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Collateral effects of antibiotics : adverse effects and drug interactions

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Back to school :

a little bit of theory

What are we speaking about ?

- Adverse event :
  harm in a patient administered a drug,
  but not necessarily caused by the drug

- Adverse drug reaction (abbreviated ADR) :
  harm directly caused by a drug at normal doses

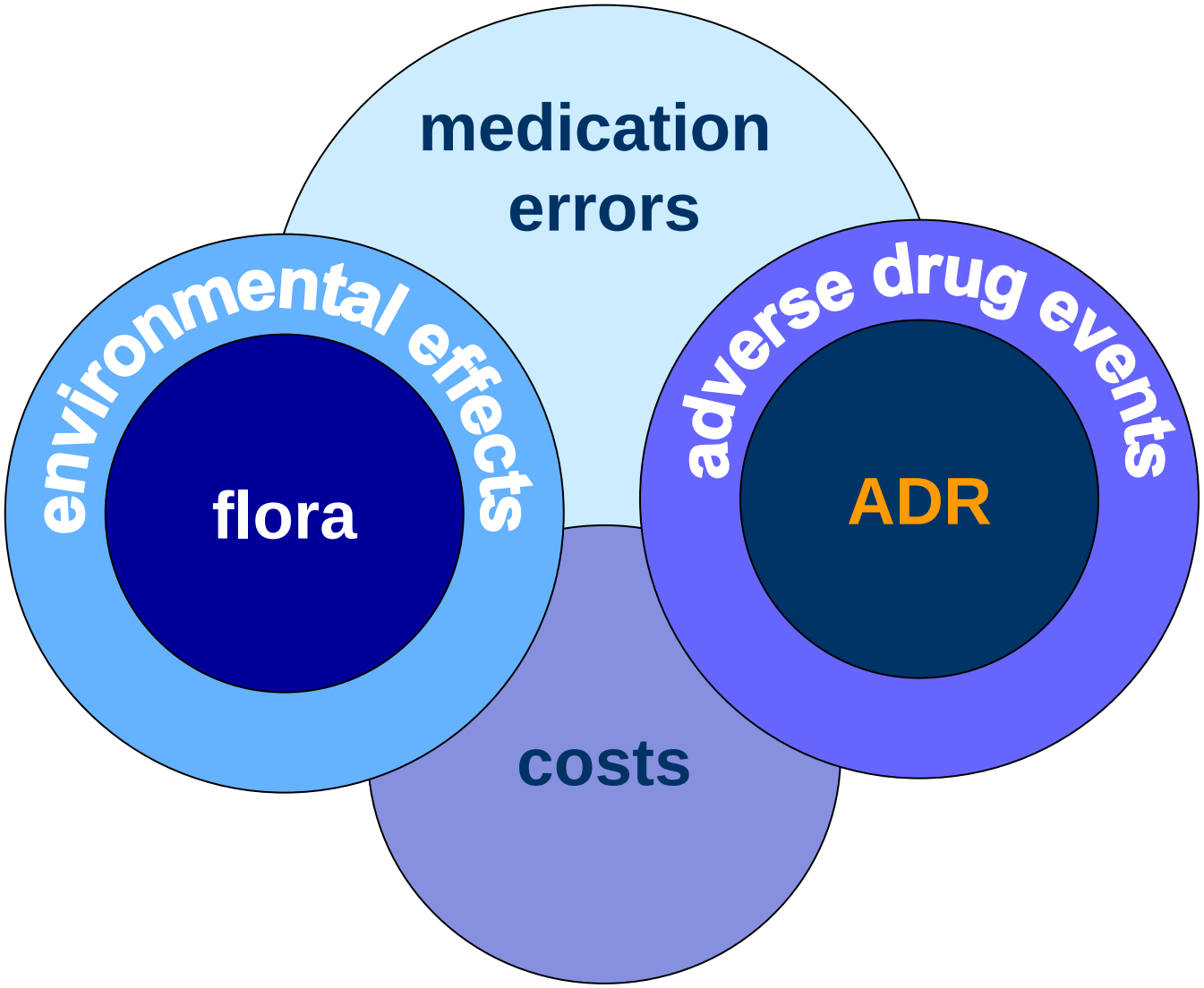
⇨ **harm has occured**

- Side effect:
  - a usually predictable or dose-dependent effect of a drug that is not the principal effect for which the drug was chosen
  - the side effect may be desirable, undesirable, or inconsequential

