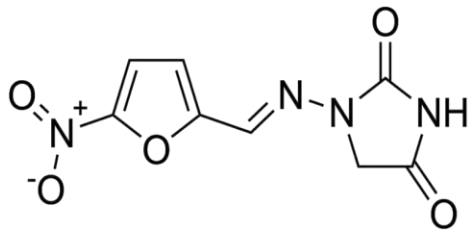

Slides on the meta-analysis of prophylaxis are deleted, because the data were too preliminary

Nitrofurantoin

What do we know?

Anouk Muller
Clinical Microbiologist, MCHaaglanden, The Netherlands

AIDA Grant Health-F3-2011-278348

History

- Developed in the 1940s
- Approved in 1953 by the FDA

Wikimedia.org

- Traditional uses:
  - Gram-negative cystitis/catheter-associated bacteriuria
  - Asymptomatic bacteriuria (in pregnancy)
  - Enterococcal cystitis

Gyssens, p.1089,2006

The use over time

From presentation of A. Huttner, AIDA meeting 2012

- Used from 1953
- Decreased use due to toxicity issues in the 1970s
- Increase use due to resistance problems to the alternative antibiotics

Recent warning in the French guidelines

- Warning on toxicity for prophylaxis

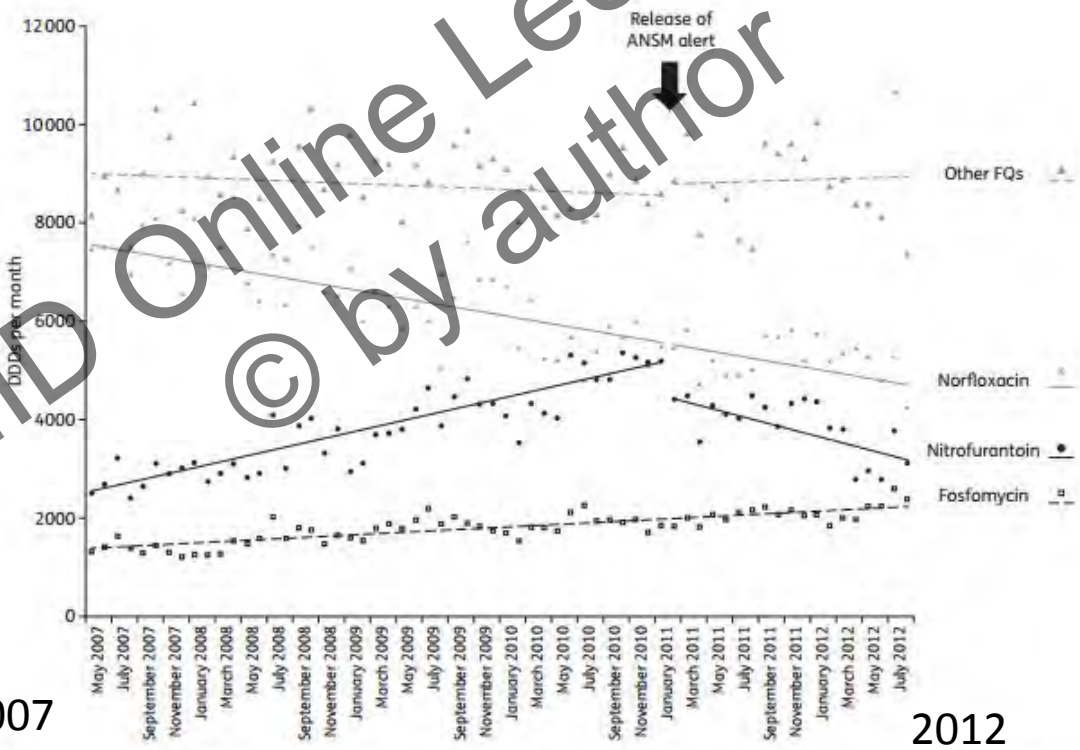

Figure 1. Graphical representation of the segmented regression modification of antibiotic use before and after the release of the ANSM alert. FQs, fluoroquinolones.

C. Slekovec, J. Leroy, A. Huttner et al. JAC, p282,2014

Different Dosages used

- treatment
  - 4 times daily 50mg
  - 2 times daily 100mg
  - 4 times daily 100mg
- prophylaxis
  - 4 times daily 50mg (short-term)
  - Once daily 50mg
  - Once daily 75mg
  - Once daily 100mg

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Current medical knowledge

- Pharmacokinetics
- Pharmacodynamics
- Clinical studies

Pharmacokinetics

4. Pharmacokinetics				
Dosage (mg)	**100 mg**			
Cmax (mg/L)	<2 after 1-4 h			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	0.5-1			
AUC24h (mg.h/L)				
Fraction unbound (%)	25-50			
Volume of distribution (L/kG)	0.6			
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption >95 % • Concentration in urine >100 mg/L			
References	• Mazzei et al Int J Ant Agents 2006; 28 suppl 1: 35-46. • Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 396-8.			

