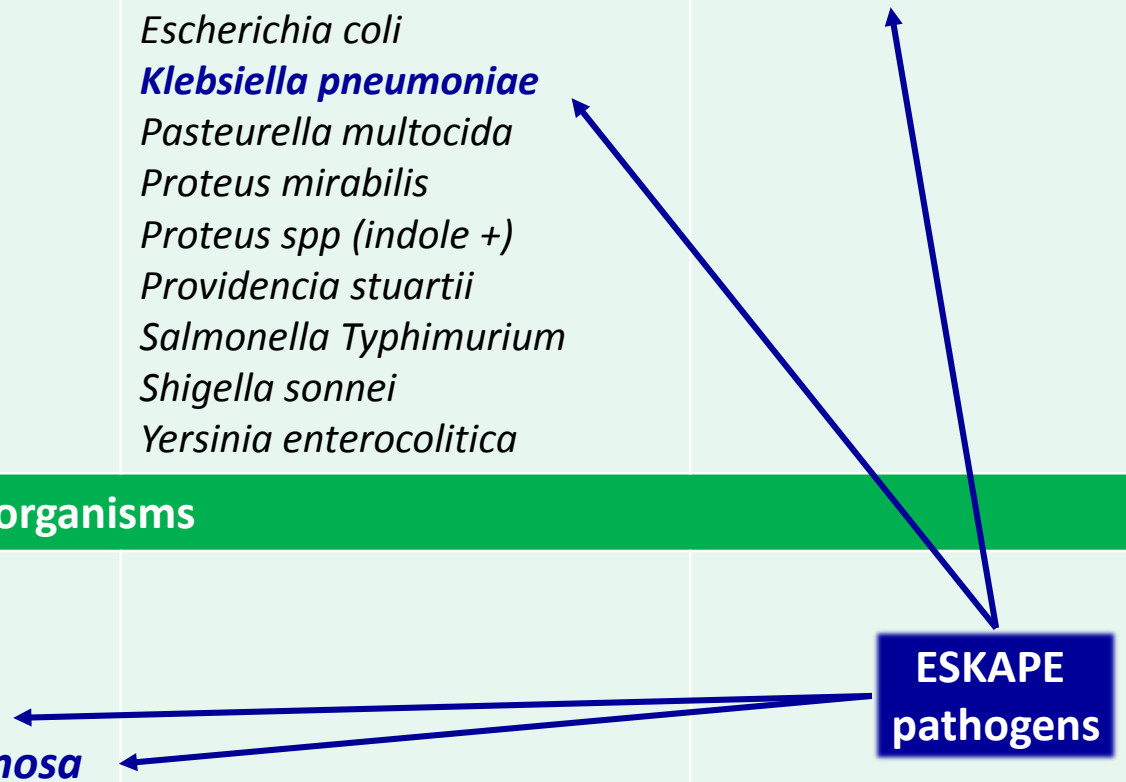
Current position: IV/IM – infections by Gram(-) bacteria

- empirical treatment:
  - ➲ complicated urinary tract infections
- documented treatment:
  - ➲ lower respiratory tract infections
  - ➲ wound infections
  - ➲ bacteraemia
- orphan drug designation:
  - ➲ *Burkholderia cepacia* infection in cystic fibrosis patients

SPC, last revision 2012

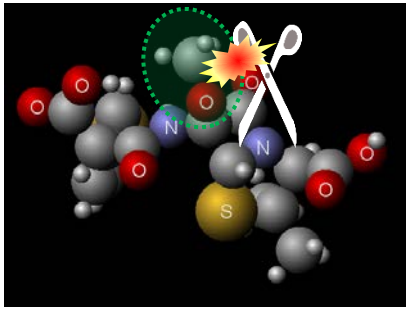
Spectrum of activity

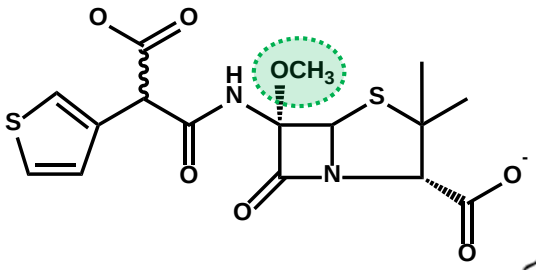
Susceptible organisms		
MIC < 1 mg/L	1 mg/L < MIC < 10 mg/L	10 mg/L < MIC < 100 mg/L
Moraxella catarrhalis *Haemophilus influenzae* *Legionella pneumophila* *Neisseria gonorrhoeae* *Neisseria meningitidis*	*Brucella abortus* *Citrobacter spp.* *Escherichia coli* ***Klebsiella pneumoniae*** *Pasteurella multocida* *Proteus mirabilis* *Proteus spp (indole +)* *Providencia stuartii* *Salmonella Typhimurium* *Shigella sonnei* *Yersinia enterocolitica*	*Serratia marcescens* ***Enterobacter spp***
Intrinsically resistant organisms		
anaerobes Gram(+) bacteria ***Acinetobacter spp*** ***Pseudomonas aeruginosa***		



SPC, last revision 2012; Van Landuyt et al, AAC 1982; 22:535-40

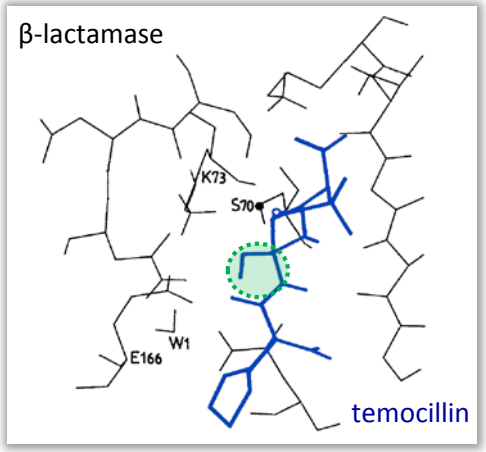
What about ESBL/carbapenemase producers ?





hydrolysis

- ☒ NDM
- ☒ VIM
- ☒ IMP
- ☒ OXA-48



NO hydrolysis

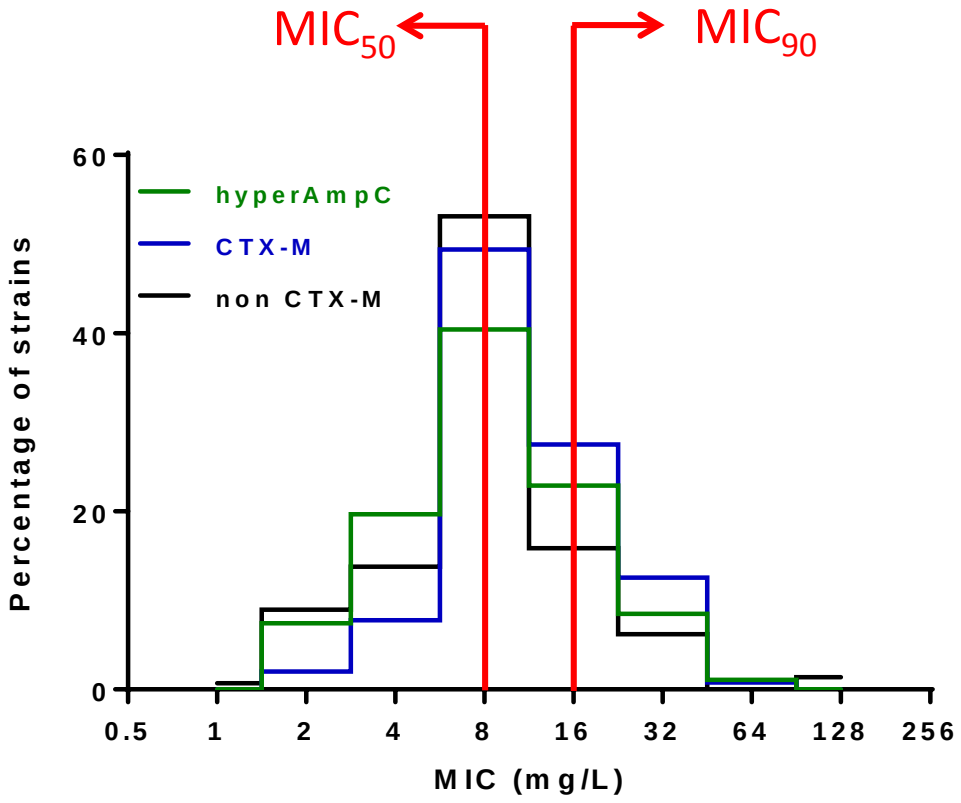
- ☑ TEM
- ☑ SHV
- ☑ CTX-M
- ☑ KPC
- ☑ most OXA

Know your local epidemiology !

Matagne et al, Biochem J 1993; 293:607-11; Livermore et al, Int J Antimicrob Agents. 2011; 37:415-9

What about ESBL/carbapenemases producers ?

Temocillin MIC distribution for ESBL and AmpC overproducers
(*E. coli, Klebiella spp, Enterobacter spp, Citrobacter spp, Serratia spp*)



Adapted from Livermore et al, JAC 2006; 57:1012-4

PK and dosage

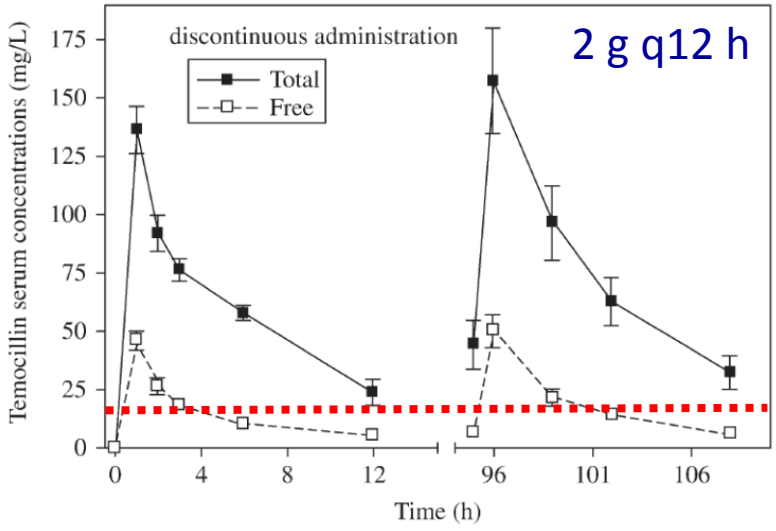
Creat. Clearance	dose	Cmax (1 g)	$T_{1/2}$	Estimated Cmin (1 g)
Normal	1-2 g q12h	173 mg/L	**4.2 h**	~ 22 mg/L
> 60 ml/min	1-2 g q12h			
30-60 ml/min	1 g q12h	120 mg/L	20 h	~ 80 mg/L
10-30 ml/min	1 g q24h	118 mg/L	17 h	
< 10 ml/min	0.5-1 g q24-48h		28 h	
hemodialysis	1 g after dialysis 0.5 g if 24 h			

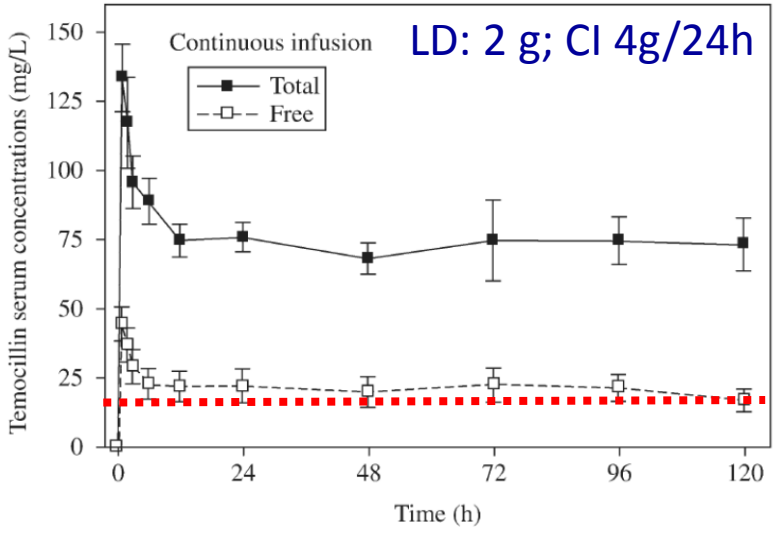
Protein binding ~ 85 %

SPC, last revision 2012

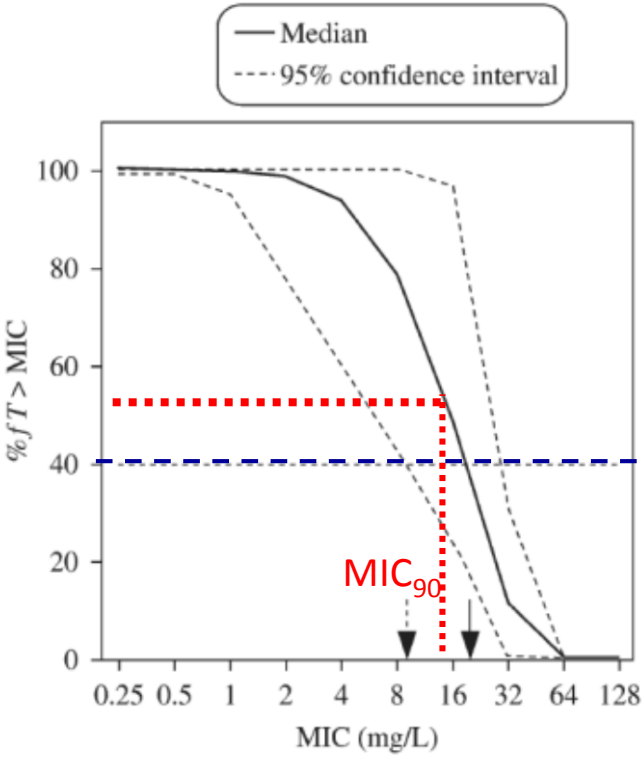
Dosage: PK/PD to the rescue

ICU patients





Monte Carlo simulation



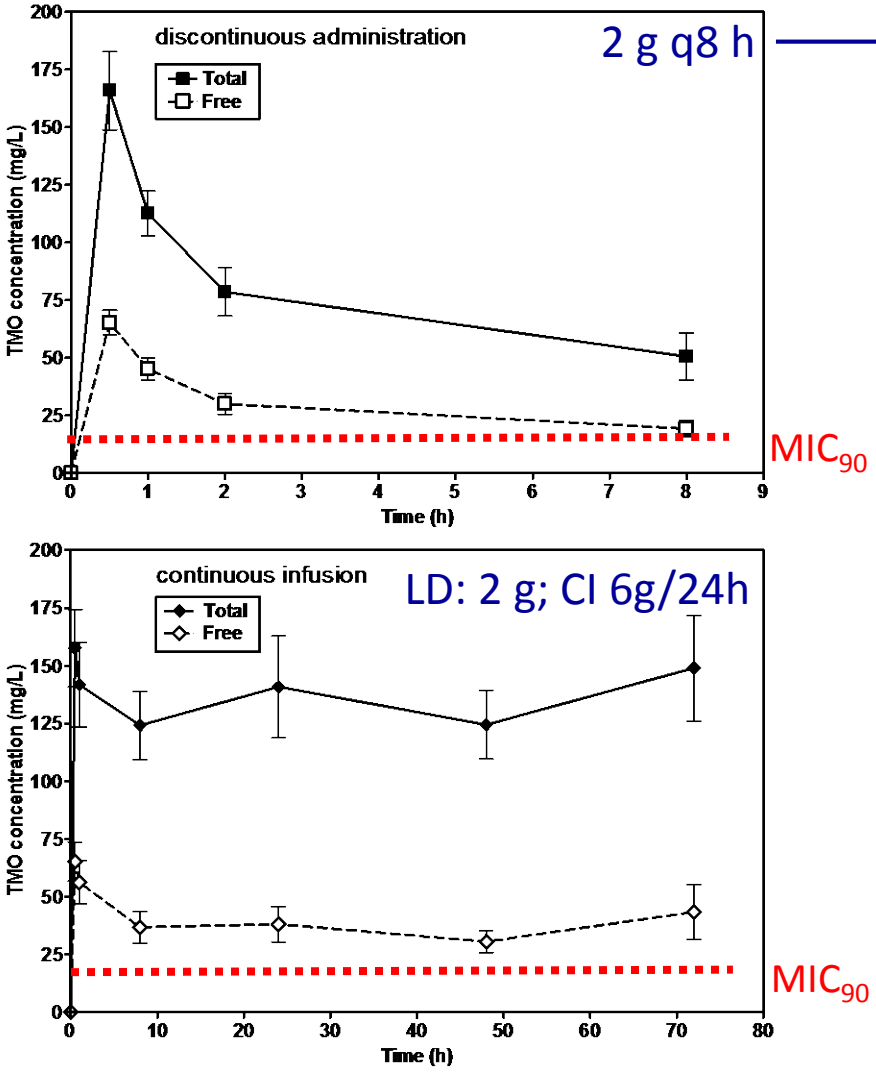
PK/PD Bkpt 8-16 mg/L

BSAC Bkpt: ≤ 8 mg/L (systemic)
≤ 32 mg/L (urinary)