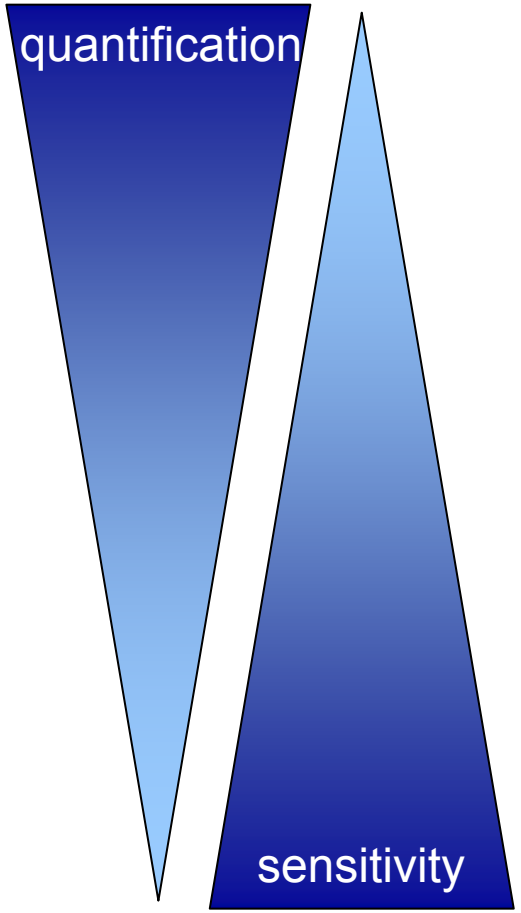
⇨ **harm may have occured**

Nebeker et al., Ann Intern Med. (2004) 140:795-801

ADR within collateral effects



How to detect ADR ?

type	characteristics	interest
clinical trials	▪ 5000-10,000 patients ▪ comparison with other drugs used in same indications ▪ no detection of very rare effects	
post-marketing studies	▪ larger number of patients ▪ less controlled ▪ possible detection of rare effects	
spontaneous reports to pharmacovigilance systems	▪ no estimation of incidence possible ▪ largely dependent on GP attention and on number of prescriptions	
case - non case studies	▪ estimation of risk for rare ADR	
case reports	▪ often only source for very rare ADR	

How to categorize ADR ?

- Type :

What about antibiotics ?

type	definition
A	augmented pharmacologic effects (dose dependent and predictable)
B	bizarre effects (or idiosyncratic) (dose independent and unpredictable)
C	chronic effects
D	delayed effects
E	end-of-treatment effects
F	failure of therapy

- **PK issues (tissue accumulation)**
- **lack of specificity for procaryotic target**

- **often rare but serious**
- **not detected before large-scale usage**

- **clinical or microbiological**
- **emergence of resistance**

Rehan et al., Eur. J. Int. Med. (2009) 20: 3–8

How to categorize ADR ?

- Severity :

What about antibiotics ?

Serious ADR
death
life-threatening
hospitalization (initial or prolonged)
disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life
requires intervention to prevent permanent impairment or damage
congenital anomaly

→ **often related to unpredictable effects**

→ **importance of monitoring**

→ **pregnancy as a CI for most AB classes**

http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm

How to categorize ADR ?