- Oral administration

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Nitrofurantoin: Rationale for the EUCAST clinical breakpoints, version 1.0

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Pharmacokin

But…. Wasn't there someting about macro or microcrystals???

4. Pharmacokinetics					
Dosage (mg)	**100 mg**				
Cmax (mg/L)	<2 after 1-4 h				
Cmin (mg/L)					
Total body clearance (L/h)					
T ½ (h), mean (range)	0.5-1				
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- Oral administration

Nitrofurantoin: Rationale for the EUCAST clinical breakpoints, version 1.0,2010

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Does the size of the crystals matter?

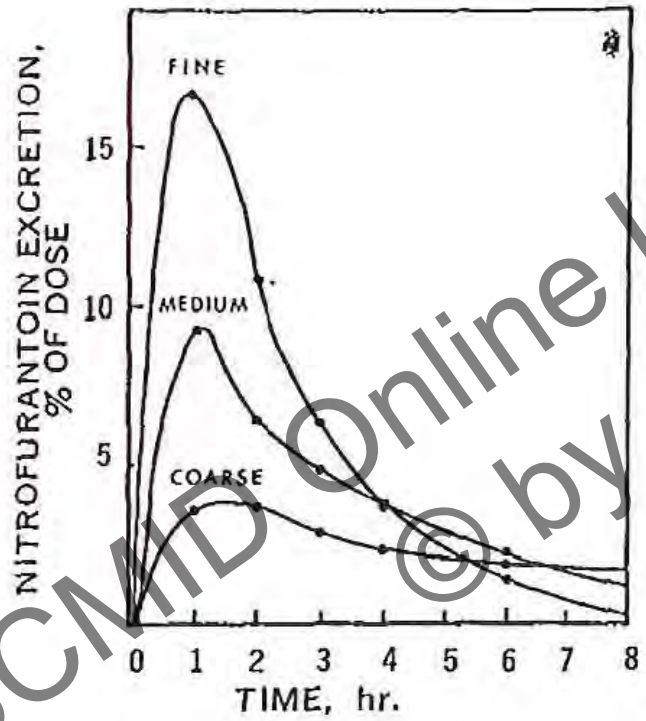

Fig. 1—Effect of crystal size of orally administered nitrofurantoin on urinary recovery rate in the rat. Key: coarse, 50–80 mesh (300–180 μ); medium, 80–200 mesh (180–75 μ); fine, 200 mesh to micronized (75–10 μ or less).

- Study in rats
- The smaller the size of the crystals, more nitrofurantoine is excreted in the urine.

Paul 1967 J Pharm Sc 56(7); p882-5

humans

TABLE II—SUMMARY OF CRITERIA MEASURED IN HUMAN VOLUNTEERS RECEIVING VARIOUS SIZES OF NITROFURANTOIN CRYSTALS[a]

Crystal Size[b] of Nitrofurantoin	(1) Max. % Excreted in Any 2-hr. Period	(2) Av. Time of Max. % Excretion, hr.	(3) Max. Urinary Concn. Attained, mg./L.	(4) Av. Time Max. Urinary Concn. Attained, hr.	(5) Total % of Initial Dose Excreted
50–60 mesh	8.3	4.9	83	5.5	19.6
80–120 mesh	12.9	4.6	124	5.0	29.8
140–200 mesh	16.6	3.8	159	4.1	32.3
200–400 mesh	17.8	3.6	156	3.4	35.4
Marketed nitrofurantoin tablets (Provide fine crystals in the 10 μ range)	20.0	3.6	151	3.0	36.1

small

[a] Each value based on 15 complete individual studies—no pooling of samples. Exceptions: 10 individuals only were available from same population for 200–400 mesh and 14 for tablets. [b] Size checked by microscopic measurement.