De Jongh et al, JAC 2008; 61:382-8

Dosage: PK/PD to the rescue

ICU patients



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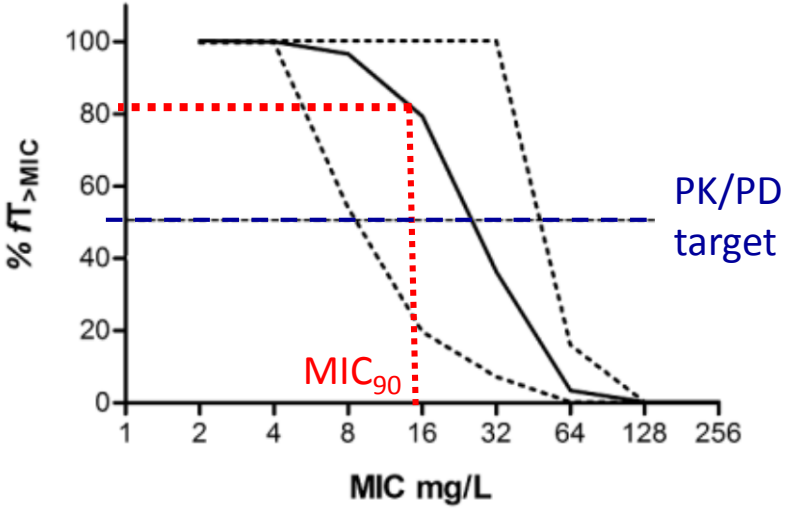

PK/PD Bkpt 8-32 mg/L

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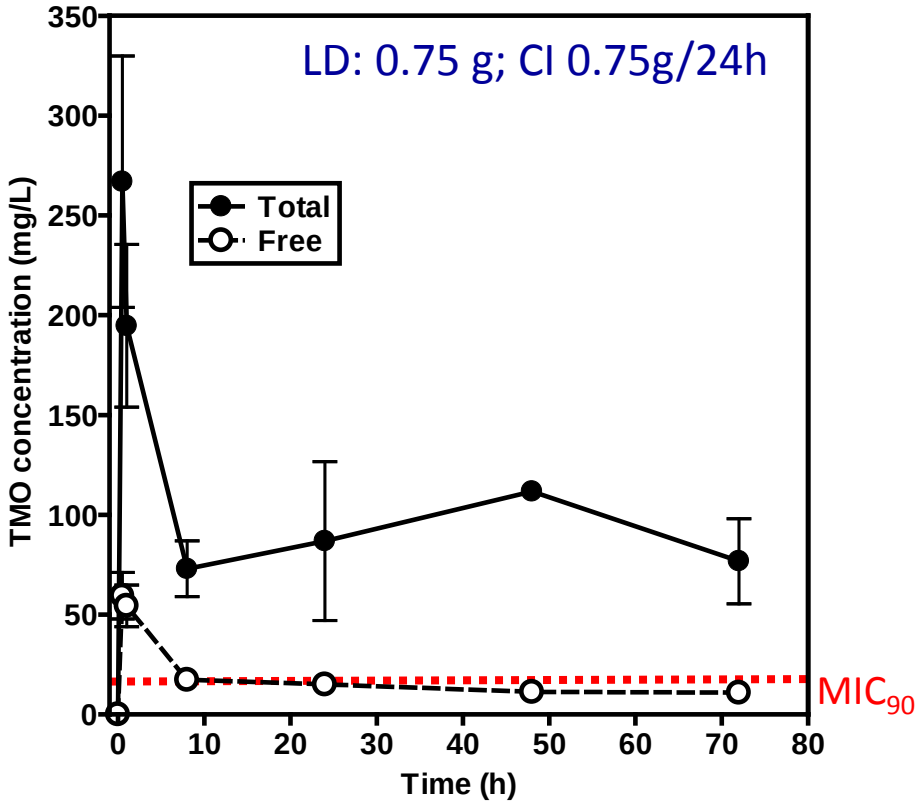
≤ 32 mg/L (urinary)

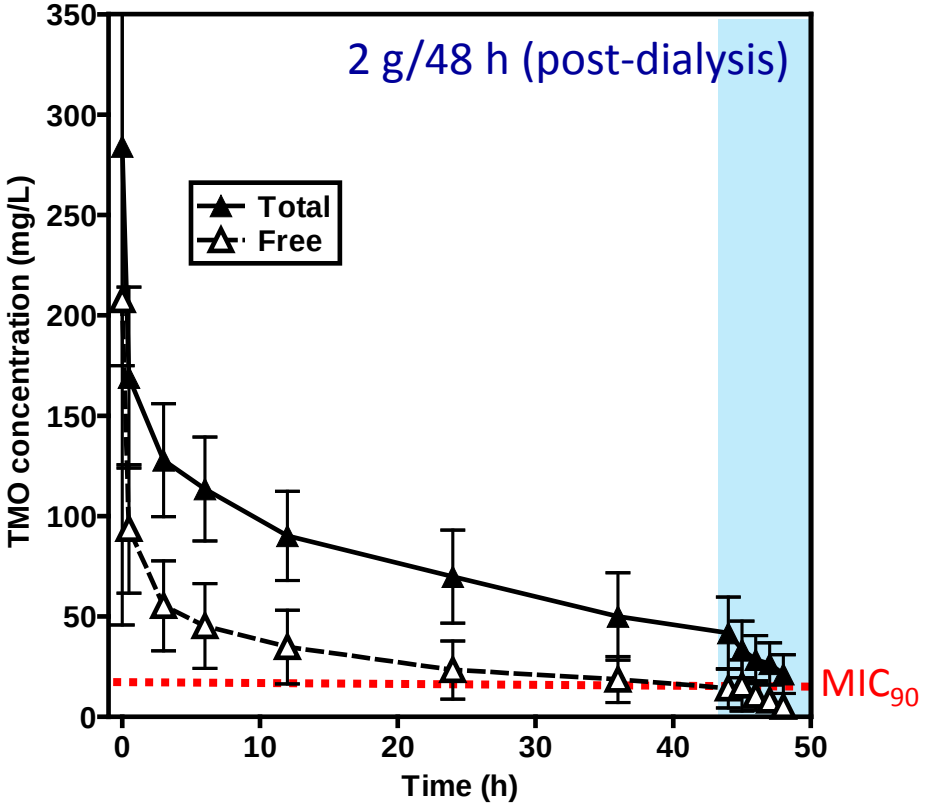
Laterre et al, JAC (2015) 70:891–898

Dosage: PK/PD to the rescue

continuous veno-venous hemofiltration



hemodialysis



Laterre et al, JAC (2015) 70:891–898; Miranda Bastos et al, ESCMID old antibiotics 2014; P26

Rapid screening test for carbapenemase

Carbapenemase distribution according to different inhibition diameters cut-offs and their performance for the detection of CPE among isolates referred to the NRLs in France and in Belgium in 2012 ($n=1354$)

			Number of isolates per carbapenemase enzyme					Performance of the detection of CPE			
	Zone diameter cut-offs (mm)	Total, 1354	OXA-48, 323	KPC, 60	VIM, 32	NDM, 20	negative, 919	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
Susceptibility breakpoints[a]	MEM <23	452	125	59	23	19	226	**52.0**	75.4	49.9	76.8
	TZP <21	1083	322	60	32	20	649	99.8	29.4	40.0	99.6
	TMO <19	952	323	54	32	18	525	98.2	42.9	44.8	98.0
Modified cut-offs	MEM <29	929	322	60	32	20	495	**99.8**	46.1	46.6	99.8
	TZP <16	790	319	59	30	19	363	**98.2**	60.5	54.0	98.6
	TMO <12	457	317	8	28	12	92	83.9	**90.0**	79.9	92.2
Combination of cut-offs	TZP <16 and TMO <12	426	315	8	26	12	65	83.0	92.9[b]	**84.7**	
	TZP ≥16 and TMO ≥12	533	2	1		1	**529**				**99.2**

MEM, meropenem 10 μg disc; TZP, piperacillin/tazobactam 100/10 μg disc; TMO, temocillin 30 μg disc; PPV, positive predictive value; NPV, negative predictive value. The results shown in bold are discussed further in the text.
[a]According to 2013 CLSI guidelines (for meropenem and piperacillin/tazobactam) and to Fuchs *et al.*[11] (for temocillin).
[b]The specificity of combined cut-offs was calculated for carbapenemase-negative isolates when at least one of the two criteria was not fulfilled.

Huang et al, JAC 2014; 69:445-50

What does temocillin bring in our arsenal ?

(1) Targeted spectrum ⇨ sparing of broad spectrum drugs

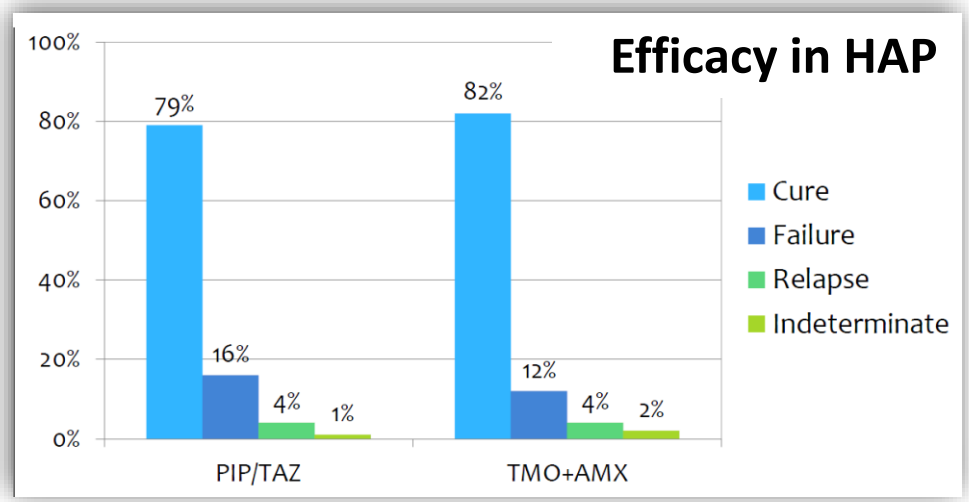
Comparative activity of the tested antibiotics against ESBL-positive and ESBL-negative *Enterobacteriaceae* isolates

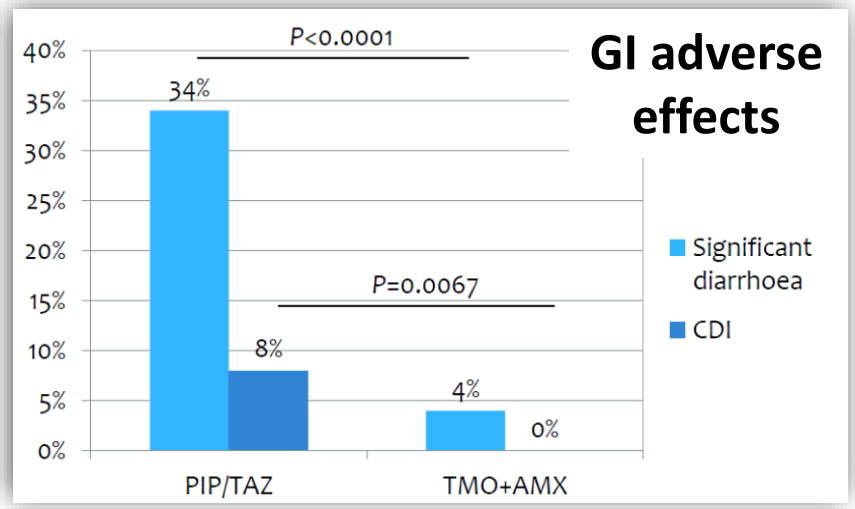
	Number of resistant isolates (%)					
No. isolates	Piperacillin-tazobactam	Ceftazidime	Meropenem	Temocillin	Amikacin	Ciprofloxacin
ESBL producing isolates (77)	34 (44.2%)	67 (87.0%)	1 (1.3%)	26 (33.8%)	14 (18.2%)	54 (70.1%)
ESBL non-producing isolates (575)	Not tested	62 (10.8%)	1 (0.2%)	27 (4.7%)	17 (3.0%)	77 (13.4%)
Fisher exact test	–	$P<0.00001$	$P=0.22$	$P<0.00001$	$P<0.00001$	$P<0.00001$

Glupczynski et al, Eur J Clin Microbiol Infect Dis 2007; 26:777–83

What does temocillin bring in our arsenal ?

(1) Targeted spectrum ⇨ sparing of broad spectrum drugs

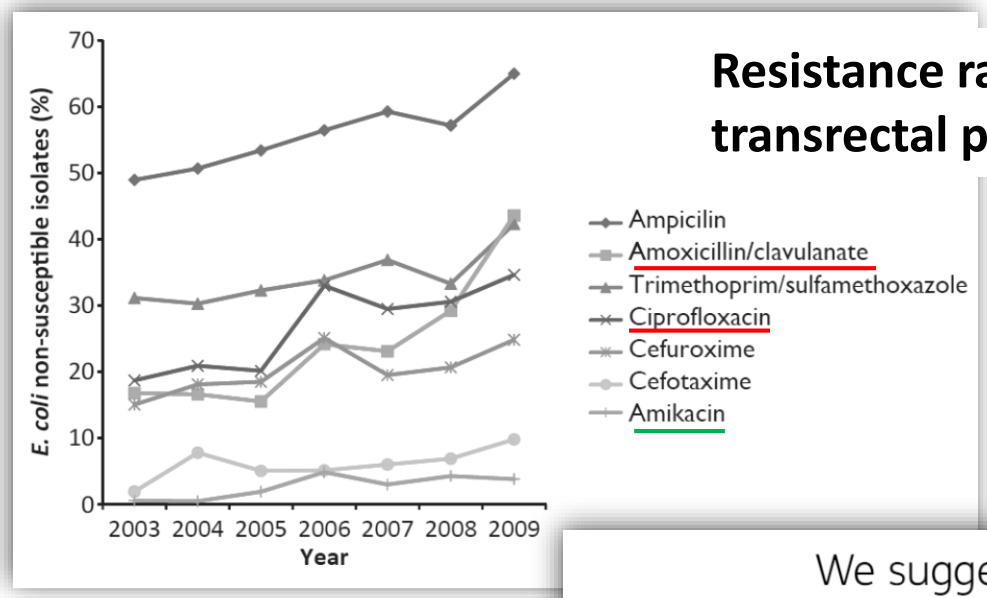




Habayeb, FIS 2013 and ECCMID 2013; O273

What does temocillin bring in our arsenal ?