- Relatedness to drug :

degree	criteria	Response to dechallenge
certain	▪ plausible time relationship to drug administration ▪ cannot be explained by concurrent disease / drugs	clinically plausible
probable likely	▪ reasonable time sequence to drug administration ▪ unlikely to be attributed to concurrent disease / drugs	clinically reasonable
possible	▪ reasonable time sequence to drug administration ▪ could also be explained by concurrent disease / drugs	lacking or unclear
unlikely	▪ temporal relationship to drug administration makes a causal relationship improbable ▪ other drugs / underlying disease provide plausible explanations	-

need to be critically examined in post-marketing studies

Nebeker et al., Ann Intern Med. (2004) 140:795-801

How to categorize ADR ?

- Frequency :

definition	frequency
very frequent	≤ 1/10
frequent	≤ 1/100
not frequent	≤ 1/1,000
rare	≤ 1/10,000
very rare	≤ 1/100,000

Importance of all types
of post-marketing surveillance systems
(phase IV)

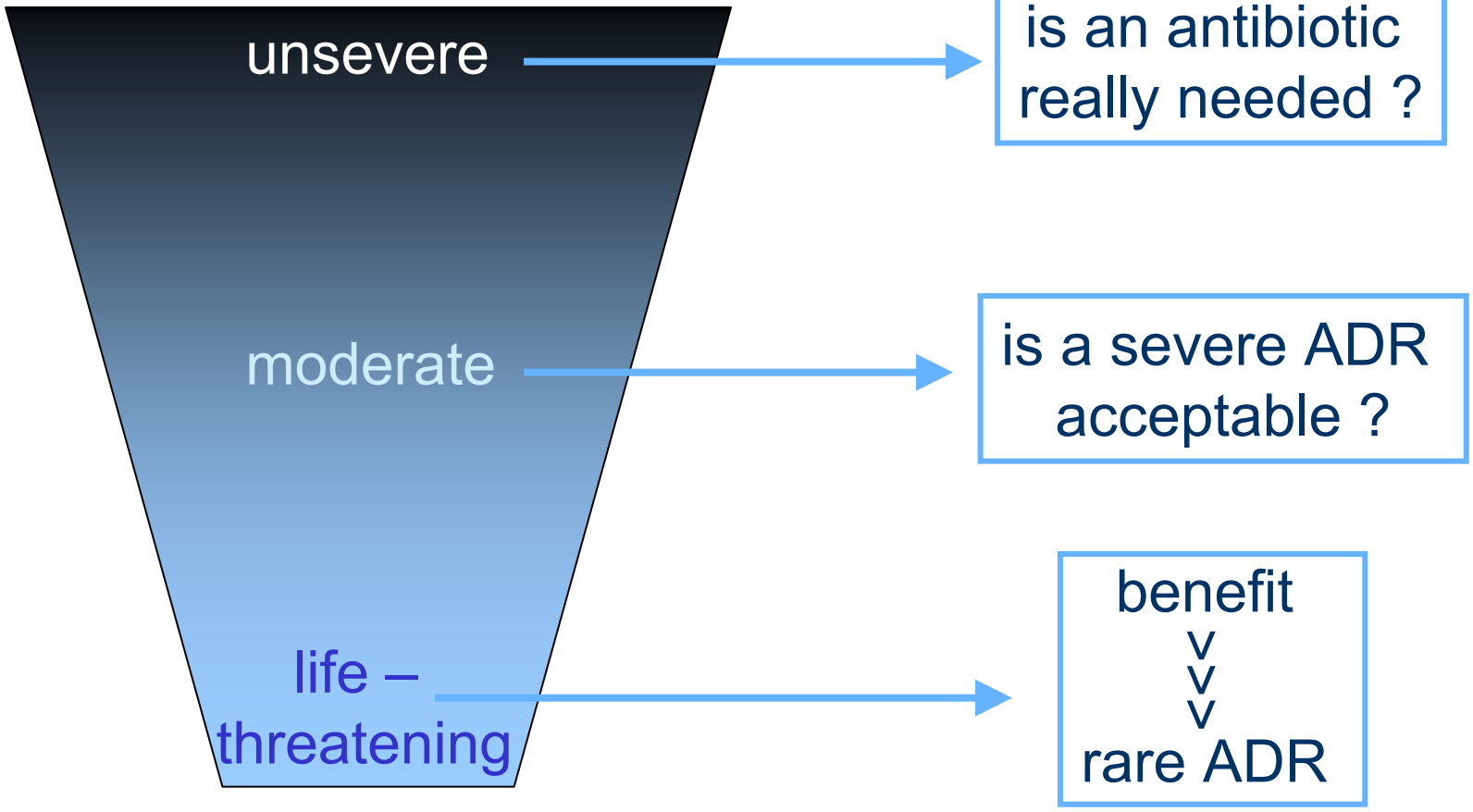
Which type of ADR can limit antibiotic use ?

weigh the benefit-risk ratio !