Paul 1967 J Pharm Sc 56(7); p882-5

Mean cumulative excretion

Fasting vs nonfasting

macrocrystal **microcrystal**

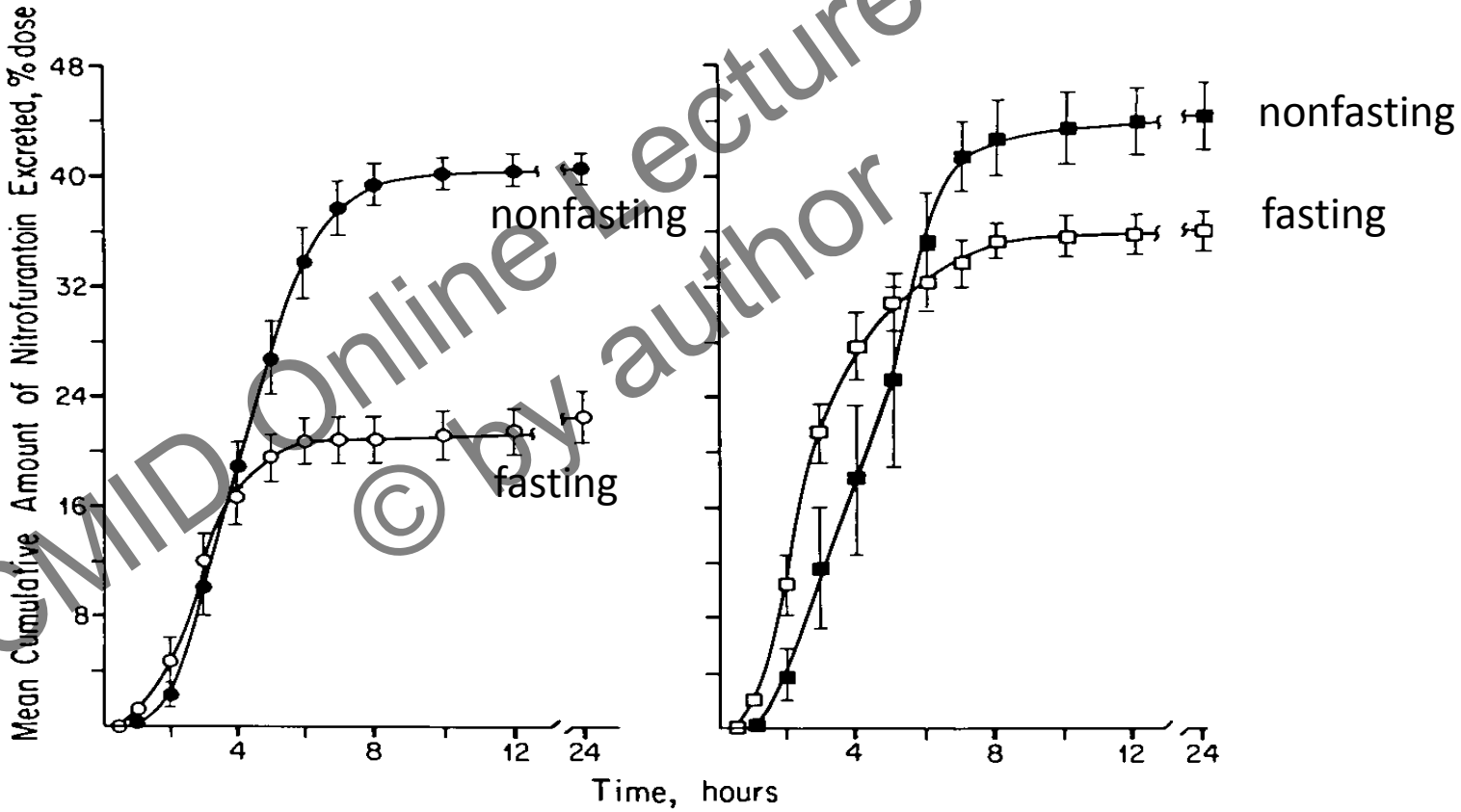

Fig. 1. Mean cumulative urinary excretion of nitrofurantoin after oral administration of a 100 mg macrocrystalline capsule to fasting (○) and nonfasting (●) subjects, and a 100 mg microcrystalline tablet to fasting (□) and nonfasting (■) subjects. N = 4; Vertical bars represent standard errors of the mean.

Summary of pharmacokinetics

- Well absorbed (primarily small intestine)
- Absorption enhanced by food
- Macrocrystalline dissolves more slowly ("slow release")
- Drug accumulates in urine
- Low serum concentrations
- Excretion by kidney and inactivated in body
- Differences between the formulations

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Next step

- To discuss the results of the pharmacokinetics we need some pharmacodynamics

Figure obtained from: http://ydyc.org/media/funny-pictures/conversation-between-friends/

Pharmacodynamics

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5. Pharmacodynamics				
*f*AUC/MIC for bacteriostasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Pharmacodynamic parameters for nitrofurantoin have not been determined. • Cells are left empty when data are not readily available.			
References				

Nitrofurantoin: Rationale for the EUCAST clinical breakpoints, version 1.0,2010

Pharmacodynamics in literature

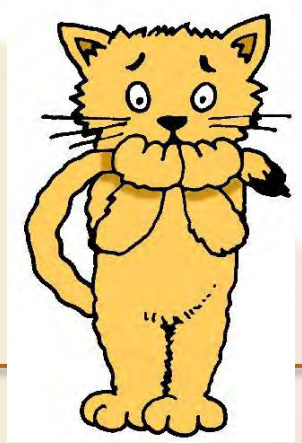
- Currently one in vitro-trial available
- 2015 JAC Lindgren et al., p1076
  - PD against common uropathogens
  - Used t1/2 of hour in plasma, but value in urine is unknown
  - Time kill curves in MH broth
  - Highly effective against E coli and S saprophyticus
  - Slower killing against E faecium
  - E coli: T>MIC best correlation with efficacy
  - BUT: Only one dose used. Therefore, no definitive conclusions can be drawn
- Futher studies on the PD are currently being performed

So, no consensus on the PK/PD index, yet.