(2) Targeted spectrum ⇨ sparing of broad spectrum drugs lack of cross resistance



Resistance rates in *E. coli* from transrectal prostate biopsy

Clinical interest

We suggest that the targeted spectrum of temocillin makes it a more appropriate option for transrectal ultrasound-guided needle biopsy prophylaxis than amikacin. We therefore preferentially supplement ciprofloxacin with temocillin using amikacin only in patients who give a history of penicillin allergy.

Steensels et al, CMI 2012; 18: 575–81

Balakrishnan & Smith; JAC 2013;68:2418-9

What does temocillin bring in our arsenal ?

(2) Targeted spectrum ⇨ sparing of broad spectrum drugs lack of cross resistance

Therapeutic results of the study at the Centre of Dermatology and Venereal Diseases of the University of Frankfurt

Dose	No. of patients		Success	Failure
	male	female		
0.5g (Group I)	11	2	11	2
1.0g (Group II)	54	8	57	5
Total (%)	65	10	68 (91)	7 (9)

Clinical efficacy against *N. gonorrheae*

Reimer et al, Drugs 1985; 29S5:210-2

Susceptibility of recent isolates (n=76)

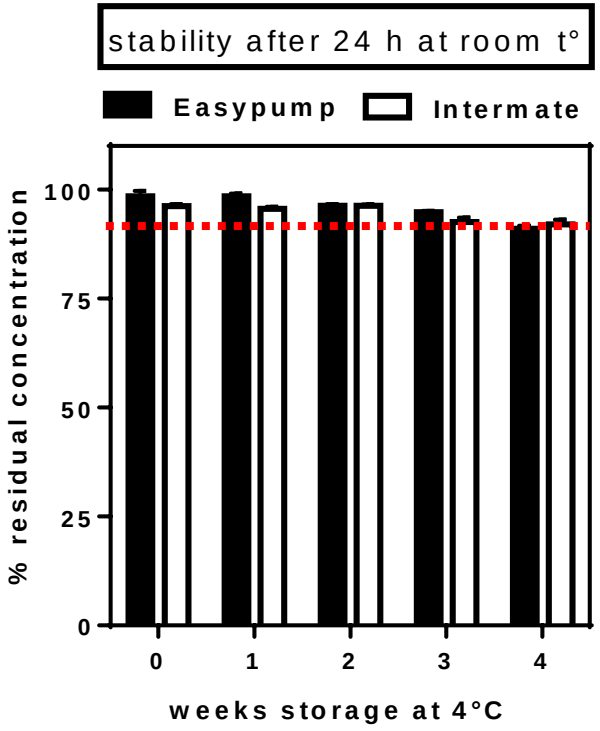
- CIP R : 49 %
- Pen I+R : 71 %
- CRO R: 0 %

median TEM MIC: 0.75 mg/L
(10-90%: 0.125-3 mg/L)

Ghathian et al, ECCMID 2013; O314

What does temocillin bring in our arsenal ?

(3) Chemical stability ⇨ Outpatient Parenteral Antibiotic Therapy



***B. cepacia* infections in CF patients**

Resistant urinary tract infections

Dube & Iqbal, FIS 2013

adapted from *Carryn et al, JAC 2010; 65:2045-6*

What does temocillin bring in our arsenal ?

(4) Salvage therapy for MDR *Burkholderia spp*

Successful Use of Temocillin as Salvage Therapy for Cervical Osteomyelitis Secondary to Multidrug-Resistant *Burkholderia cepacia*

Marcela Rodriguez,[1] Miranda Nelson,[2] James E. Kelly,[3] Alexis Elward,[2] and Sharon Celeste Morley[2]
[1]Department of Pediatrics, Southern Illinois University School of Medicine, Springfield; and Departments of [2]Pediatrics, and [3]Radiology, Washington University School of Medicine, St Louis, Missouri

Journal of the Pediatric Infectious Diseases Society pp. 1–4, 2013. DOI:10.1093/jpids/pis110

Journal of Cystic Fibrosis 5 (2006) 121 – 124
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Temocillin in the treatment of *Burkholderia cepacia* infection in cystic fibrosis

Anastasios Lekkas, Khin M. Gyi, Margaret E. Hodson *

Monday , 06 October 2008

ERS SOCIETY every breath counts

London 3 Session 298 14:45-16:45
ECS E-Communication Session : Cystic fibrosis: new mechanisms, monitoring and treatment tools

A UK experience of temocillin in the treatment of adult cystic fibrosis patients

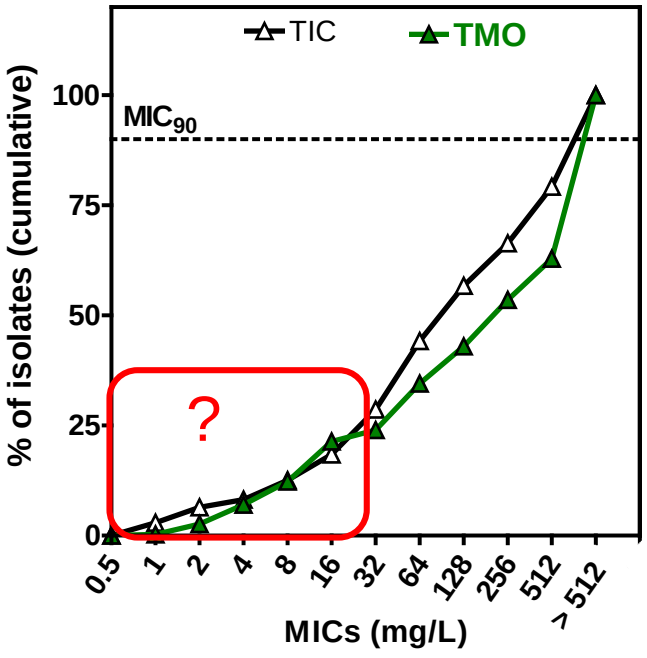
K. Nimako, K. McNulty, J. Hull, T. Ho (Camberley, United Kingdom)

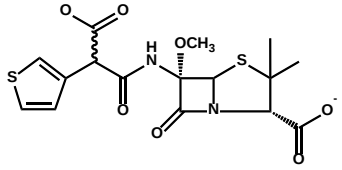
Conclusions

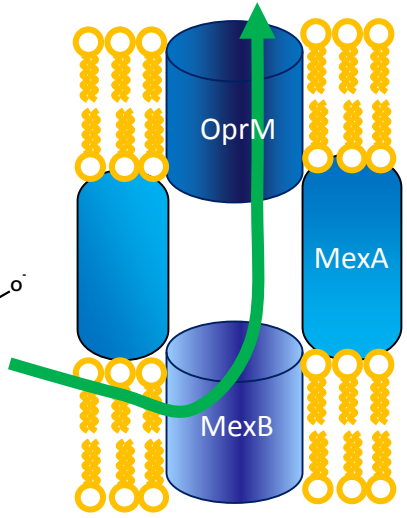
Our findings suggest that temocillin administration is well tolerated in CF and in this cohort was associated with a significant improvement in BMI and WCC. This improvement was seen in patients with *P. aeruginosa* infection as well as those with proven *B. cepacia*. Further studies are needed to further evaluate the role of temocillin in CF.

What about *Pseudomonas aeruginosa* ?

Temocillin vs ticarcillin MIC distribution for *P. aeruginosa* collected from CF patients (n= 335)





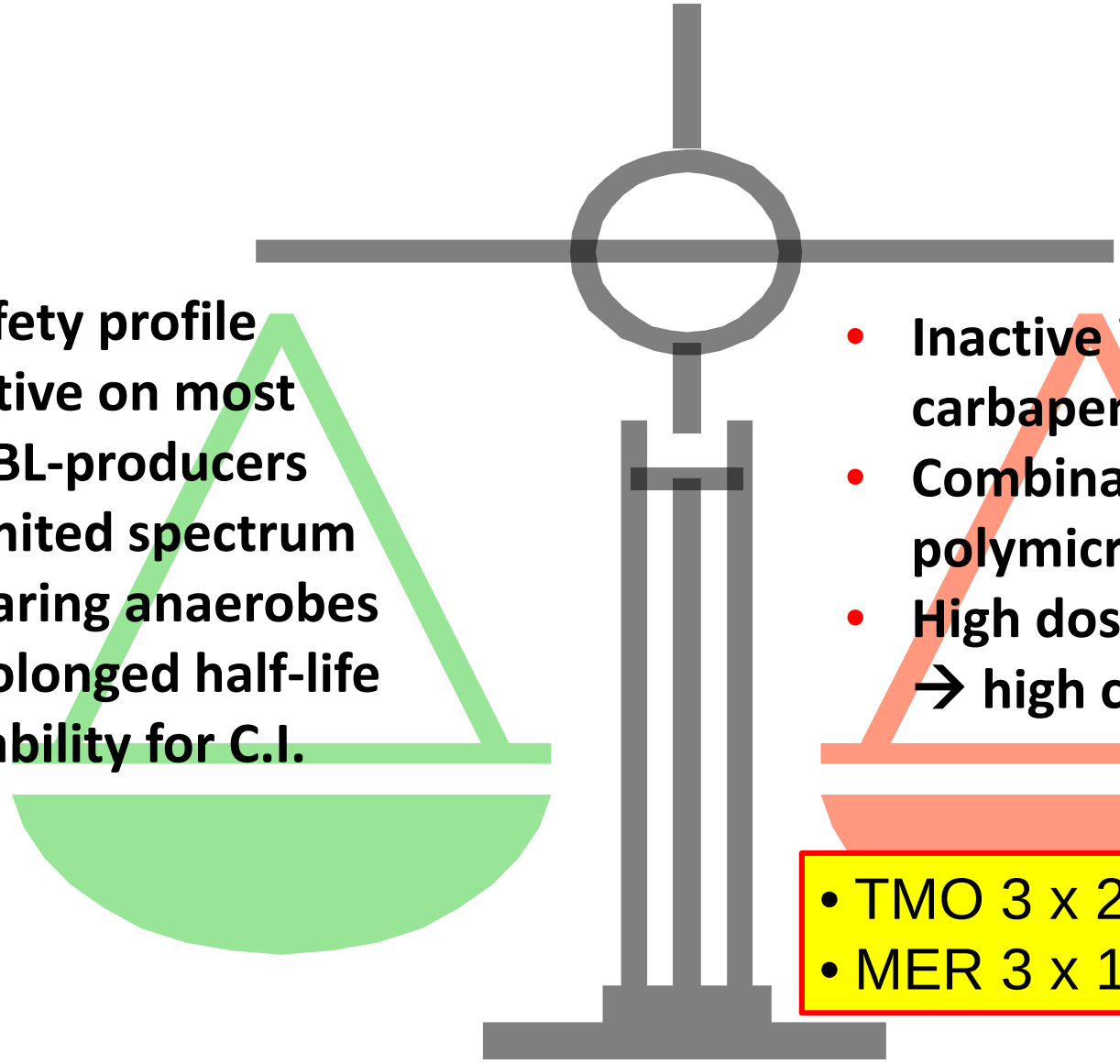


Strain/genotype	MIC (mg/L)
PAO1	256
PAO1 ΔmexAB-oprM	4
CF strain; deletion in *mexB*	1
CF strain; deletion in *mexA*	2
CF strain; mutation in *mexA*	32

efflux non functional !

Buyck et al, JAC 2012; 67:771-5; Chalhoub et al, ESCMID old antibiotics 2014, P02

Temocillin PROS and CONS

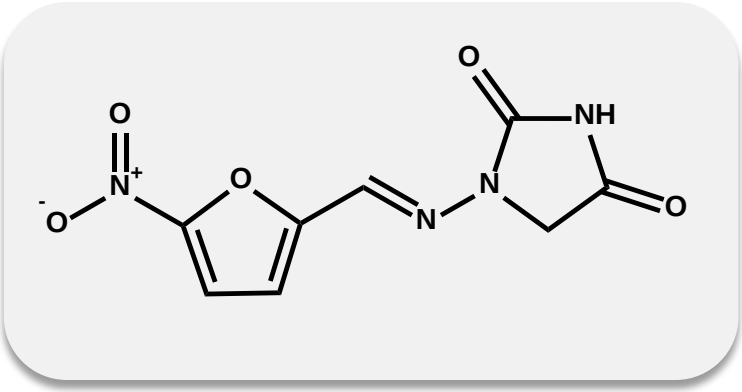


- Safety profile
- Active on most ESBL-producers
- Limited spectrum
- sparing anaerobes
- Prolonged half-life
- Stability for C.I.