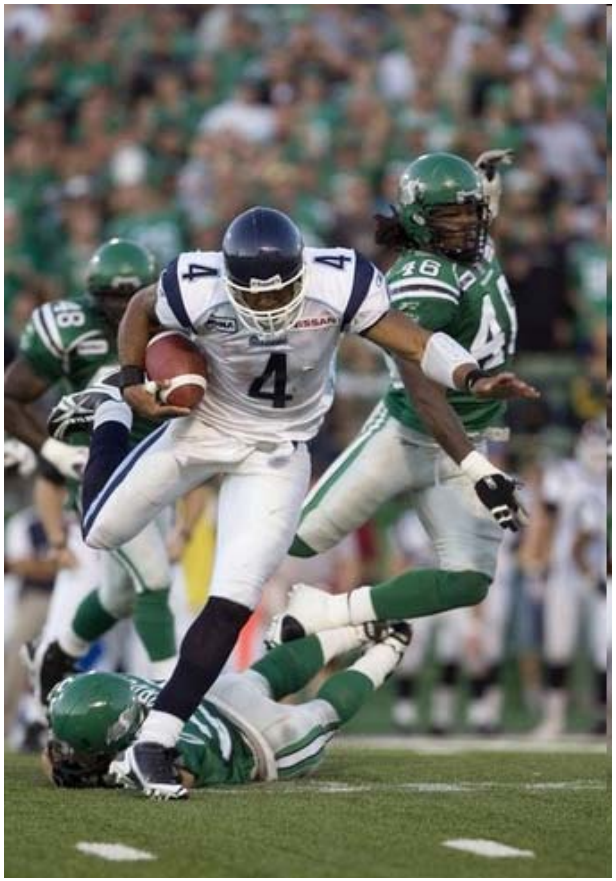
Which type of ADR can limit antibiotic use ?

benefit :
depends on
the severity of infection

risk :
what shall you accept ?