Gaps

- Detailed PK information on different formulations
- Pharmacokinetics of nitrofurantoin in the elderly
- Consensus on the PK/PD-target

- So actually, we need the correct or optimal dose



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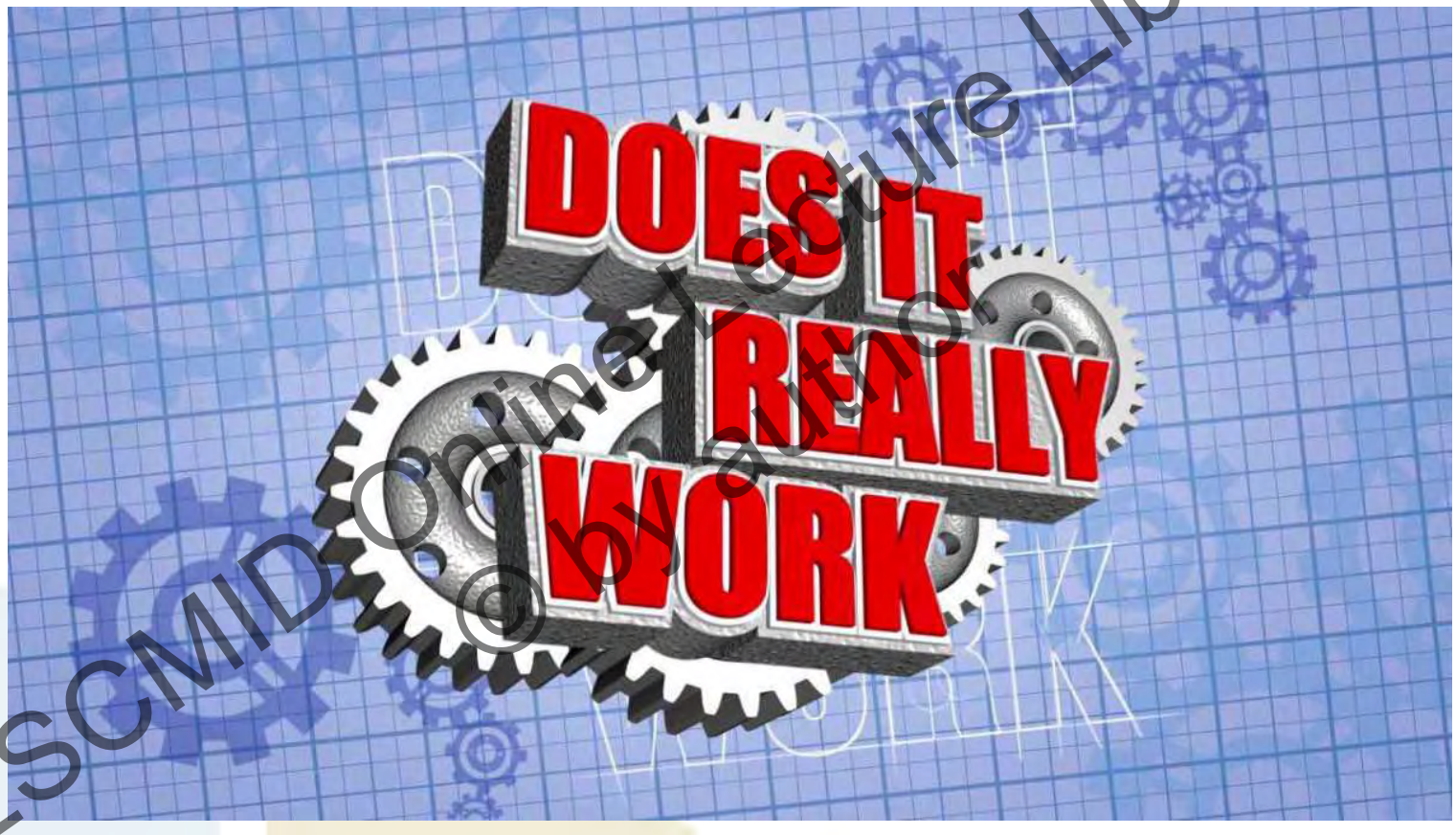

