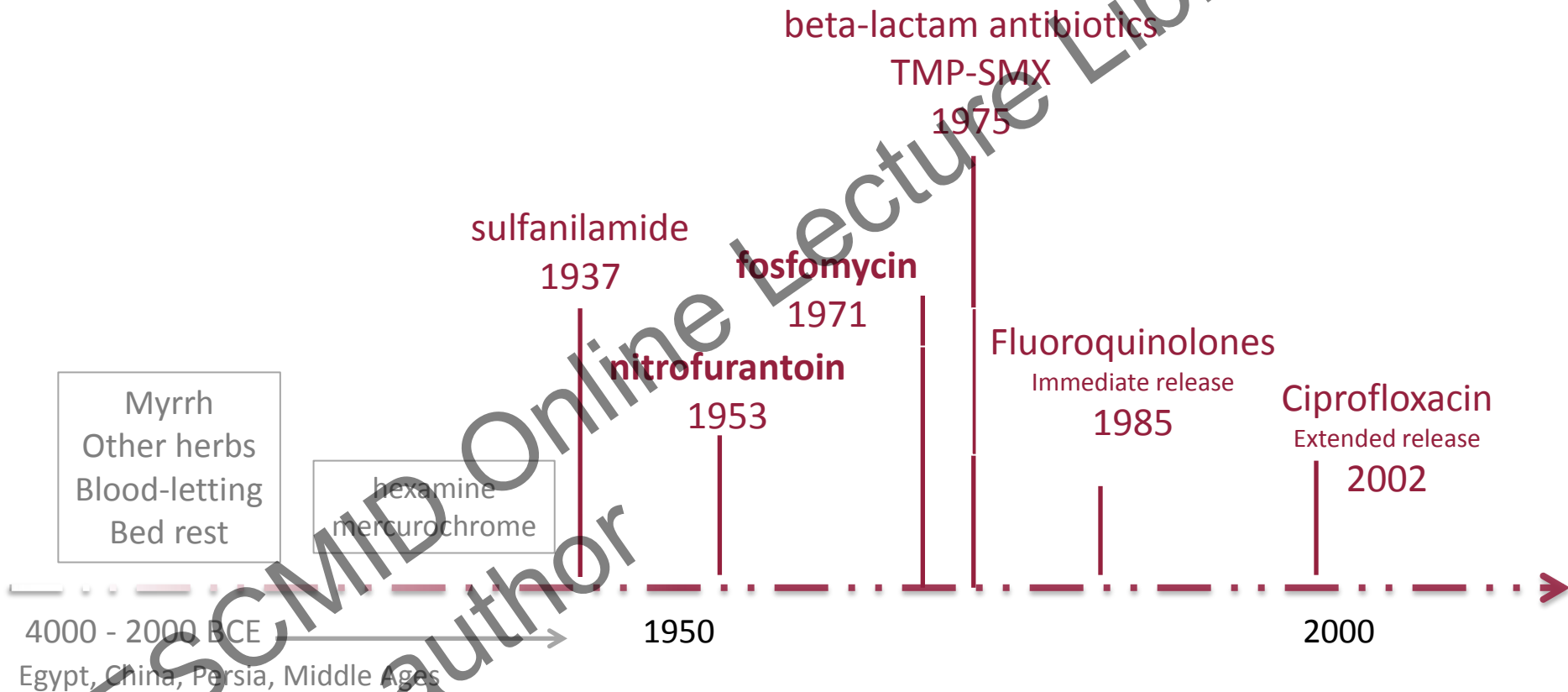


Fosfomycin trometamol

Angela Huttner MD

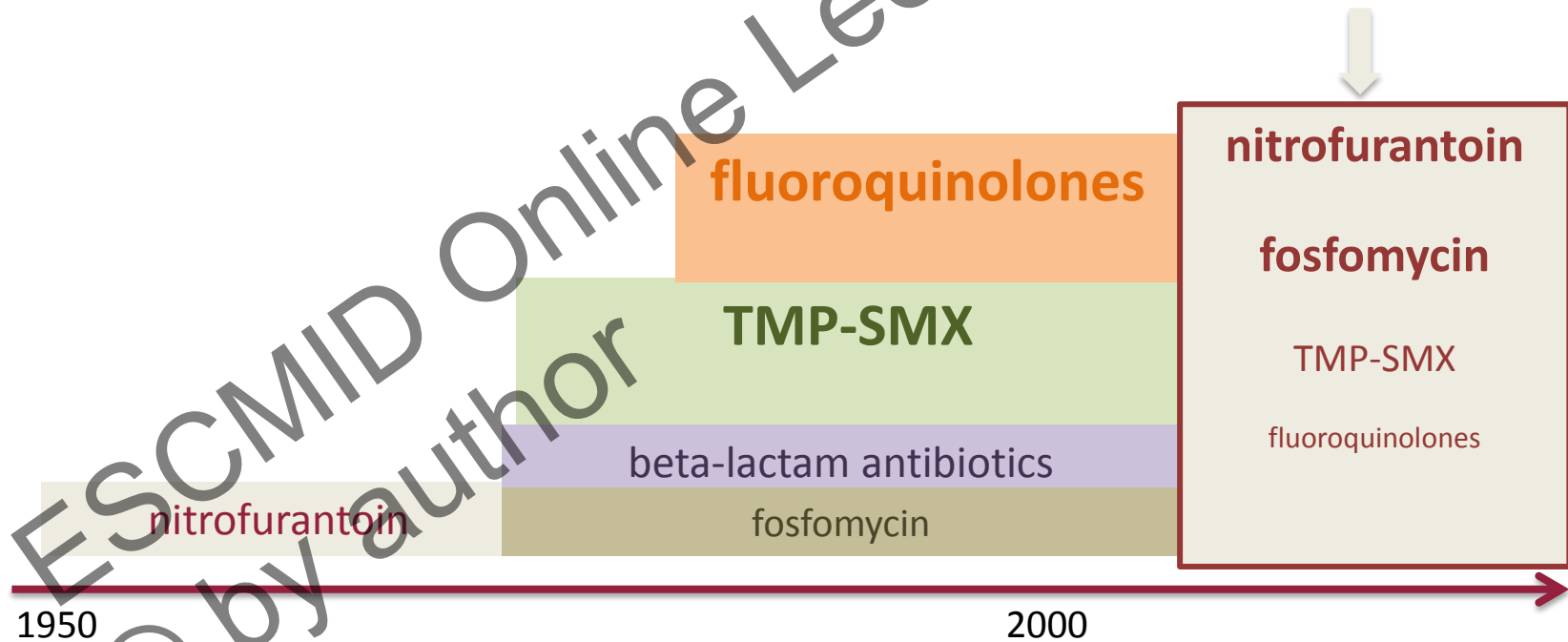
Infection Control Program
Division of Infectious Diseases
University Hospitals of Geneva

Urinary tract infection: old & new strategies

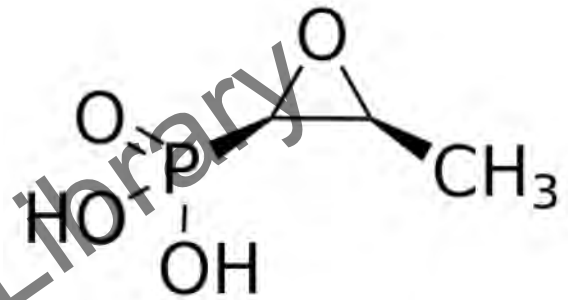


Uncomplicated lower urinary tract infections: trends in antibiotic use

Genevan guidelines 2010
European guidelines 2011
US guidelines 2011
Swiss guidelines 2013