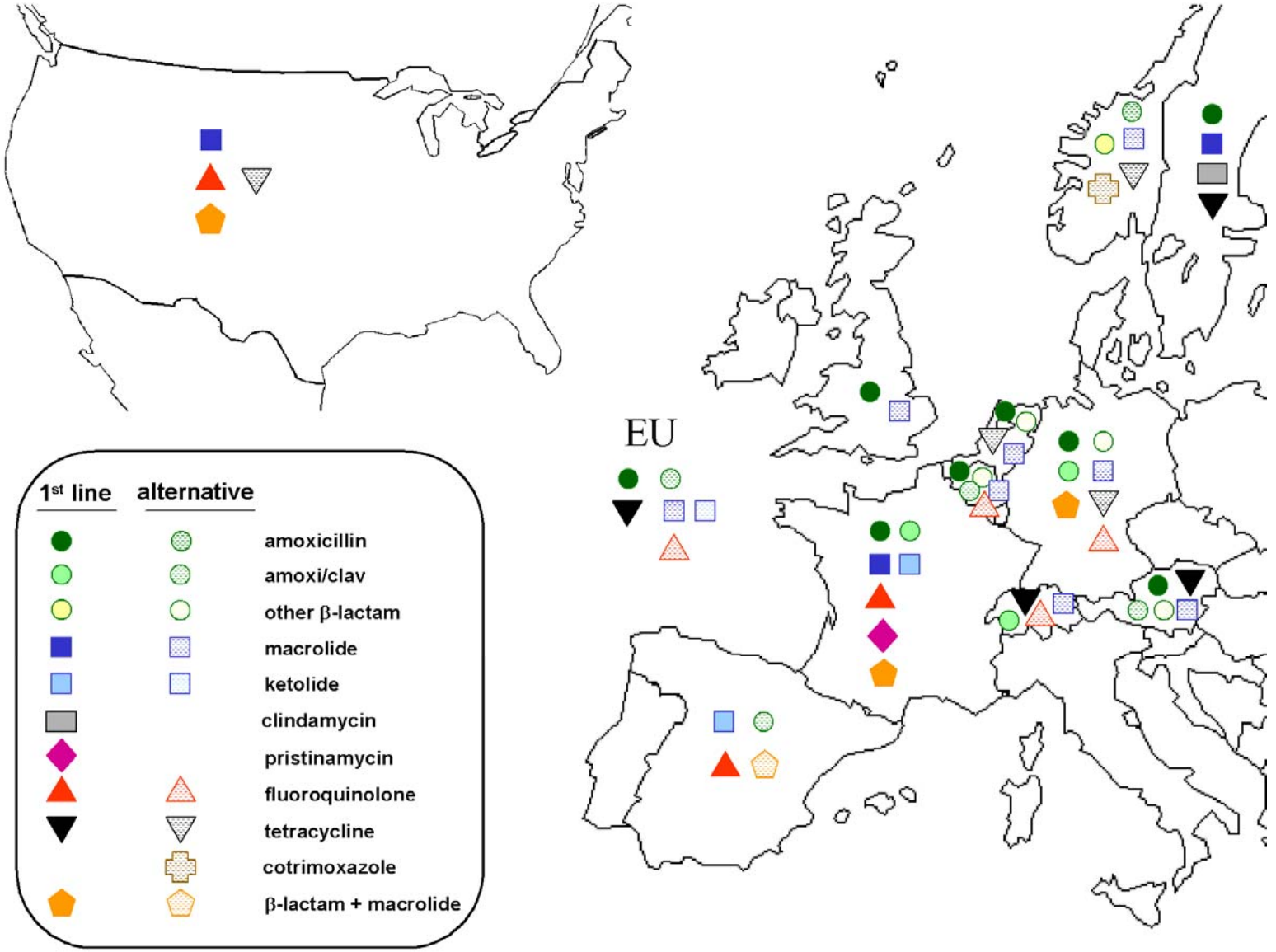


Safety profile
of the most widely used antibiotics



Toronto argonaut

Antibiotics recommended in CAP (outpatients)



Carbonnelle et al., ICC (2009) poster 315

ADR with antibiotics recommended in CAP (SmPC)

Class	Most frequent or serious ADR
β-lactams (AMX-CLAV)	• Anaphylactic reactions • *Clostridium difficile* -associated colitis • Digestive tract: diarrhoea, nausea • Hepatic toxicity, including hepatitis and cholestatic jaundice • CNS : agitation, anxiety, insomnia, confusion, convulsions, …
Macrolides (CLR/AZI)	• Drug interactions (CYP450) • *Clostridium difficile* -associated colitis • Digestive tract: diarrhoea, nausea, vomiting, abnormal taste • Hepatic toxicity, including hepatitis and cholestatic jaundice • Cardiac toxicity (arrhythmias, TdP) • CNS: headache, confusion, …
Ketolides (TEL)	• Visual disturbance • Loss of consciousness • Respiratory failure in patients with myastenia gravis
Tetracyclines	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile* -associated colitis • Digestive tract: anorexia, dysphagia, nausea, vomiting, diarrhoea, … • Esophagitis and esophageal ulcerations • Hepatotoxicity • Photosensitivity • Blood cells: hemolytic anaemia, neutro-/ thrombocytopenia, eosinophilia

ADR with antibiotics recommended in CAP (SmPC)