- Inactive if carbapenemase/OXA-48
- Combination needed if polymicrobial infection
- High doses required → high cost…

- TMO 3 x 2 g = 108 €
- MER 3 x 1 g = 41-47 €

Nitrofurantoin (class of nitrofuranes)



- **IUPAC:** 1-[(E)-(5-nitrofuran-2-yl)methylideneamino]imidazolidine-2,4-dione
- **Passport number**: ATC code JO1XEO1
- **WHO Status:** essential medicine
- **Birthdate:** 1953
- **Current address:** Pharma Logistics, Beersel (reseller for Mercury Pharmaceuticals Ltd)

Current position: oral treatment of urinary tract infections

- empirical treatment:

  - Traitement des infections urinaires basses aiguës et prévention des infections urinaires basses
  - chroniques récidivantes. Prophylaxie des interventions transurétrales (cathétérisation, cystoscopie,
  - sonde permanente) ou après intervention chirurgicale des voies urinaires.complicated urinary tract infections

SPC, last revision 2012

Nitrofurans: mode of action and specificity *vs* nitromidazoles

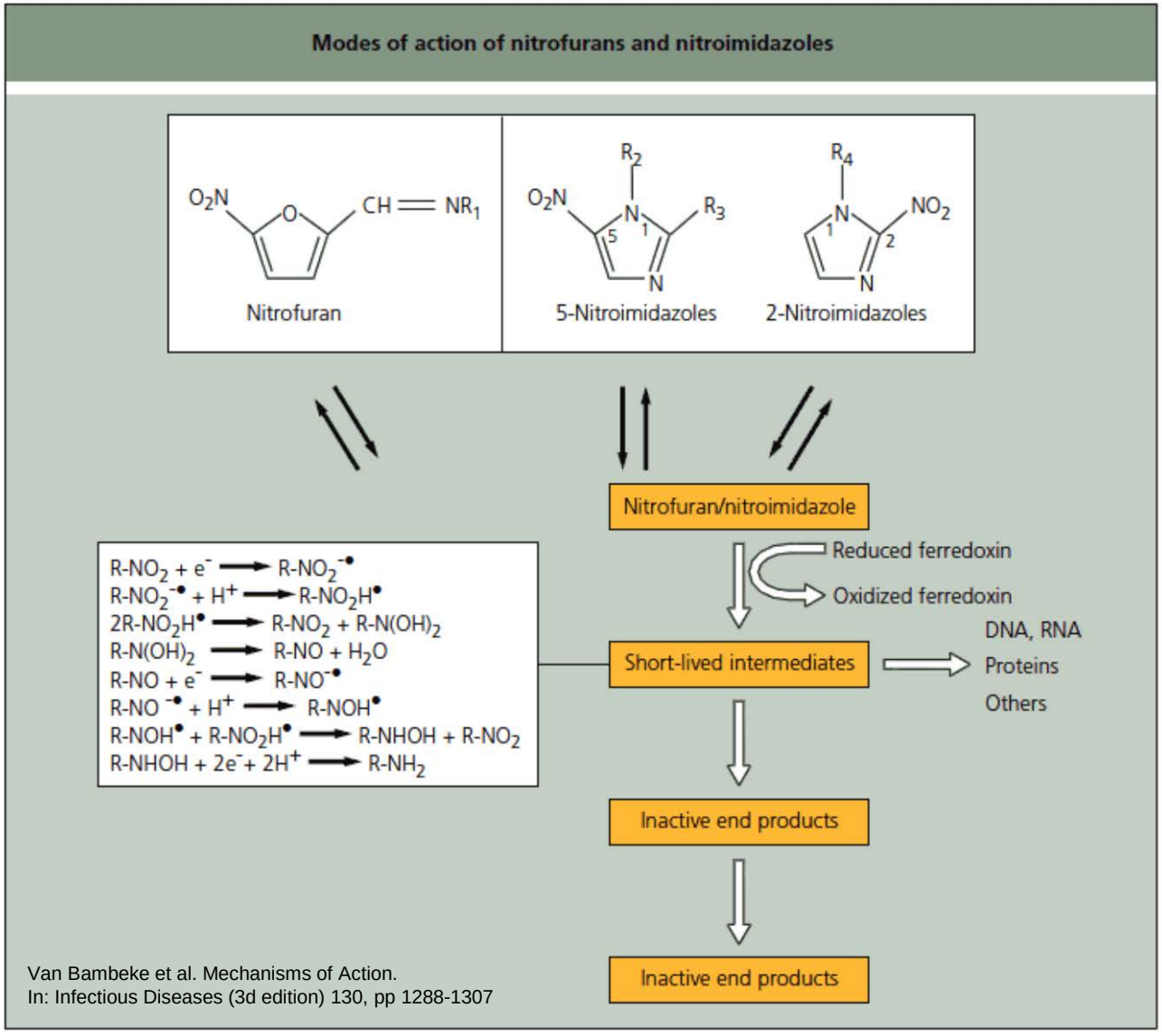


Fig. 130.18 Structures and modes of action of nitrofurans and nitroimidazoles. The molecules must be reduced to form highly reactive products that interact with intracellular targets.

- nitroimidazoles must be fully reduced to generate the highly reactive species (hydroxylamines) that cause damage, and **exert activity only against truly anaerobic and microaerophilic bacteria.**
- singly reduced nitrofurans may directly inhibit the activity of enzymes involved in the degradation of glucose and pyruvate and covalently bind to proteins and DNA by an alkylation reaction, **and are equally active against anaerobic and aerobic bacteria.**

Nitrofurans: spectre d'activité

- Germes usuellement sensibles:
  - *Escherichia coli*, *Enterococci* (ex. *Streptococcus faecalis*), *Citrobacter*, *Klebsiella*, *Enterobacter*,
  - *Staphylococci, Enterococci* (ex. *Streptococcus faecalis*)

- Germes usuellement résistants
  - *Proteus*, *Serratia*, *Pseudomonas*
  - Certaines souches d'Enterobacter et de Klebsiella

Nitrofuratoin: MICs (EUCAST)

Antimicrobial wild type distributions of microorganisms

Antimicrobial: **Nitrofurantoin** (Method: **MIC**)

	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Acinetobacter spp	0	0	0	0	0	0	1	1	4	2	34	0	ND
Enterobacter spp	0	0	1	3	5	6	6	10	7	2	2	0	ND
Enterococcus faecalis	0	0	1	1	31	535	163	7	7	1	0	0	32.0
Enterococcus faecium	0	0	0	0	1	15	40	331	754	781	263	0	256.0
Escherichia coli	0	0	1	15	155	1304	2022	323	96	17	5	0	64.0
Proteus mirabilis	0	0	0	0	0	0	0	0	5	7	13	0	ND
Proteus spp	0	0	0	0	0	0	0	3	10	9	28	0	ND
Staphylococcus aureus	0	0	2	9	35	742	794	34	0	0	0	0	32.0
Staphylococcus coagulase negative	0	0	0	0	0	10	4	1	0	0	0	0	ND
Staphylococcus epidermidis	0	0	0	0	0	1	127	3	0	0	0	0	ND
Staphylococcus saprophyticus	0	0	0	0	3	40	28	0	0	0	0	0	32.0
Streptococcus agalactiae	0	0	0	3	31	10	2	0	0	0	0	0	16.0

Ac-

EUCAST breakpoint

Pharmacocinétique / pharmacodynamie

- Absorption: 40% to 50% (improved if taken with food) the microcrystalline form is more rapidly and completely absorbed but is associated with more gastrointestinal side effects.
- Very low serum concentrations (often undetectable)
- Very high urine concentrations (50-250 mg/L)
- No or insufficient concentrations in renal and uretheral tissues (e.g., prostate)

Conklin JD. Antibiot Chemother (1971). 1978;25:233-52. Review. PubMed PMID: 352255.

→ **Concentration thérapeutique uniquement dans l'urine** !
Essentiellement bactériostatique

Nitrofurantoine: interactions

Interactions souhaitées:

- aliments ou les produits ralentissant la vidange gastrique:

  ↗ **biodisponibilité**
- Urines acides: ↗ **augmentent l'activité**

Interactions indésirables:

- Antacides: ↘ **absorption**
- probénécide et sulfinpyrazone:

  ↘ excrétion tubulaire et ↗ des taux sériques

  → ↗ **de toxicité** et ↘ **d'efficacité**
- Fluroquinolones: **antagonisme** microbiologique (ne pas associer)

Nitrofurantoine: effets secondaires

- troubles digestifs défavorables à une bonne compliance

- réactions allergiques, généralement de type cutanées

- infiltrations pulmonaires diffuses réversibles
  → **Interrompre le traitement car risque vital !**

- anémie hémolytique réversible
  chez les sujets déficients en glucose-6-P-déshydrogénase

- polynévrite lors de traitements prolongés, surtout chez les insuffisants rénaux (peut devenir irréversible).
  → **interrompre le traitement**

Nitrofuranes: contre-indications

- **Anurie, oligurie ou insuffisance rénale**
  (clairance de la créatinine < 60 ml/min)
  → augmentation du risque de toxicité et moins efficace suite à la diminution de l'excrétion du médicament.

- **Trois premiers mois de la grossesse**
  → passage de la barrière foeto-placentaire

- **Deux dernières semaines de la grossesse et allaitement**
  → métabolisme immature du nouveau-né.

- **Enfants de moins de 6 ans**

- **Déficience en G6PD**

- **Polynévrite**

Nitrofurantoin: clinical data

1. **Old data**
   - clinical cure rate: 88% to 92%
   - microbiologic cure rate of 81% to 92%.1
   - 4 randomized trials: equivalence to 3-day course of trimethoprim-sulfamethoxazole or ciprofloxacin
   - equivalent to one dose of fosfomycin.

CAUTION:

- persistence of the pathogen in the periurethral, vaginal, and rectal areas unless ≥7 days treatment (maybe 5 days ?)
- infections due to Proteus and Pseudomonas spp. do not respond.

Gupta et al. Clin Infect Dis. 52:e103-e120 2011 PMID 21292654

Nitrofurantoin: clinical data

More recent data (27 “clinical trials” publications since 2010)

The main message is that it works !

- High susceptibility in Germany and in France

  Schmiemann et al. J. Resistance profiles of urinary tract infections in general practice--an observational study. BMC Urol. 2012 Nov 21;12:33. doi: 10.1186/1471-2490-12-33. PMID: 23171154

  Neuzillet et al. French results of the ARESC study: clinical aspects and epidemiology of antimicrobial resistance in female patients with cystitis. Implications for empiric therapy. Med Mal Infect. 2012 Feb;42(2):66-75. doi: 10.1016/j.medmal.2011.07.005. PMID: 22264668.
  (same results in Poland, Russia…)

- Prophylaxis for 1 week is beneficial in the prevention of urosepsis and endotoxemia in patients with larger stones and hydronephrosis

  Bag et al. One week of nitrofurantoin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. Urology. 2011 Jan;77(1):45-9. doi: 10.1016/j.urology.2010.03.025. PMID: 20570319.

Nitrofurantoine: mode d'emploi

4.2 Posologie et mode d'administration

Conseil: prendre la Furadantine MC de préférence lors d'un repas ou avec de la nourriture, du lait ou du yaourt, pour optimaliser la biodisponibilité et la tolérance.

Posologie

* Traitement des infections urinaires basses aiguës:

- adultes et enfants de plus de 12 ans: 200 à 400 mg par jour en 3 à 4 administrations (avec les repas et au coucher).

- enfants à partir de 6 ans: 4 à 6 mg/kg de poids et par jour, en 4 administrations.

* Prophylaxie lors d'interventions:
Le jour précédant l'intervention et les 3 jours qui suivent: 50 mg x 4 par jour.

* Prophylaxie des infections urinaires récidivantes:
50 à 100 mg au coucher; enfants: 1 à 2 mg par kg de poids au coucher.
En cas de clairance de la créatinine < 60 ml/min, ne pas administrer la Furadantine MC.

La Furadantine MC est contre-indiquée chez les enfants de moins de 6 ans

Nitrofurantoin: do we need to be “alert” ?

In February 2011, the French Agency for the Safety of Medicine and Health Products (ANSM) published a drug monitoring alert concerning nitrofurantoin.

This letter reported new cases of severe hepatic and pulmonary toxicity after prolonged treatments with nitrofurantoin.

Severe adverse effects:

- 1 per 20551 nitrofurantoin overall prescriptions;
- 1 per 7666 long-term prescriptions (>1 month).

Slekovec et al. When the precautionary principle disrupts 3 years of antibiotic stewardship: nitrofurantoin in the treatment of urinary tract infections. J Antimicrob Chemother. 2014 Jan;69(1):282-4. doi: 10.1093/jac/dkt328. PMID: 23960043.

Nitrofurantoin: do we need to be “alert” ?

In February 2011, the French Agency for the Safety of Medicine and Health Products (ANSM) published a warning alert concerning nitrofurantoin.

As a consequence…

This was based on cases of severe hepatic and pulmonary toxicity after prolonged treatments with nitrofurantoin.

National guidelines were suspended, while nitrofurantoin’s use as prophylaxis for UTIs was strongly discouraged.

One year later the ANSM issued its new guidelines, stating that:

i. Nitrofurantoin is **responsible for severe pulmonary and hepatic toxicity**;

ii. Nitrofurantoin should be used for documented cystitis due to susceptible microorganisms **only when no other antimicrobial presenting a better benefit/risk ratio can be used orally**;

iii. Nitrofurantoin can nevertheless be considered for empirical treatment in cases of urgency or **in the setting of a previous history of multidrug-resistant bacteria**; and

iv. Nitrofurantoin must not be used as prophylaxis.

Slekovec et al. When the precautionary principle disrupts 3 years of antibiotic stewardship: nitrofurantoin in the treatment of urinary tract infections. J Antimicrob Chemother. 2014 Jan;69(1):282-4. doi: 10.1093/jac/dkt328. PMID: 23960043.

Nitrofurantoin: do we need to be “alert” ?

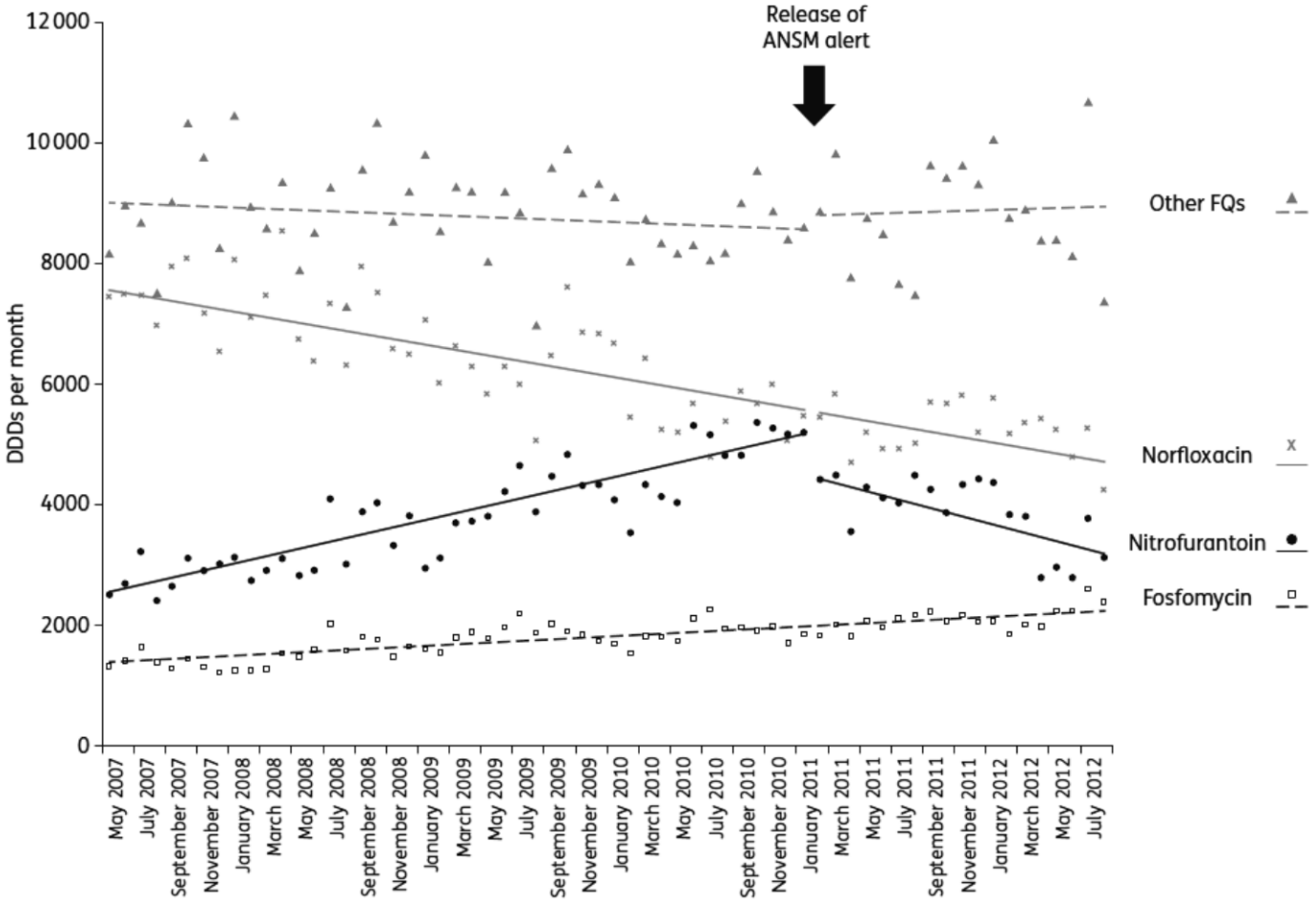
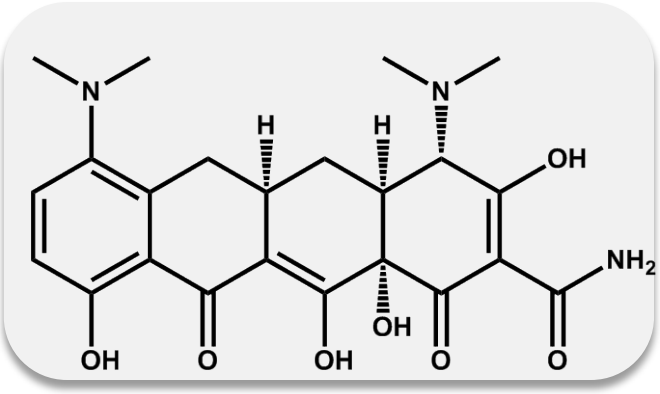


Figure 1. Graphical representation of the segmented regression modification of antibiotic use before and after the release of the ANSM alert. FQs, fluoroquinolones.