Clinical trials in the literature

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Meta-analysis

- Treatment for UTI
- Prophylaxis for UTI

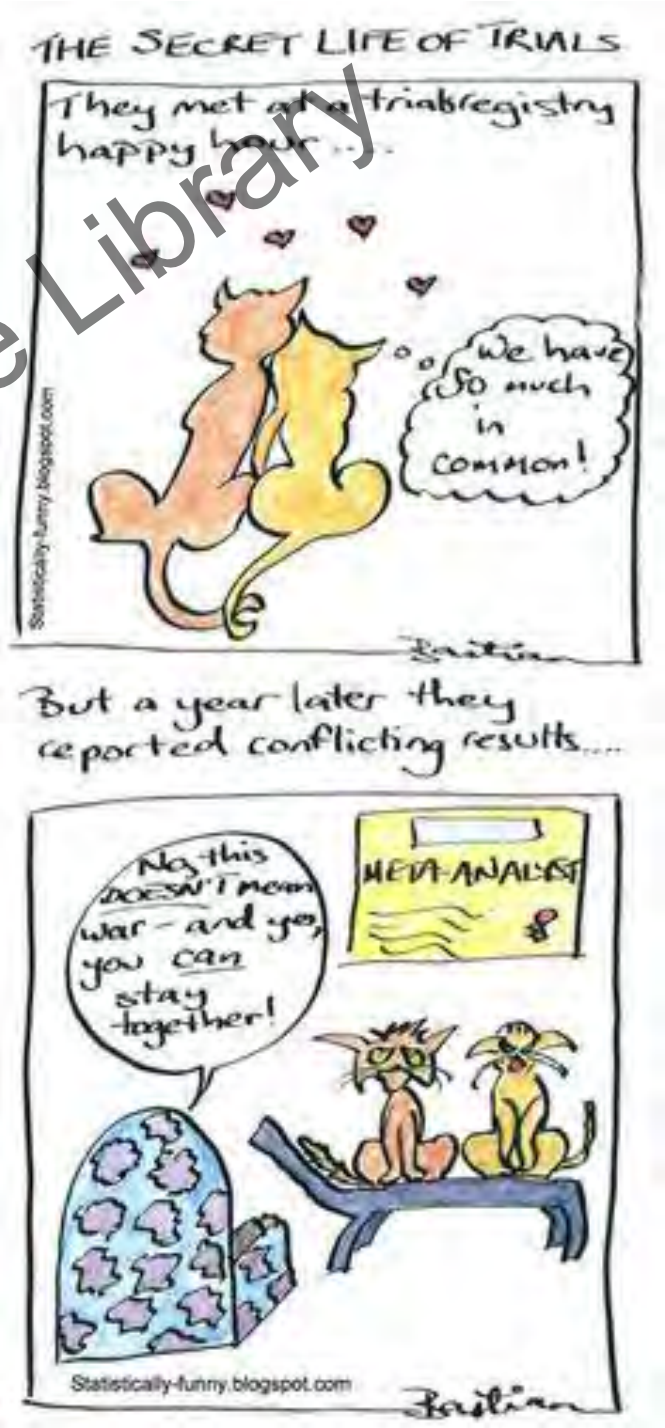

Figure:Medical humour on Pinterest | Medical, Co

Treatment of UTI

Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials

Angela Huttner[1]*, Els M. Verhaegh[2], Stephan Harbarth[1], Anouk E. Muller[3], Ursula Theuretzbacher[4] and Johan W. Mouton[5,6]

Table 1. Inclusion criteria for studies considered for the review of nitrofurantoin's efficacy and toxicity for therapy of lower UTI

	Included:	Excluded:
Study design	• controlled clinical trials	• uncontrolled trials
Participants	• human patients of all ages and both genders in all settings	• animal studies • *in vitro* studies
Interventions	• oral nitrofurantoin at any dose ≤14 days for treatment of UTI[a]	• nitrofurantoin combined with another antibacterial targeting uropathogens • nitrofurantoin for prostatitis • nitrofurantoin for prophylactic purposes • nitrofurantoin for treatment of conditions outside the urinary tract
Comparators	• placebo • no treatment • a different drug • nitrofurantoin at a different dose, frequency or duration	• nitrofurantoin with another antibacterial targeting uropathogens

[a]In literature published before 1990, asymptomatic bacteriuria was often considered sufficient for a diagnosis of UTI.