Class	Most frequent or serious ADR
Fluoroquinolones (LVX/MXF)	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile* -associated colitis • Digestive tract: nausea, diarrhoea • Musculoskeletal (tendinopathies) and cartilage toxicity • Prolongation of the QTc interval and isolated cases of torsade de pointes • Hematologic toxicity • Hepatotoxicity • CNS effects: headache, insomnia, dizziness, convulsions • Peripheral neuropathy • Photosensitivity
Sulfamides (SMX/TMP)	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile* -associated colitis • Digestive tract: anorexia, dysphagia, nausea, vomiting, diarrhoea, … • Blood cells: agranulocytosis, anemia, thrombocytopenia, leukopenia, neutropenia, hypoprothrombinemia, methemoglobinemia, eosinophilia • Metabolic and Nutritional: hyperkalemia

Carbonnelle et al., ICC (2009) poster 315

Examples :
2 life-threatening ADR
critically examined by registration authorities

- hepatotoxicity
- cardiotoxicity

Toronto City Hall

Hepatotoxicity

- Usually **idiosyncratic** (can be associated with other allergic reactions). [1]
- **Clavulanic acid**: genetic deficiency in glutathione S-transferases ? [2] (longer latency period than other antibiotics…)
- **Macrolides**: related to reactive metabolites (nitrosoalkanes) that covalently bind to proteins, forming modified antigens (immunoallergic hepatitis) [3]
- **Tetracyclines**: related to inhibition of mitochondrial β-oxidation of fatty acids [4]
- **Fluoroquinolones**: remains anecdotal and unpredictable,[1] except for for molecules with substituent-generating reactive intermediates
  - difluoroaniline (temafloxacin and trovafloxacin) [5]
  - cyclopropylamine (trovafloxacin; for which co-exposure to lipopolysaccharide may also be critical) [6]

1. *Robles & Andrade, Rev Esp Quimioter. (2008) 21:224-33*
2. *Lucena et al., Hepatology (2008) 48:588-96.*
3. *Pessayre et al., J Antimicrob Chemother (1985) 16 Suppl A: 181-94*
4. *Freneaux et al., Hepatology (1988) 8: 1056-62*
5. *Blum et al., Clin Infect Dis (1994) 18: 946-50; Chen et al., N Engl J Med (2000) 342:359-60; Lucena et al., Clin Infect Dis (2000) 30: 400-1*
6. *Sun et al., Chem Res Toxicol (2008) 21:711-9; Shaw et al., Toxicol Sci. (2009) 107:270-80*

Hepatotoxicity *

Antibiotic	population	Incidence rate (CI) per 100,000 users	reference
fluoroquinolones (w/o moxifloxacin)	Outpatient clinic, Sweden (1995-2005)	0.7 (0.5-1.1)	[1]
moxifloxacin	Outpatient clinic, Sweden (1995-2005)	0.08 (0.0-0.5)	[1]
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)	[2]
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)	[2]
amoxicillin-clavulanic acid	General practice research database, United Kingdom (1991-1992)	22.5 (14.7-34.4)	[3]

1. De Valle et al., Aliment Pharmacol Ther (2006) 24:1187-95
2. Perez et al., Epidemiology (1993) 4: 496-501
3. Garcia-Rodriguez et al., Arch Intern Med (1996) 156: 1327-32

* international consensus:

AAT/Alk. phos. ratio (hepatocellular: ≥ 5; cholestatic: ≤ 2 ; mixed: > 2 and < 5)

Van Bambeke & Tulkens, Drug Saf. (2009) 32:359-378

Severe hepatotoxicity *

Antibiotic	Acute liver failure [a]	Critical event
moxifloxacin	6.6	1.6
levofloxacin	2.1	2.2
trovafloxacin	58	42.9
amoxi-clav	10	
clarithromycin		1.0
azithromycin		1.0
telithromycin	23	5.8