Fosfomicin trometamol

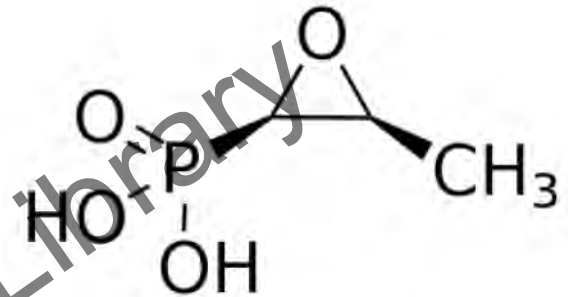


Cis-1,2-epoxypropyl phosphonic acid

- Phosphonic acid derivative
- Isolated in 1968 from Streptomyces strains
- Available since 1971 (Spain)
- Oral fosfomicin approved only for the treatment and prophylaxis of lower urinary tract infections



Fosfomicin trometamol



Cis-1,2-epoxypropyl phosphonic acid

- Mechanism of action
 - Inhibits the MurA enzyme (peptidoglycan synthesis)
 - Bactericidal
- Spectrum of activity
 - Gram-negative
 - E.coli, Proteus sp., Serratia, Salmonella typhi*
 - Gram-positive
 - S. aureus, S. epidermidis, E. faecalis*

EXCEPT

Pseudomonas sp.

Acinetobacter sp.

Listeria monocytogenes

Bacteroides fragilis

Fosfomycin trometamol: pharmacokinetics

- Bioavailability: 34 – 41%
- Elimination half-life: 5.7 hours
- Protein binding: negligible
- Excretion: primarily urine, unchanged
- Distribution: favorable
 - Serum, soft tissues, lung, bone, cerebrospinal fluid, heart valves, prostate

Fosfomycin trometamol: pregnancy & lactation

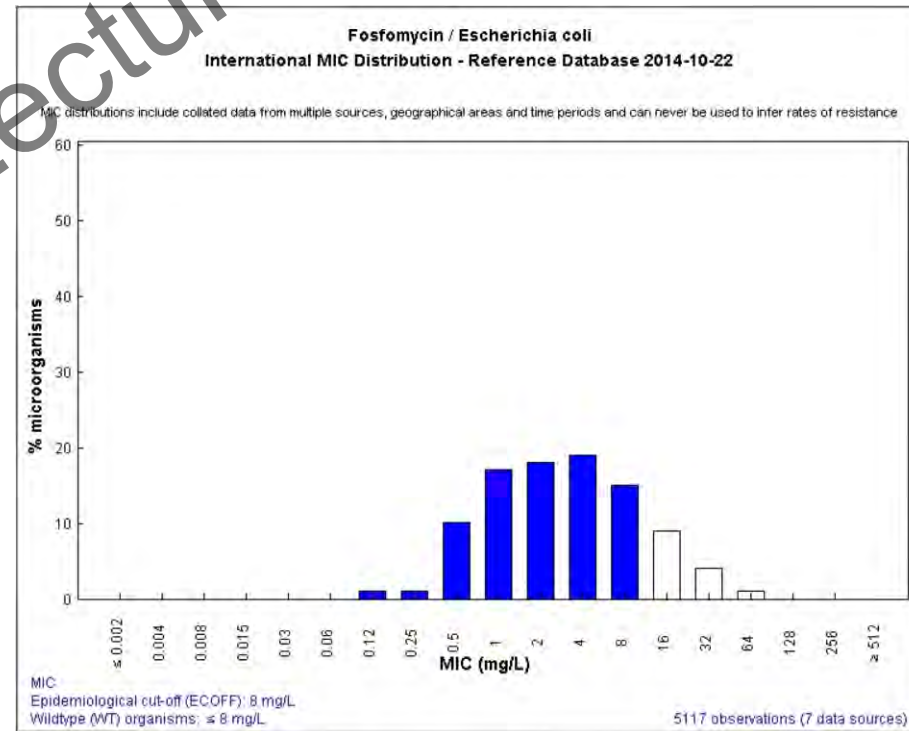
- Crosses placental barrier
- FDA pregnancy category B
 - No teratogenicity/ adverse fetal effects observed in humans or animals
- Fosfomycin disodium (iv)
 - Low levels found in human milk (8% of serum levels)

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Fosfomicin trometamol: resistance

Multiple resistance mechanisms

- Uptake systems inhibited
- “Fosfomicin resistance enzymes”
 - fosA & fos X: attack carbon 1
 - fosC adds a phosphate group
- Though some mechanisms are plasmid-encoded, as yet little cross-resistance with other antibacterials



Fosfomycin trometamol: resistance

- *E. coli* resistance rates 3- 10%
 - Spain (single-center): 95 – 100% susceptibility
 - Korea: 95%
 - Africa: 100%
- But many data collected before 2012...