Slekovec et al. When the precautionary principle disrupts 3 years of antibiotic stewardship: nitrofurantoin in the treatment of urinary tract infections. J Antimicrob Chemother. 2014 Jan;69(1):282-4. doi: 10.1093/jac/dkt328. PMID: 23960043.

Minocycline identity card



- **IUPAC:** too long… (see http://en.wikipedia.org/wiki/Minocycline)
- **Passport number**: ATC code J01AA08
- **Birthdate:** 1967
- **Birthplace**: Lederlee laboratories
- **Current address:** many

Current position: oral administration … but for what ?

4.1 Indications thérapeutiques

Klinotab est indiqué pour le traitement de formes moyennes à graves d'acné vulgaire inflammatoire

SPC, last revision 2013

Minocycline: you can get many … but pay attention aux “EEN” !

CBIP BCFI **Centre Belge d'Information Pharmacothérapeutique**

Accueil | Bon à savoir | Répertoire | Folia | ATC | Télécharger | Chercher | Log in/Enregistrer

minocycline 50 mg (oral)

EEN			Quantité	Prix (en €)	Tick. mod. ordinaire (€)	Tick. mod. préfer.(€)	Index	Remb. réf.	INAMI
ATC	Minocycline Sandoz (Sandoz)	compr.	20 x	7,84	1,18	0,71	5,90	⊖	b
ATC	Minocycline EG (Eurogenerics)	compr.	42 x	11,79	2,54	1,52	6,04	⊖	b
ATC	Minocycline EG (Eurogenerics)	caps.	42 x	11,79	2,54	1,52	6,04	⊖	b
ATC	Mino-50 (Pharma Logistics)	compr.	42 x	11,80	2,55	1,53	6,07	⊖	b
ATC	Minocycline Sandoz (Sandoz)	compr.	42 x	12,35	2,74	1,64	6,52	⊖	b

minocycline 100 mg (oral)

EEN			Quantité	Prix (en €)	Tick. mod. ordinaire (€)	Tick. mod. préfer.(€)	Index	Remb. réf.	INAMI
ATC	Klinotab (Pharma Logistics)	compr. (séc.)	30 x	11,85	2,56	1,54	8,53	⊖	b
ATC		compr.	30 x	12,34	2,73	1,64	9,10	⊖	b
ATC	cs)	compr.	30 x	12,70	2,86	1,71	9,53	⊖	b
ATC	Minocycline Sandoz (Sandoz)	compr.	30 x	12,70	2,86	1,71	9,53	⊖	b
ATC	Minocin (Pharma Logistics)	caps.	10 x	7,60	1,10	0,66	11,00	⊖	b
ATC	Minotab (Pharma Logistics)	compr. (séc.)	10 x	7,60	1,10	0,66	11,00	⊖	b
ATC	Minocycline Sandoz (Sandoz)	compr.	10 x	7,81	1,17	0,70	11,70	⊖	b
ATC	Minocycline Sandoz (Sandoz)	compr.	20 x	12,60	2,82	1,69	14,10	⊖	b
ATC	Minocin (Pharma Logistics)	caps.	20 x	24,27	24,27	24,27	121,30		

Excipients à effet notoire
sorbitol; jaune orang S (E110)
Source: AFMPS

Tétra- et glycyl-cyclines: pharmacocinétique et posologie

	dose *po*	pic sérique (mg/l)	absorption (% de la dose)	liaison prot. (%)	$t_{1/2}$ (h)
oxytétracycline	250–500 mg 4x/jour	0.9	58	35	10
tétracycline	250–500 mg 4x/jour	2.2	77	65	6-8
minocycline	100-200 mg 1x/jour ou 100 mg 2x/jour	2.5	95	76	15
doxycycline	100-200 mg 1x/jour ou 100 mg 2x/jour	2.5	93	93	15-20
tigécycline	100 mg 1x/jour (IV)	1-1.5	--	70-90	27

Minocycline: out of acne ?

AAC Journals.ASM.org

Antimicrobial Agents and Chemotherapy 2013;57:2252–2258

Therapeutic Efficacy of Macrolides, Minocycline, and Tosufloxacin against Macrolide-Resistant *Mycoplasma pneumoniae* Pneumonia in Pediatric Patients

Yasuhiro Kawai,[a] Naoyuki Miyashita,[b] Mika Kubo,[a] Hiroto Akaike,[a] Atsushi Kato,[a] Yoko Nishizawa,[a] Aki Saito,[a] Eisuke Kondo,[a] Hideto Teranishi,[a] Satoko Ogita,[a] Takaaki Tanaka,[a] Kozo Kawasaki,[a] Takashi Nakano,[a] Kihei Terada,[a] Kazunobu Ouchi[a]

Department of Pediatrics[a] and Department of Internal Medicine 1,[b] Kawasaki Medical School, Okayama, Japan

Minocycline: out of acne ?

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Antimicr

Therapeutic Effic
against Macrolid
Pediatric Patient

Yasuhiro Kawai,[a] Naoyuki Miyas
Hideto Teranishi,[a] Satoko Ogita,
Department of Pediatrics[a] and Departm

TABLE 5 Clinical efficacies of macrolides, minocycline, and tosufloxacin against MR *M. pneumoniae* pneumonia

Treatment group (no. of patients) or parameter[a]	No. (%) of patients whose fever disappeared within 48 h after antibiotic administration	Avg no. of days of fever after antibiotic administration
AZM (27)	11 (41)	3.06[b]
CLR (23)	11 (48)	3.15[b]
TFX (62)	43 (69)	2.31
MIN (38)	33 (87)	1.83
P value for:		
AZM vs CLR	0.698	0.869
AZM vs TFX	0.017	0.062
AZM vs MIN	0.0002	0.002
CLR vs TFX	0.067	0.081
CLR vs MIN	0.001	0.008
TFX vs MIN	0.047	0.152

[a] AZM, azithromycin; CLR, clarithromycin; MIN, minocycline, TFX, tosufloxacin.
[b] Antibiotic changed to TFX or MIN at the second visit for 10 patients in the AZM group and 13 in the CLR group.

Minocycline: out of acne ?

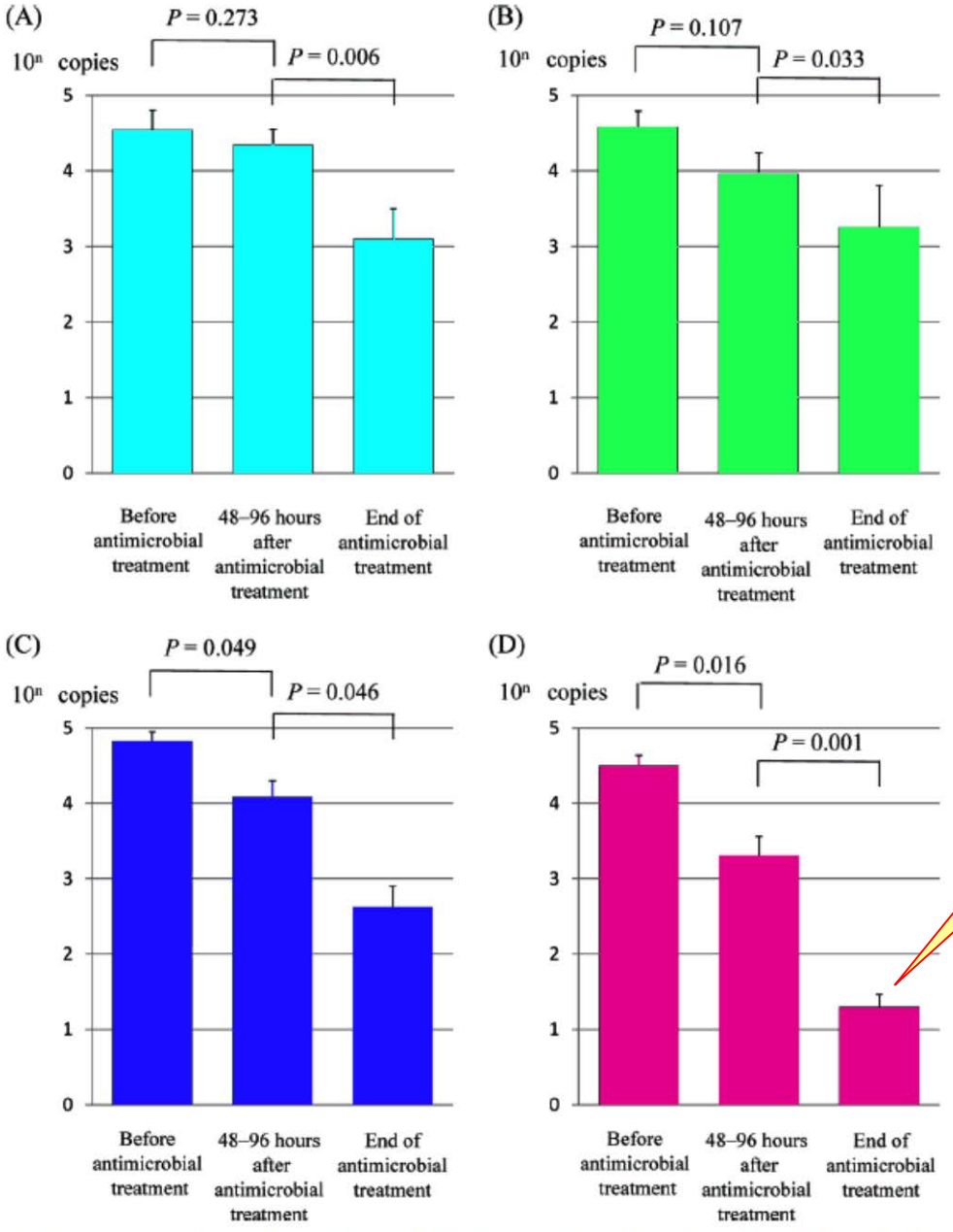

FIG 2 Mean MR *M. pneumoniae* DNA copy numbers estimated from real-time PCR results at three time points before and after antibiotic treatment. Data for 27 patients receiving azithromycin (A), 23 patients receiving clarithromycin (B), 62 patients receiving tosufloxacin (C), and 38 patients receiving minocycline (D) are shown. Bars indicate standard errors.

Minocycline: out of acne ?

frontiers in MICROBIOLOGY

Front Microbiol. 2014 Oct 20;5:551.

REVIEW ARTICLE
published: 20 October 2014
doi: 10.3389/fmicb.2014.00551

A new strategy to fight antimicrobial resistance: the revival of old antibiotics

Nadim Cassir[1,2]*, Jean-Marc Rolain[1] and Philippe Brouqui[1,2]

[1] *Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UM63 CNRS 7278 IRD 198 INSERM U1095, Facultés de Médecine et de Pharmacie, Aix-Marseille Université, Marseille, France*

[2] *Institut Hospitalo-Universitaire en Maladies Infectieuses et Tropicales, Hôpital Nord, Assistance Publique - Hôpitaux de Marseille, Marseille, France*

Molecule	Pathogens	Sites of infection	References
Minocycline (IV, PO)	MRSA	SSTI BJI Osteomyelitis IE (prosthetic valve) Bacteremia	Clumeck et al., 1984; Lawlor et al., 1990; Moreno et al., 1994; Ruhe et al., 2005; Cenizal et al., 2007; Ruhe and Menon, 2007

Minocycline: an anti-*Staphyloococcus aureus* ?

Clin. Infect.Dis. 2005;40:1429–1434. doi:10.1086/429628

MAJOR ARTICLE

Use of Long-Acting Tetracyclines for Methicillin-Resistant *Staphylococcus aureus* Infections: Case Series and Review of the Literature

Jörg J. Ruhe, Thomas Monson, Robert W. Bradsher, and Anupama Menon

Division of Infectious Diseases, Department of Medicine, University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

Background. Few data exist on the efficacy of the long-acting tetracyclines doxycycline and minocycline against methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Methods. The medical records of 24 patients with serious tetracycline-susceptible MRSA infections who were treated with doxycycline or minocycline were reviewed. A review of the literature on the use of these antibiotics for treatment of both methicillin-susceptible and methicillin-resistant *S. aureus* infection was also performed.

Results. Complicated skin and skin-structure infections were most common (67%). Clinical cure was achieved in 20 (83%) of 24 patients in our case series. Both drugs were well-tolerated. The review of the literature on a total of 85 patients with *S. aureus* infection revealed similar results.

Conclusions. Long-acting tetracyclines may be a reasonable treatment alternative for patients with certain types of MRSA infection.

Minocycline: an anti-*Staphylooc*

Clin. Infect.Dis. 2005;40:1429–1434. doi:10.1086/4

Use of Long-Acting Tetracyc
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Healthcare System, Little Rock, Arkansas

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Conclusions. Long-acting tetracyclines may be a reaso
types of MRSA infection.

Table 2. Types of infection and clinical outcomes in 24 adult patients with methicillin-resistant *Staphylococcus aureus* infection treated with long-acting tetracyclines.

Type of infection, drug treatment received	Proportion (%) of patients	Proportion (%) of patients with cure
Skin and skin-structure infection	16/24 (67)	…
Doxycycline	11/16 (69)	10/11 (91)
Minocycline[a]	5/16 (31)	5/5 (100)
Osteomyelitis	4/24 (17)	…
Minocycline	4/4 (100)[b]	2/4 (50)
Urinary tract infection	2/24 (8)	…
Doxycycline	2/2 (100)[c]	2/2 (100)
Septic arthritis[d]	1/24 (4)	…
Minocycline	1/1 (100)[e]	0/1 (0)
Bacteremia and/or sepsis	1/24 (4)	…
Minocycline	1/1 (100)	1/1 (100)
All	24/24 (100)	20/24 (83)
Doxycycline	13/24 (54)	12/13 (92)
Minocycline	11/24 (46)	8/11 (73)

[a] Two patients received minocycline and rifampin combined.
[b] Two patients received minocycline and rifampin combined, and 1 patient received minocycline and trimethoprim-sulfamethoxazole combined.
[c] Both patients were elderly men with underlying genitourinary abnormalities, but no Foley catheter in place, who presented with symptoms of urosepsis.
[d] Septic arthritis of the shoulder joint.
[e] Patient received minocycline and rifampin combined.