J Antimicrob Chemother 2015; 70: 2456–2464

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search

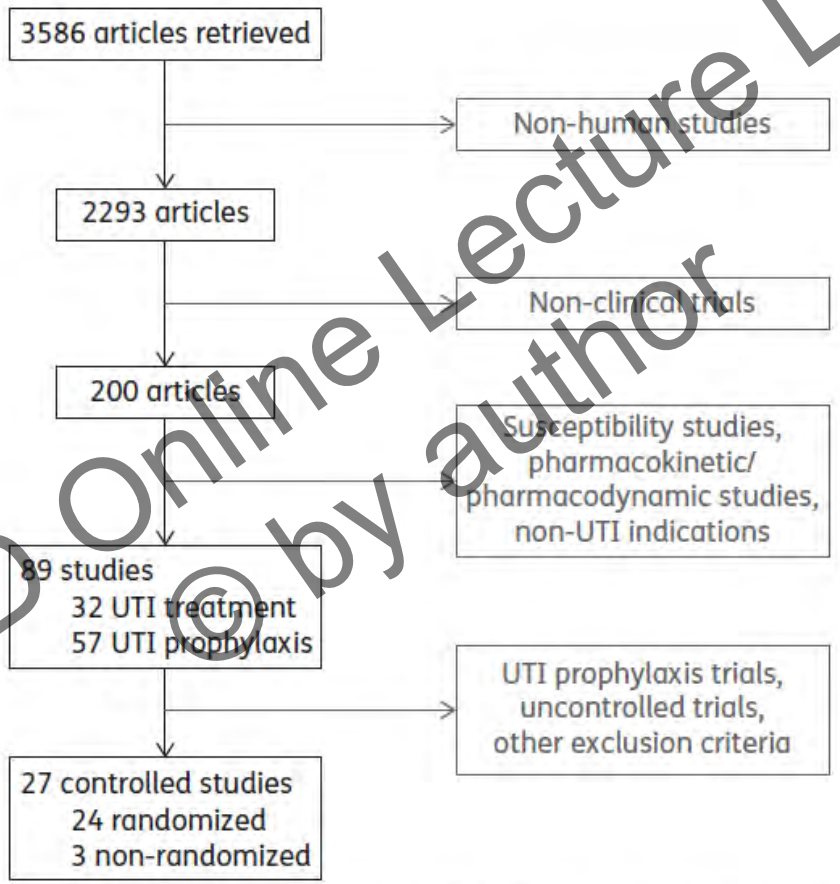


Figure 2. Flow chart for the retrieval of studies evaluated in the review of nitrofurantoin's efficacy and toxicity.

J Antimicrob Chemother 2015; 70: 2456–2464

Clinical efficacy in treatment of UTI

Not significant for one of the subgroups

Test for overall effect P=0.56

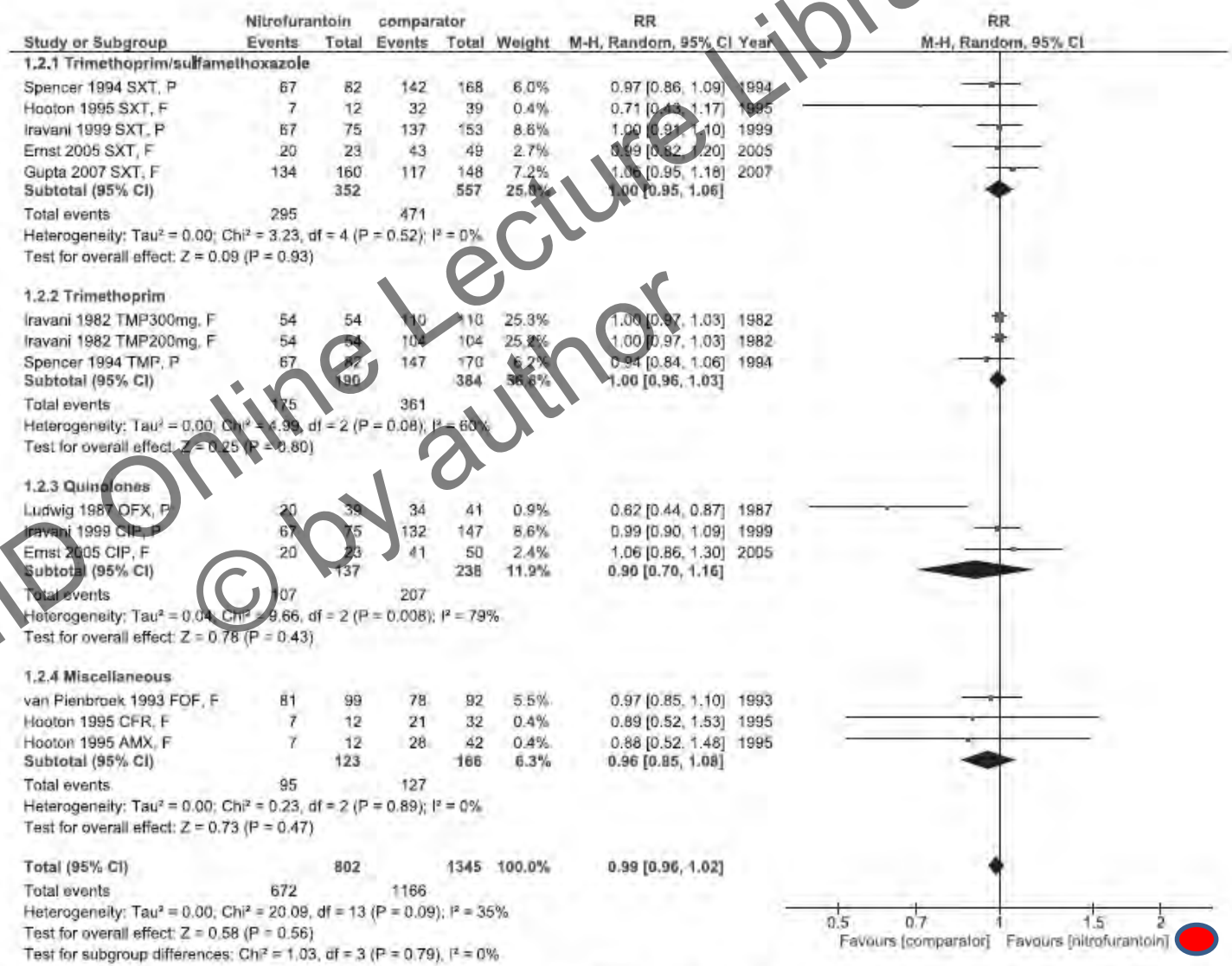


Figure 3. Results of the meta-analysis for clinical efficacy. F, fair; P, poor (no studies were deemed to be of high or excellent quality); AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