J Antimicrob Chemother 2010; **65**: 2459–2463
doi:10.1093/jac/dkq346 Advance Access publication 16 September 2010

Journal of
Antimicrobial
Chemotherapy

Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli*

Jesús Oteo¹, Verónica Bautista¹, Noelia Lara¹, Oscar Cuevas¹, Margarita Arroyo¹, Sara Fernández¹, Edurne Lázaro², Francisco J. de Abajo³ and José Campos^{1,4*} on behalf of the Spanish ESBL-EARS-Net Study Group†

Fosfomycin trometamol: efficacy

Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women

- E. Van Pienbroek, J. Hermans, A.A. Kaptein and J.D. Mulder

1993 double-blind randomized controlled trial (RCT)

- 231 women with lower UTI
- Fosfomycin 3 g po vs. nitrofurantoin 50 mg qid x 7 days
- Outcomes at 6 weeks post-enrollment:
 - Clinical cure: 85% fosfo vs. 82% nitro
 - Side effects (day 9): 15% fosfo vs. 9% nitro
- Selection, performance, reporting biases...

Fosfomycin trometamol: efficacy

- 1997 US double-blind RCT

>1000 women with lower UTI

Fosfomycin vs TMP/SMX vs ciprofloxacin

	Fosfomycine (N=771)	TMP/SMX (N=197)	Ciprofloxacin (N=222)
Microbiologic success	77%	93%	93%
Clinical success	70%	94%	96%

Forest Laboratories, 1997:

- **“Single-dose clinical efficacy in more than 770 female patients (82% microbiological eradication, 70% clinical success)”**

RE: **NDA # 50-717**
Monurol (fosfomycin tromethamine) Sachet
MACMIS ID# 5544

Dear Mr. Rashkovsky:

Letter from FDA to Forest Laboratories, 1997

Reference is made to Forest Laboratories, Inc.'s (Forest) journal advertisement (SAP #2649) for Monurol that appears in the June 1, 1997, Vol 126, edition of Annals of Internal Medicine and brochure #SAP 2648. The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed the advertisement and promotional labeling and finds them to be in violation of the Federal Food, Drug, and Cosmetic Act and the applicable regulations. Specifically, DDMAC objects to the following claim:

“Single-dose clinical efficacy in more than 770 female patients (82% microbiological eradication, 70% clinical success)”

This claim is misleading because it fails to reveal material facts in light of the efficacy representation. Specifically, the ad that contains this claim fails to mention that the claim is based on a comparative study. It also fails to mention the efficacy rates of the other products used for efficacy comparison in the clinical study, or the efficacy evaluation time points, as stated in the approved product labeling (PI).

Preserving old antibiotics for the future

Assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent drugs



AIDA WORK PACKAGE 2: RCT NITROFURANTOIN VS. FOSFOMYCIN

- Phase 4, multicenter open-label trial
 - Geneva, Switzerland / Lodz, Poland / Tel Aviv, Israel
- Launched in October 2013
- 600 women with acute lower UTI

Nitrofurantoin
100 mg tid x 5 days

vs.

Fosfomycin
3 g single dose

Superiority trial

Preserving old antibiotics for the future

Assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent drugs



AIDA WORK PACKAGE 2: RCT NITROFURANTOIN VS. FOSFOMYCIN

- Stay tuned for results...

Nitrofurantoin
100 mg tid x 5 days

vs.

Fosfomycin
3 g 2-dose approach??

Superiority trial

Preserving old antibiotics for the future

Assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent drugs



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