Minocycline: an anti-*Staphyloococcus aureus* ?

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Table 3. Review of the literature on patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) infections treated with long-acting tetracyclines.

Reference	No. of participating patients	Age, mean years (range)	Strain isolated	Type of infection, no. (%) of infected patients	Type of tetracycline	No. (%) of patients with cure
[12]	25	62 (18–88)	MRSA	Pneumonia, 9 (36)	Minocycline plus rifampin	19 (76)
				Osteomyelitis, 4 (16)		
				SSSI, 4 (16)		
				Other, 8 (32)[a]		
[13]	1	45	MRSA	Prosthetic aortic valve endocarditis, 1 (100)	Minocycline	1 (100)
[14]	15	61 (25–74)	MSSA	SSSI, 10 (67)	Minocycline	12 (80)
				Pneumonia, 5 (33)		
[15]	10	Unknown	MSSA	SSSI, 10 (100)	Minocycline	8 (80)
[16]	15	56 (22–83)	MSSA	SSSI, 15 (100)	Minocycline	15 (100)
[17]	2	69 (54–84)	MSSA	Pneumonia, 2 (100)	Minocycline	2 (100)
				SSSI, 1 (50)		
[18]	1	33	MSSA	Osteomyelitis, 1 (100)	Minocycline	1 (100)
[19]	13	35 (22–48)	MSSA	SSSI, 13 (100)	Doxycycline	13 (100)
[20]	3	unknown	MSSA	Osteomyelitis, 3 (100)	Doxycycline plus rifampin	1 (33)

NOTE. SSSI, skin and skin-structure infection.

[a] Septic thrombophlebitis ($n = 3$), urinary tract infection ($n = 3$), endocarditis ($n = 1$), and liver abscess ($n = 1$).

Minocycline: out of acne ?

CLINICAL RESEARCH *J Am Soc Nephrol* 22: 1939–1945, 2011. doi: 10.1681/ASN.2010121306

Minocycline-EDTA Lock Solution Prevents Catheter-Related Bacteremia in Hemodialysis

Rodrigo Peixoto Campos,*§ Marcelo Mazza do Nascimento,† Domingos Candiota Chula,‡ and Miguel Carlos Riella*†

*Center for Health and Biological Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil; †Division of Nephrology, Hospital Universitário Evangélico de Curitiba, Curitiba, Brazil; ‡Clínica de Doenças Renais do Novo Mundo, Curitiba, Brazil; §Division of Nephrology, Hospital São Lucas, Campo Largo, Brazil

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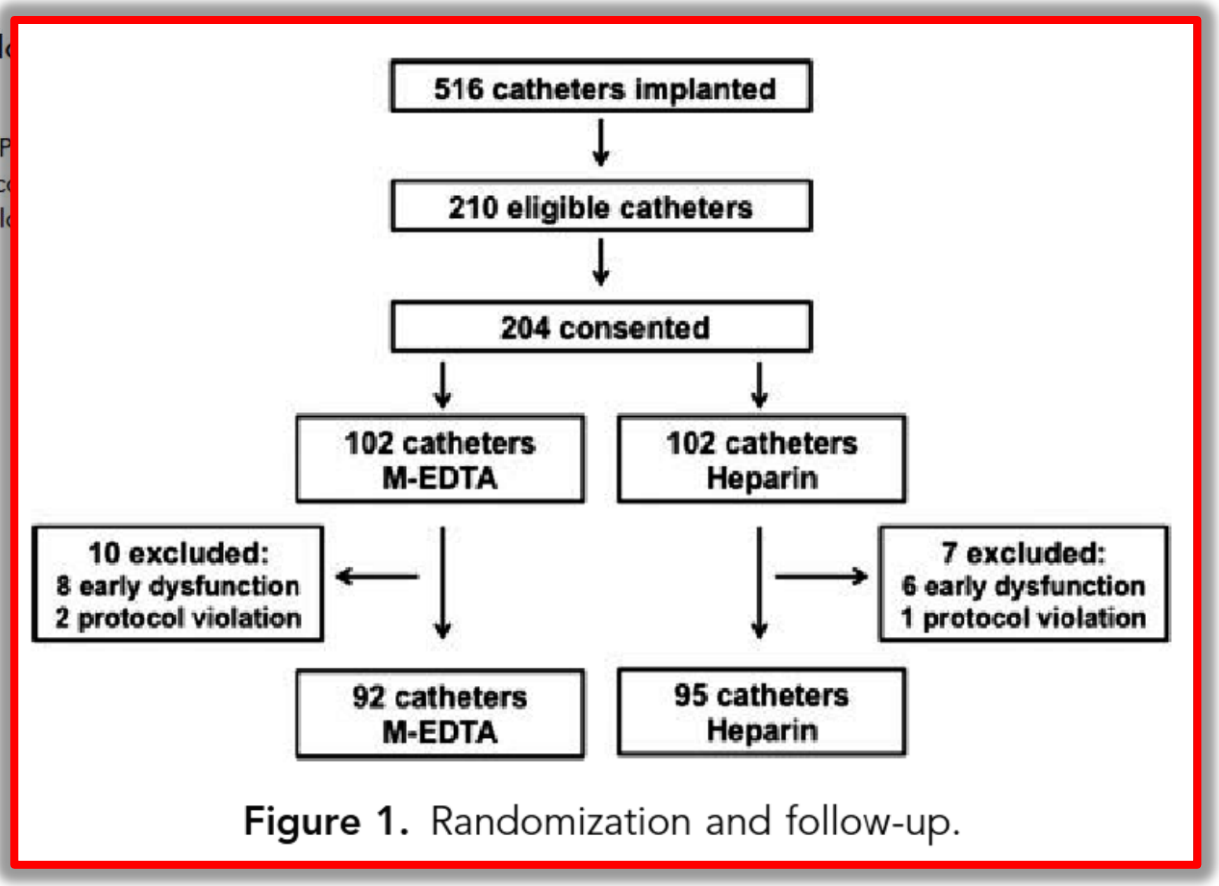

Figure 1. Randomization and follow-up.

Minocycline: out of acne ?

CLINICAL RESEARCH *J Am Soc Neph*

Minocycline-EDTA Lo
Related Bacteremia i

Rodrigo Peixoto Campos,*§ Marcel
and Miguel Carlos Riella*†

*Center for Health and Biological Sciences, P
Nephrology, Hospital Universitário Evangélic
Mundo, Curitiba, Brazil; §Division of Nephrol

Table 2. Catheter-related bacteremia (CRB) and dysfunction

Events	M-EDTA	Heparin	*P* Value
CRB incidence	5	19	0.003
CRB per 1000 catheter-days	1.1	4.3	0.005
CRB-free survival by day 90 (%)	91.3%	69.3%	
Mean CRB-free survival (days)	85.5	74.9	
Dysfunction incidence	20	14	0.21
Dysfunction per 1000 catheter-days	4.6	3.2	0.31

Table 3. Microorganisms isolated in CRB

Microorganisms *(count)*	M-EDTA	Heparin
Coagulase negative Staphylococcus	3	3
Staphylococcus aureus	2	5
Escherichia coli	—	3
Enterobacter aerogenes	—	3
Klebsiella pneumoniae	—	1
Enterococcus sp	—	1
Pseudomonas aeruginosa	—	1
Proteus mirabilis	—	1
Stenotrophomonas maltophilia	—	1

Minocycline: out of acne ?

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Mundo, Curitiba, Brazil; §Division of Nephrology, Hospital São Lucas, Cam

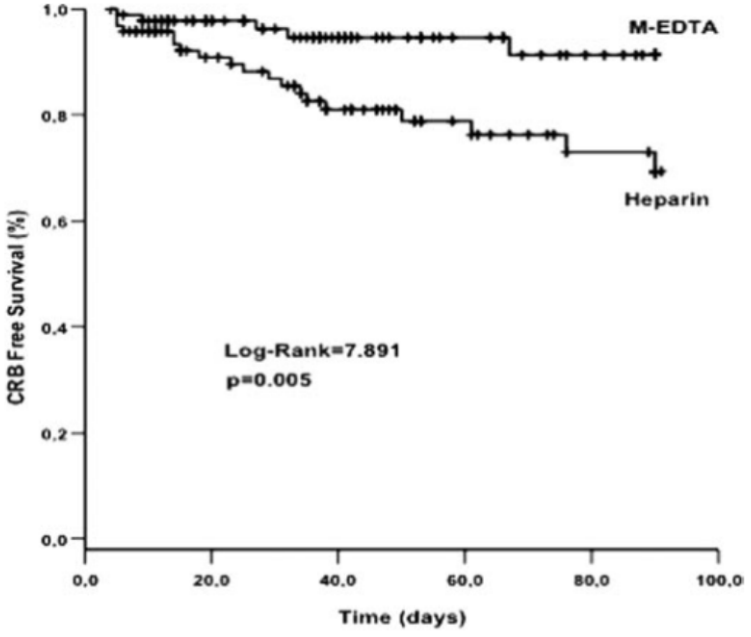
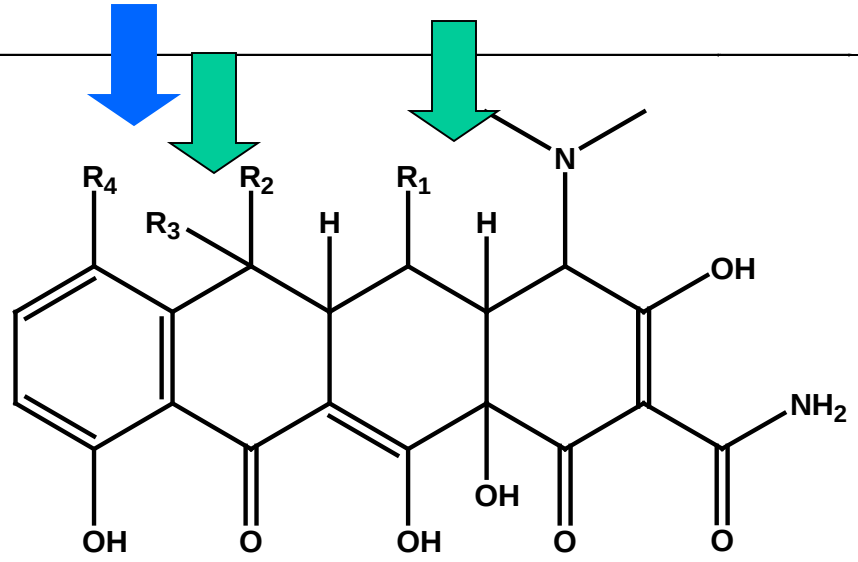


Figure 2. Kaplan-Meier analysis of the probability that patients would remain free of catheter-related bacteremia (CRB) for all catheters.

May be I should have looked also at doxycycline ?



molécule	-R_4	-R_3	-R_2	-R_1
tetracycline	-H	-OH	-H	-H
doxycycline	-H	-CH_3	-H	-OH
minocycline	-$N(CH_3)_2$	-H	-H	-H

Ici, nous avons plus d'indications officielles… mais pourquoi ?

4.1 Indications thérapeutiques

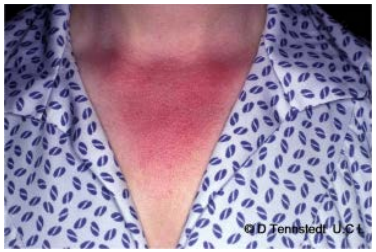
La doxycycline, un antibiotique à large spectre, est efficace dans le traitement des affections suivantes:

- Infections provoquées par le Chlamydia:
  - lymphogranulome vénérien
  - urétrite non compliquée / cervicite, épididymite et orchite provoquée par chlamydia trachomatis
- Syphilis en cas d'allergie à la pénicilline
- Infections provoquées par des mycoplasmes: surtout pneumonie par mycoplasmes pneumoniques.
- Rickettsies: typhus exanthématique
- Infections provoquées par des bacilles:
  - Infections gastro-intestinales : traitement adjuvant du choléra
- Infections de la peau et des tissus mous: les acnés vulgaires papulo-pustuleuses
- Maladie de Lyme: au moment de l'infection cutanée (érythème migrant) et dans l'arthrite au stade I.
- Malaria provoqué par le Plasmodium falciparum
  Exceptionnellement, la doxycycline peut être utilisée dans la prophylaxie de la malaria lors de séjours brefs dans des régions spécifiques où les souches sont résistantes à la méfloquine et à la chloroquine.
  La doxycycline peut également être utilisée, le plus souvent en association avec de la quinine, dans le traitement de la malaria, provoquée par des souches multi-résistantes

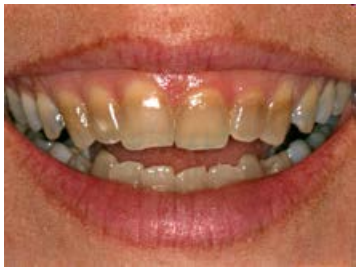
Compte tenu du grand nombre de souches à staphylocoques et à streptocoques résistantes, la sensibilité des souches doit être connue avant le traitement.

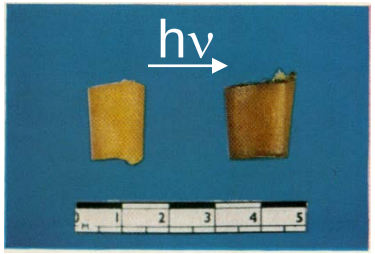
SPC, last revision 2013

Effets secondaires des tétracyclines



- effet photosensibilisant
  risque augmenté en présence d'autres médicaments photosensibilisants
  (AINS, amiodarone, sulfamides, …)





J Clin Pathol. (1962) 15:112–115.

- fixation aux os et aux dents (coloration jaune)
  → contre-indiqué chez les enfants et les femmes enceintes

- adhérence oesophagienne et ulcération
  → administration en position assise avec un grand verre d'eau, 30 min avant repas

- rarement, toxicité hépatique ou rénale

- thrombophlébite lors de l'injection intra-veineuse

Interactions médicamenteuses

- Formation de complexes non résorbés avec les ions bi- ou tri-valents (calcium, magnésium, fer, zinc, bismuth)

Prendre à distance des aliments ou médicaments qui en contiennent

Quelques exemples :
antacides, sucralfate, didanosine, multivitamines, renalate de strontium…

- réduction de l'absorption digestive
  avec colestyramine
- métabolisme accru en présence d'inducteurs hépatiques
  Quelques exemples : carbamazépine, phénytoïne
- risque d'hémorragie avec les anticoagulants oraux
  (réduction de la production de Vit K par flore digestive)
- risque d'hypertension intracrânienne et de photosensibilisation
  avec isotrétinoïne (traitement de l'acné !)
- perte d'efficacité des contraceptifs oraux
  (réduction du métabolisme intestinal des conjugués aux oestrogènes)

Sulfaméthoxazole / Thrimetoprim

Sulfaméthoxazole + triméthoprime (co-trimoxazole)

Posologie

per os:
1,6 g sulfaméthoxazole + 320 mg triméthoprime p.j. en 2 prises

Bactrim (Roche)

[sulfaméthoxazole 800mg + triméthoprime 160mg]
compr. Forte (séc.)