JAC 2015; 70: 2456–2464

Microbiologic cure of treatment UTI

Only subgroup Quinolones significant different

Quinolones are better compared to nitrofuranoin P=0.02

Test for overall effect: Siginificant in favour of comparator (p=0.002)

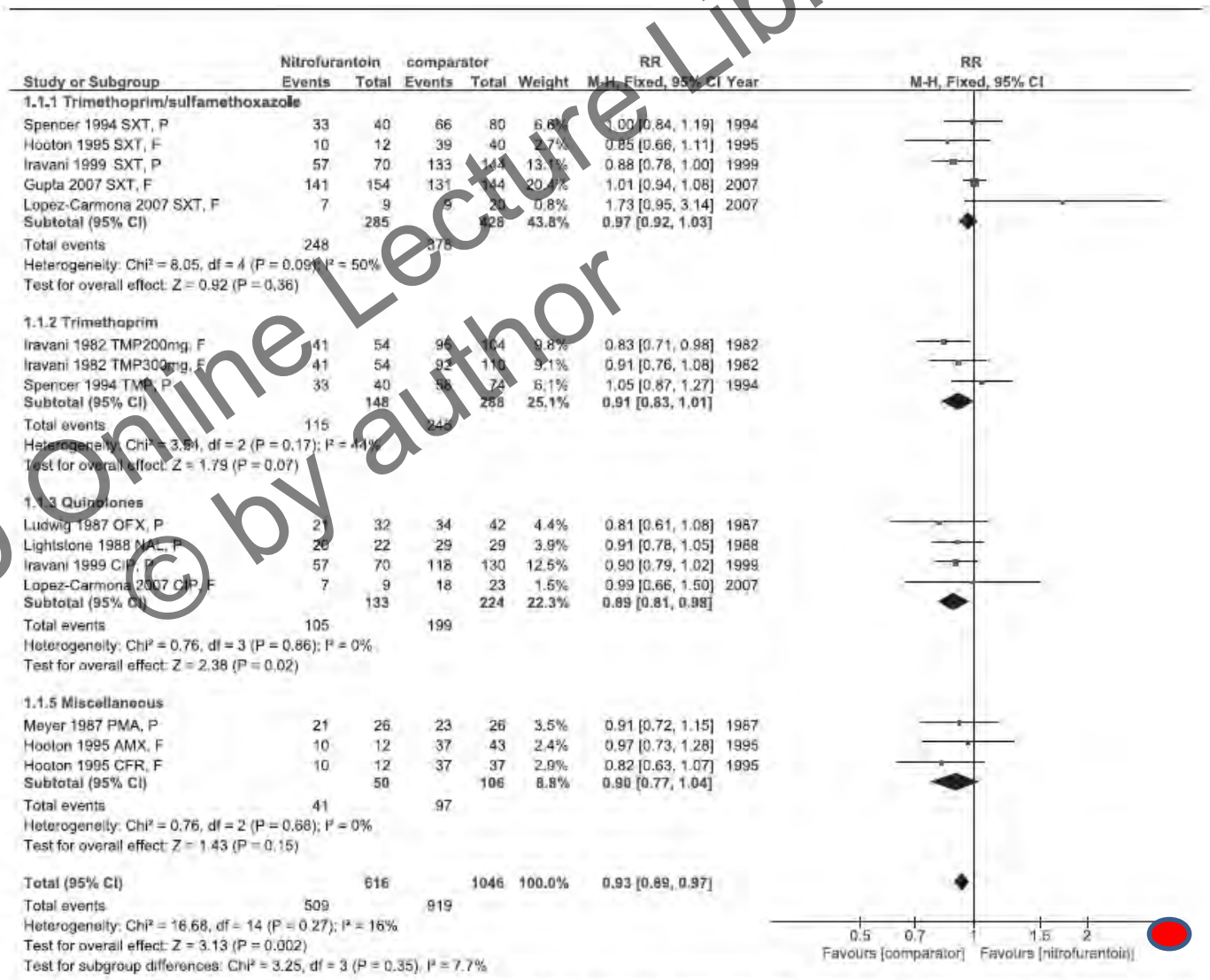


Figure 4. Results of the meta-analysis for microbiological cure. F, fair; P, poor; AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