€	10	℞	b	€ 7,21

Eusaprim (Aspen)

[sulfaméthoxazole 400mg + triméthoprime 80mg]
compr.

€	20	℞	b	€ 7,06
€	50	℞		€ 6,88

[sulfaméthoxazole 800mg + triméthoprime 160mg]
compr. Forte (séc.)

€	10	℞	b	€ 7,06
€	30	℞		€ 7,31

[sulfaméthoxazole 200mg + triméthoprime 40mg **/ 5ml**]
sir.

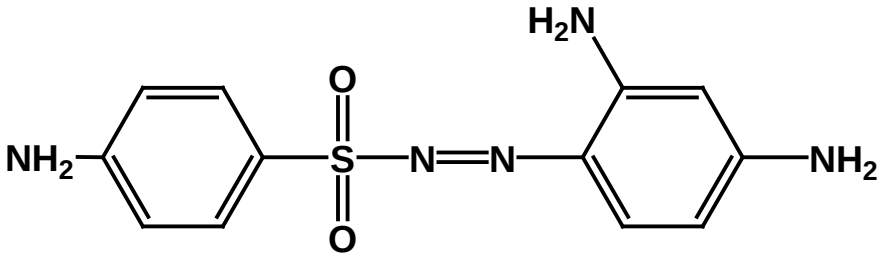
€	100 ml	℞	€ 6,41

[sulfaméthoxazole 400mg + triméthoprime 80mg **/ 5ml**]
amp. perf.

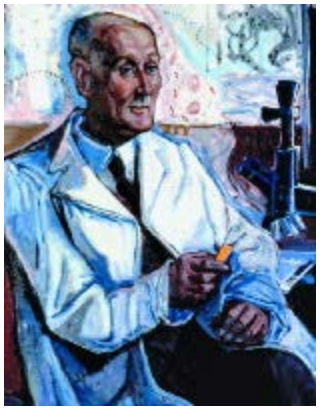
€	10	U.H.	[€ 9]

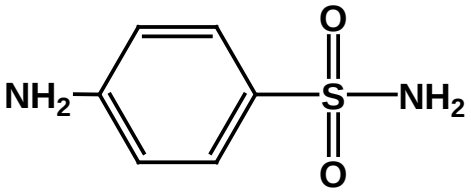
Un peu d'histoire...

Premiers antibiotiques entièrement synthétiques,
Dérivés du prontosil (chimie des colorants)



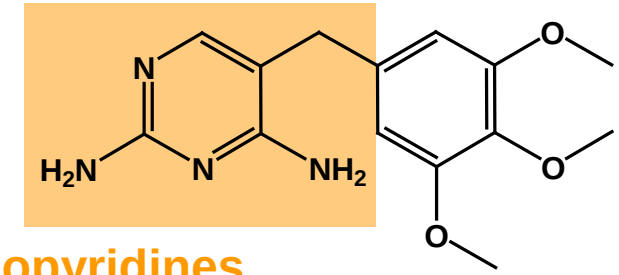
Prontosil, la prodrogue du sulfanilamide



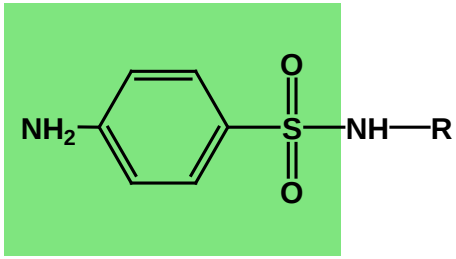


G. Domagk, prix Nobel en 1939
pour avoir démontré l'effet antibactérien des sulfamides
dans des modèles animaux

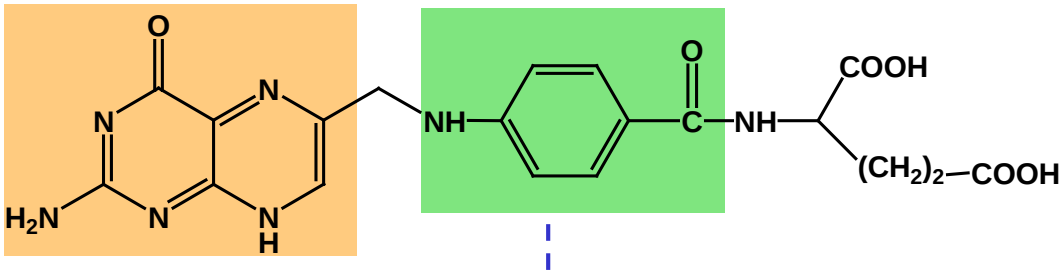
Sulfamides et diaminopyridines, inhibiteurs de la synthèse de l'acide tétrahydrofolique



diaminopyridines



sulfamides

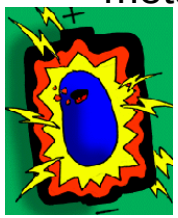


acide folique

procaryotes:
produit du
métabolisme bactérien

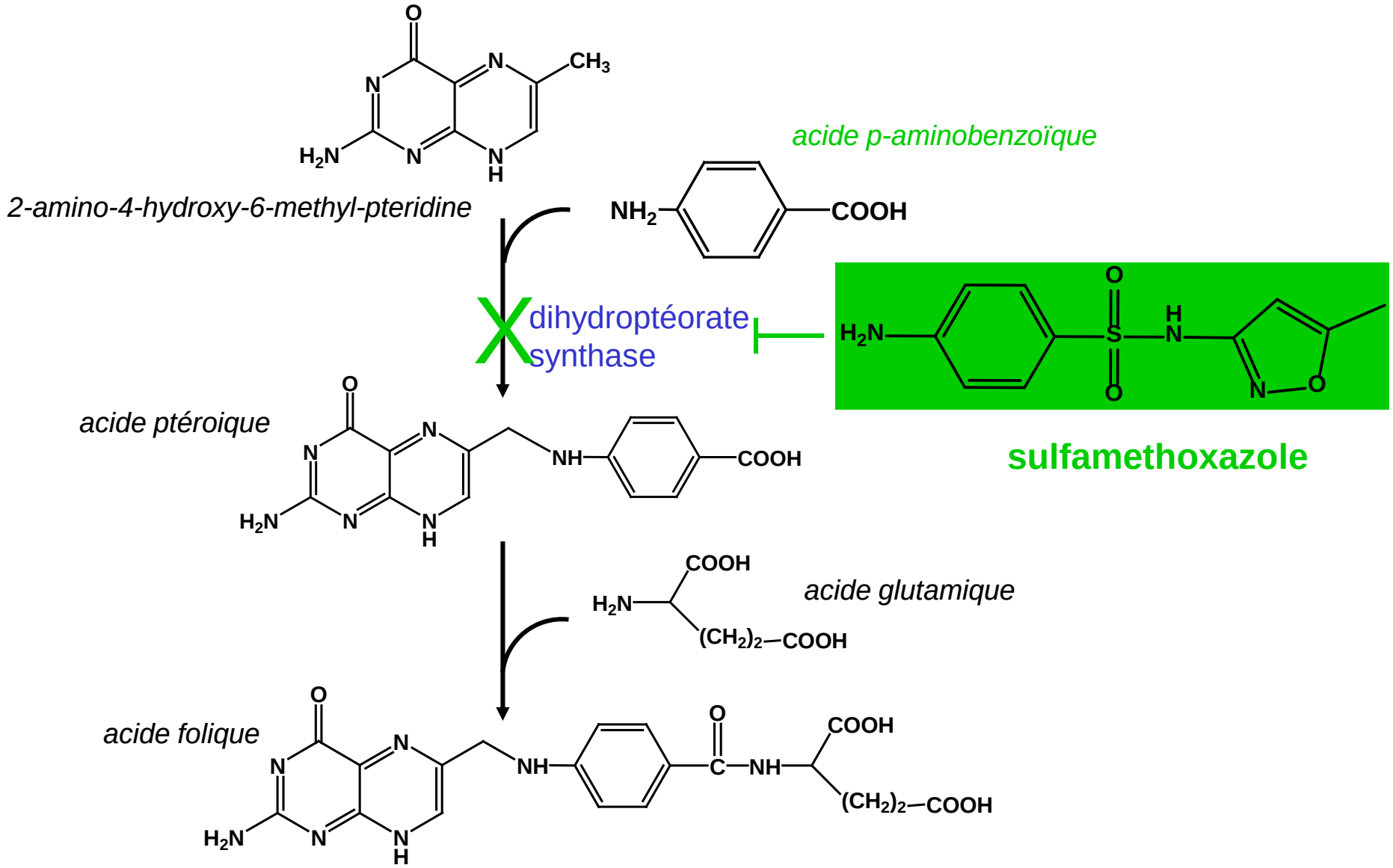
Co-facteur pour la synthèse des purines & pyrimidines

eucaryotes:
= vitamine B9;
alimentation



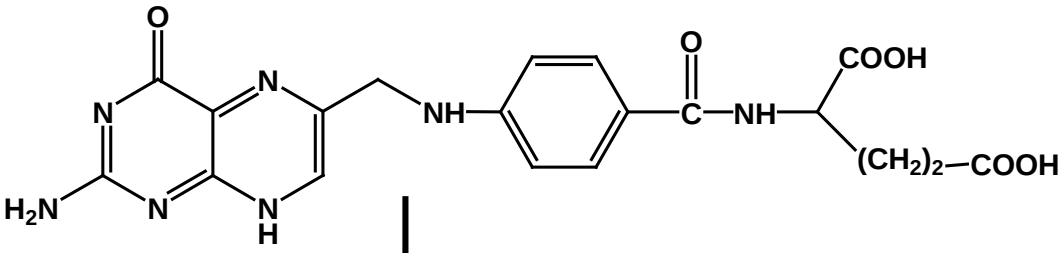
synthèse : cible spécifique

Sulfamides et triméthoprim, inhibiteurs de la synthèse de l'acide tétrahydrofolique

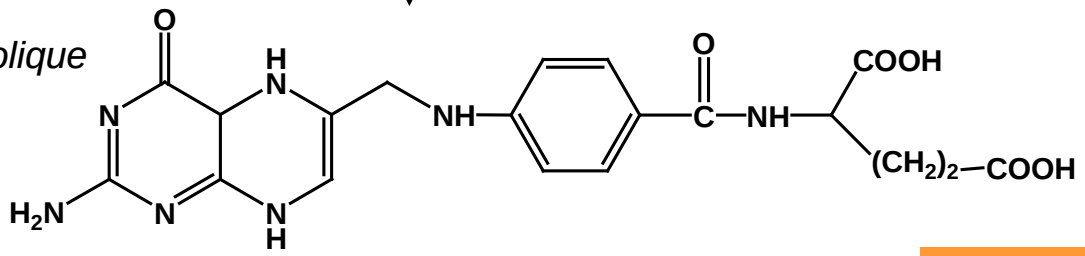


Sulfamides et triméthoprim, inhibiteurs de la synthèse de l'acide tétrahydrofolique

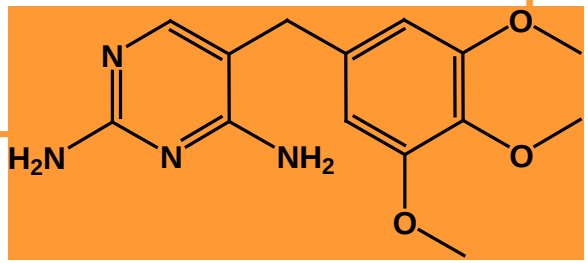
acide folique



acide dihydrofolique

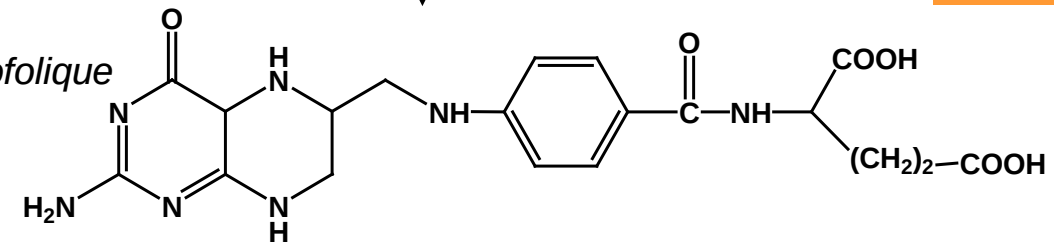


trimethoprim



dihydrofolate réductase

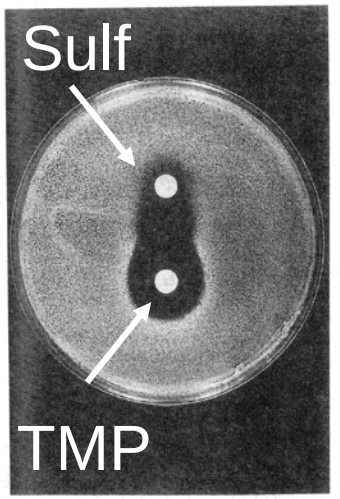
acide tetrahydrofolique



Propriétés anti-microbiennes

- Antibiotiques bactériostatiques,
  mais agissent en synergie

- Spectre large:
  Gram(+) et Gram(-) en combinaison (SMX/TMP)
  certains parasites



Synergistic effect between sulfonamides and trimethoprim against a sulfonamide-resistant (MIC > 1000 µg/mL) *S. aureus*.

Résistance

Sulfamides: - hyperproduction d'acide p-aminobenzoïque
- mutation de l'enzyme cible

Diaminopyridines - surproduction de la DHFR
- production d'une 2ème DHFR de moindre affinité

Propriétés pharmacocinétiques

- **Absorption**: bonne par voie orale;
  disponible sous forme de combinaison

- **Distribution:**
  - diffusion dans les liquides interstitiels et le LCR
    (mais germes responsables de méningites devenus résistants …)
  - liaison importante aux prot. plasmatiques

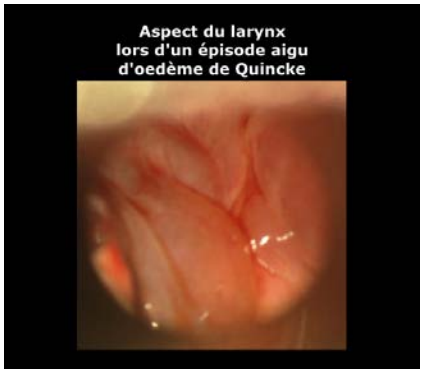
interactions médic.