JAC 2015; 70: 2456–2464

Treatment of UTI

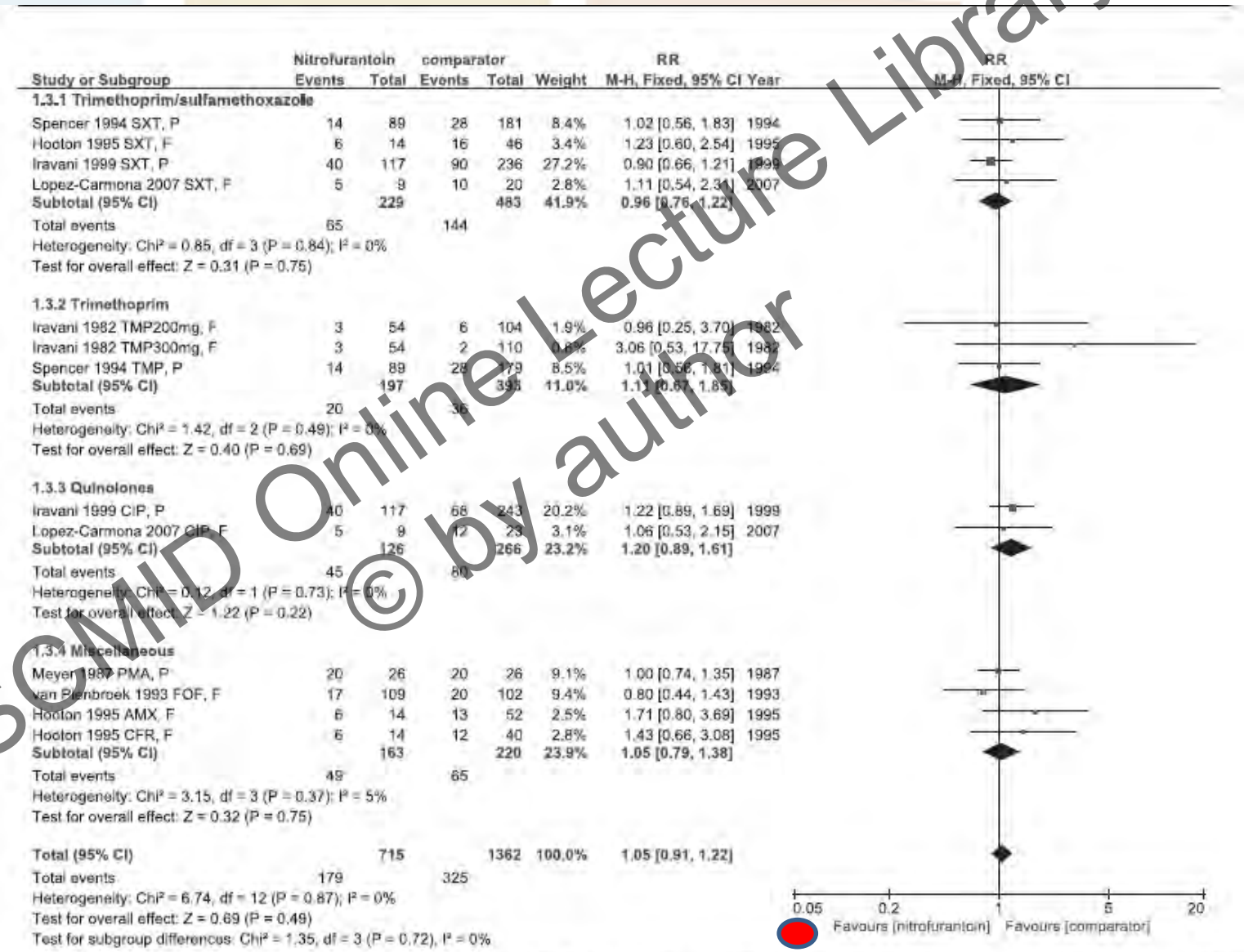
- Clinical cure rates comparable to the other drugs: between 50-100%
- Micobiological effect: 40-90%: inferior to the comparators
- Placebo: ~40% cure both clinical and microbiological for the treatment of UTI

toxicity

- Short term use:
  - nausea, abdominal discomfort and headaches
  - fatigue
  - 5-16% of patients (one study 49%)

- Long term use:
  - Same as for short-term use
  - Taking nitrofurantoin for months or years
  - pulmonary fibrosis and hepatotoxicity
  - Fatalities have been described

Adverse effect nitrofurantoin treatment



No placebo's

P=0.49

Figure 5. Results of the meta-analysis for adverse effects. F, fair; P, poor; AMX, amoxicillin; CFR, cefadroxil; CIP, ciprofloxacin; FOF, fosfomycin; NAL, nalidixic acid; OFX, ofloxacin; PMA, pipemidic acid; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole.

Conclusion

- PK:
  - many data are lacking
  - Optimal dose unknown
- PD: no consensus on the PK/PD index
- Clinical trials:
  - Nitrofurantoin is effective
  - Both in treatment and prophylaxis
  - Be carefull for side-effects in long-term prophylaxis

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acknowledgment

- FP7 project AIDA

- Angela Huttner
- Els Verhaegh