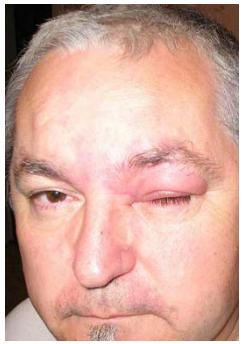
- **Elimination**:
  - voie rénale
  - métabolisme hépatique partiel

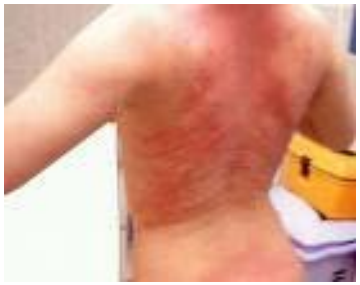
indication dans infections urinaires

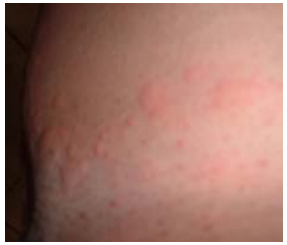
Effets secondaires

- réactions toxiallergiques potentiellement graves
  oedème de Quincke, troubles respiratoires, rash







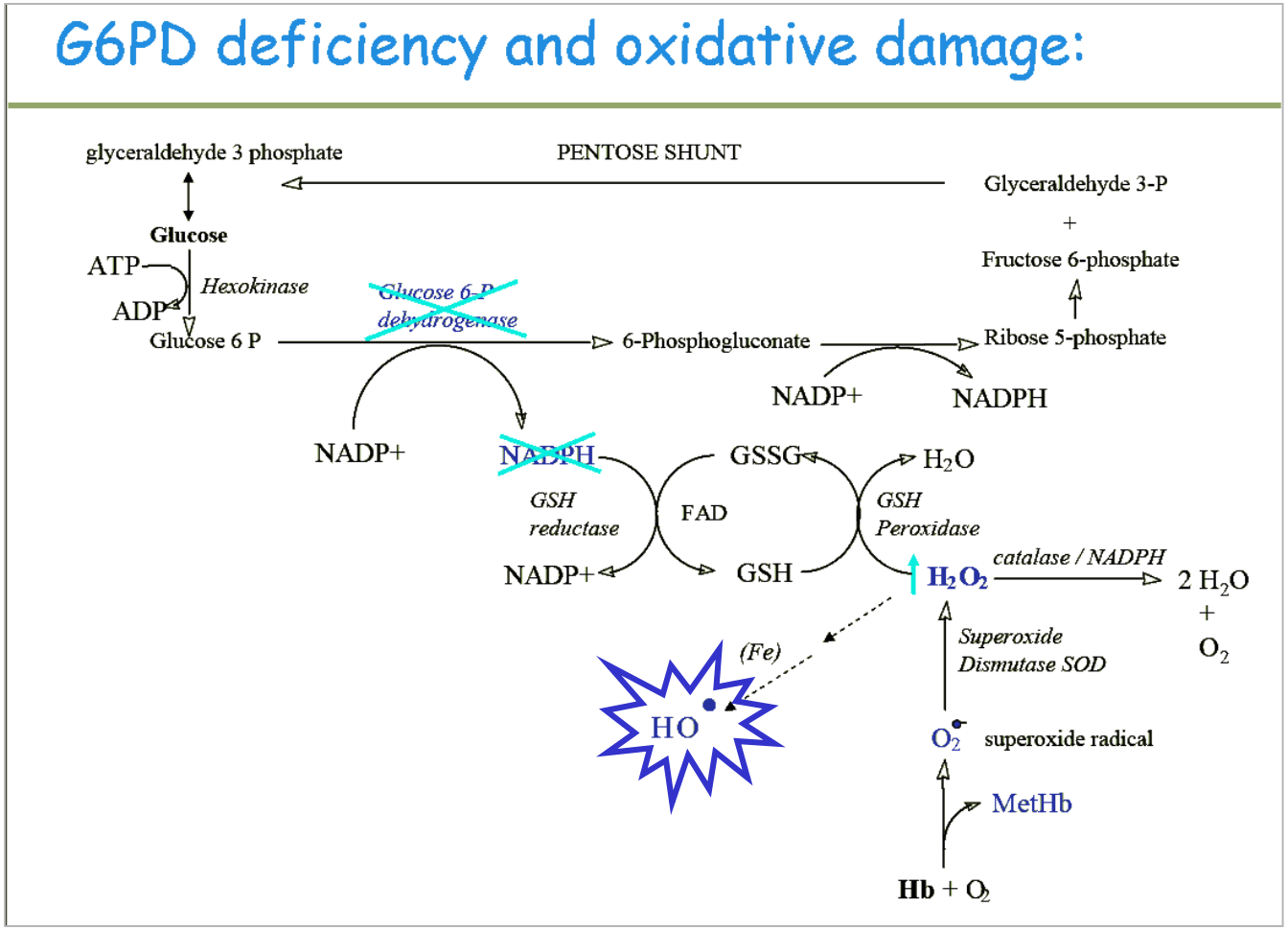


- occasionnellement:

- troubles hématologiques (neutro- ou thrombopénie)
- cristalluries (métabolites peu solubles)
- troubles digestifs (nausées, vomisements, diarrhées)
- troubles neurologiques (asthénie, céphalée)
- hémolyse, chez les patients déficients en glucose-6P-déshydrogénase.

Effets secondaires

- hémolyse, chez les patients déficients en glucose-6P-déshydrogénase: POURQUOI ?



Gare aux médicaments à effets hémolytiques ou oxydants !

Effets secondaires

- hémolyse, chez les patients déficients en glucose-6P-déshydrogénase: QUOI ?

Drugs which induce hemolytic anemia in G6PD deficient individuals

In the modern world, individuals with G6PD deficiency typically exhibit few ill effects, until:

Acetanilide
Aminopyrine
Aspirin
Chloroquine
Dapsone
Dimercaprol
Furazolidine
Mepacrine
Methylene Blue
Naphthalene
Nitrofurantoin
Pamaquin, Pantaquin
Phenacetin
Phenylhydrazine
Primaquine *
Probenecid
Salicylates
Sulfa drugs
Toluidine blue

Reference: New Engl J Med. 324, 169-74 (1990).

Interactions médicamenteuses

- déplacement de la liaison aux prot. d'autres médicaments
  → ↗ effet: coumariniques
  sulfamides hypoglycémiants
  méthotrexate

- interférences métaboliques
  ↘ métabolisme des phénytoïnes (sauf sulfamethoxazole)
  ↗ métabolisme de la cyclosporine

Mieux vaut prévenir que guérir ….

Occurrence of overanticoagulation and time spent within, above and under the therapeutic range by patients using co-trimoxazole

Outcome	Co-trimoxazole	
	PDR+[b] (n=28)	PDR-[b] (n=15)
INR >4.5, no. (%)	3 (10.7)	25 (89.3)
INR > 6.0, no. (%)	1 (3.6)	4 (26.7)
Time within therapeutic range, mean % (95%CI)[c]	71.1 (60.4–81.8)	51.8 (34.6–69.0)
Time above therapeutic range, mean % (95%CI)	15.0 (5.7–24.3)	20.3 (10.7–29.8)
Time under therapeutic range, mean % (95%CI)	14.0 (5.6–22.2)	27.9 (7.7–48.1)

Preventive Drug Reduction

Schalekamp et al Eur J Clin Pharmacol. (2007) 63: 335–343

Indications (officielles): un peu de tout…

4.1 Indications thérapeutiques

Bactrim ne doit en principe être utilisé que lorsque les autres traitements disponibles sont, soit inefficaces, soit mal tolérés. La décision d'utiliser Bactrim doit tenir compte, dans un pays donné, de l'évolution de la sensibilité des germes vis-à-vis du produit et des autres antibiotiques disponibles.

Infections respiratoires
Exacerbation aiguë d'affections pulmonaires chroniques, otite moyenne chez l'enfant, lorsqu'il y a de bonnes raisons de préférer Bactrim à un antibiotique seul; traitement et prophylaxie (primaire et secondaire) de la pneumonie à Pneumocystis jirovecii chez l'adulte et l'enfant.

Infections uro-génitales
Infections des voies urinaires, chancre mou.

Infections gastro-intestinales
Fièvre typhoïde et paratyphoïde, shigellose (souches sensibles de Shigella flexneri et Shigella sonnei lorsqu'un traitement antibactérien est indiqué), diarrhée des voyageurs à Escherichia coli entérotoxinogène et choléra (comme adjuvant à la réhydratation et à la correction des électrolytes).

Autres infections bactériennes
Infections causées par une large gamme d'organismes (traitement possible en association avec d'autres antibiotiques), par ex. brucellose, ostéomyélite aiguë et chronique, nocardiose, actinomycétome, toxoplasmose et blastomycose sud-américaine.

Sulfamethoxazole/trimethoprim: if we need it …

frontiers in MICROBIOLOGY

Front Microbiol. 2014 Oct 20;5:551.

REVIEW ARTICLE
published: 20 October 2014
doi: 10.3389/fmicb.2014.00551

A new strategy to fight antimicrobial resistance: the revival of old antibiotics

Nadim Cassir[1,2]*, Jean-Marc Rolain[1] and Philippe Brouqui[1,2]

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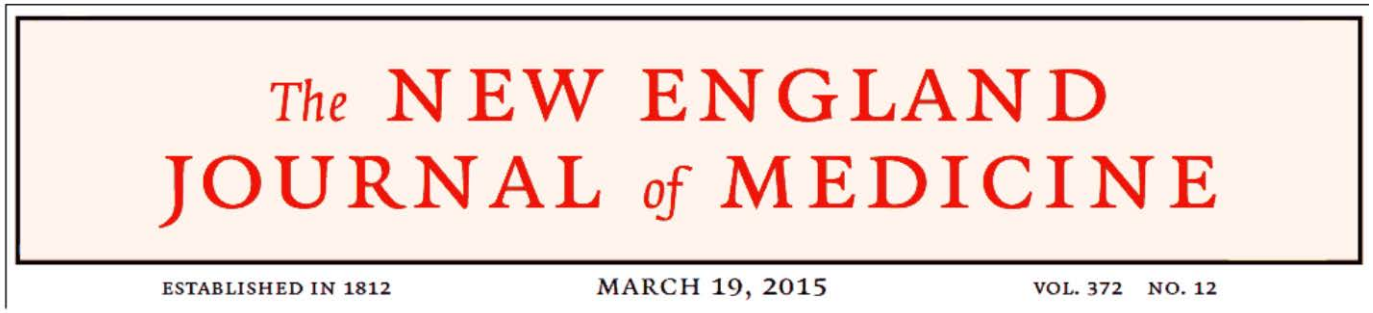
[2] *Institut Hospitalo-Universitaire en Maladies Infectieuses et Tropicales, Hôpital Nord, Assistance Publique - Hôpitaux de Marseille, Marseille, France*

Molecule	Pathogens	Sites of infection	References
Trimethoprim-sulfamethoxazole (TMP/SMX) (IV, PO)	CA and HA-MRSA *E. americana*	SSTI BJI Osteomyelitis IE (prosthetic valve) Meningitis Bacteremia COPD exacerbation	Shafqat et al., 1971; Seligman et al., 1973; Bengtsson et al., 1974; Tamer and Bray, 1982; Levitz et al., 1984; Stein et al., 1998; Cenizal et al., 2007; Pound et al., 2007; Nguyen et al., 2009; Goldberg et al., 2010; Cadena et al., 2011; Messina et al., 2011; Di Carlo et al., 2013

Sulfamethoxazole/trimethoprim: even better than you tought



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 19, 2015 VOL. 372 NO. 12

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections

Loren G. Miller, M.D., M.P.H., Robert S. Daum, M.D., C.M., C. Buddy Creech, M.D., M.P.H., David Young, M.D., Michele D. Downing, R.N., M.S.N., Samantha J. Eells, M.P.H., Stephanie Pettibone, B.S., Rebecca J. Hoagland, M.S., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

Drug dosage:

- **Clindamycin**: 2 x 150-mg tablets every 8 h
- **TMP-SMX**: 60 mg / 800 mg every 12 h

  (Belgium standard dosage: 160/800 Q12h)

Sulfamethoxazole/trimethoprim: even better than you tought

The NEW ENGLAND JOU

ESTABLISHED IN

Clindamyc
f

Loren G. Miller, M.D., M.P
Michele D. Do
Rebecca J. Ho

Table 2. Wound Culture Results at Baseline.*

Culture Result	Clindamycin Group (N=264)	TMP-SMX Group (N=260)	All Patients (N=524)
		no. of patients (%)	
No culture obtained	110 (41.7)	118 (45.4)	228 (43.5)
Culture obtained but no growth	6 (2.3)	6 (2.3)	12 (2.3)
Culture obtained but no results	4 (1.5)	3 (1.2)	7 (1.3)
Positive culture	144 (54.5)	133 (51.2)	277 (52.9)
Staphylococcus aureus	108 (40.9)	109 (41.9)	217 (41.4)
MRSA	84 (31.8)	83 (31.9)	167 (31.9)
Clindamycin-resistant	12 (4.5)	9 (3.5)	21 (4.0)
TMP-SMX–resistant	1 (0.4)	0	1 (0.2)
MSSA	25 (9.5)	27 (10.4)	52 (9.9)
Clindamycin-resistant	3 (1.1)	3 (1.2)	6 (1.1)
TMP-SMX–resistant	0	0	0

* The denominator for the calculation of percentages is the number of patients in the intention-to-treat population for each group. Patients are counted once for each species identified. MRSA denotes methicillin-resistant *S. aureus*, and MSSA methicillin-susceptible *S. aureus*.

Sulfamethoxazole/trimethoprim: even better than you tought

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Rebecca J. Hoagland, M.S., and Henry F. Chambers, M.D., for t

This looks as good as the “new” antibiotics

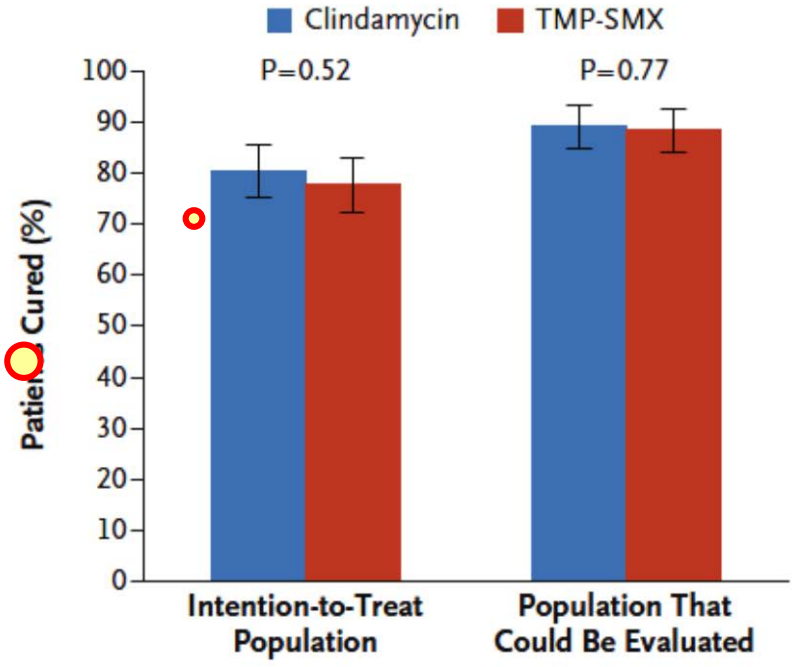

Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

The graph shows the proportion of patients cured by the time of the test-of-cure visit in the intention-to-treat population and the population that could be evaluated. The actual confidence level was 95.60% after adjustment for interim analyses.

Conclusions

- An antibiotic is an antibiotic …
- If the bacteria are susceptible (EUCAST breakpoints, please), it SHOULD work no matter older it is
- BUT be prepared for :
  - ignorance of best dosages and schedules
    → we simply do not know them …
    → follow the literature … and try…
  - Toxicities
    → read the SmPC
    → contact pharmacovigilance
- And, please, follow susceptibility patterns in YOUR environment…
  → require an MIC because an MIC is an MIC…