→ **withdrawn from the market**

→ **restricted indications**

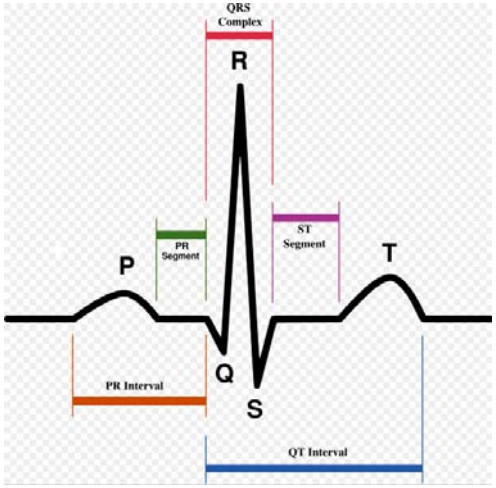
[a] Empiric Bayes Geometric Mean (EBGM) study
www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt ; presented December 2006 to FDA

Liver failure was defined as "acute or severe liver injury with encephalopathy, liver transplant following acute illness, death in the setting of acute liver injury (hospital. with transaminase elevation, or hyperbilirubinaemia, or clinical jaundice)"

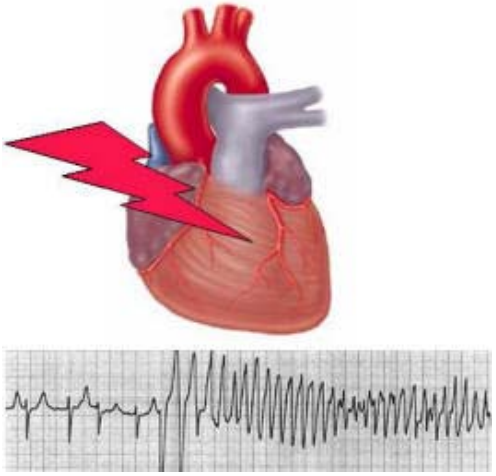
* FDA reporting rate per 10,000,000 prescriptions (spontaneous reports)

Van Bambeke & Tulkens, Drug Saf. (2009) 32:359-378

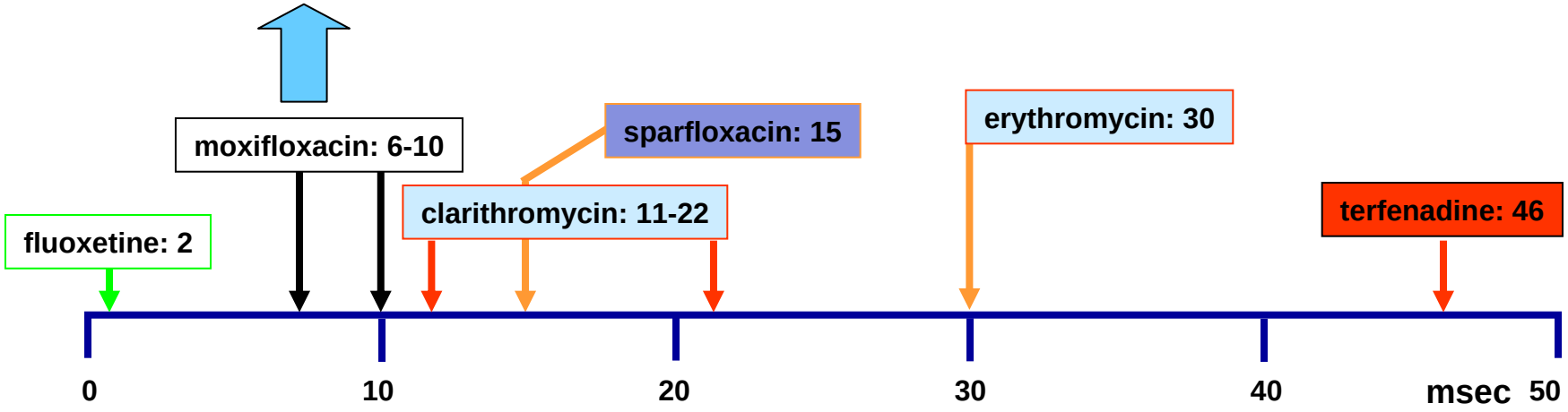
QTc prolongation



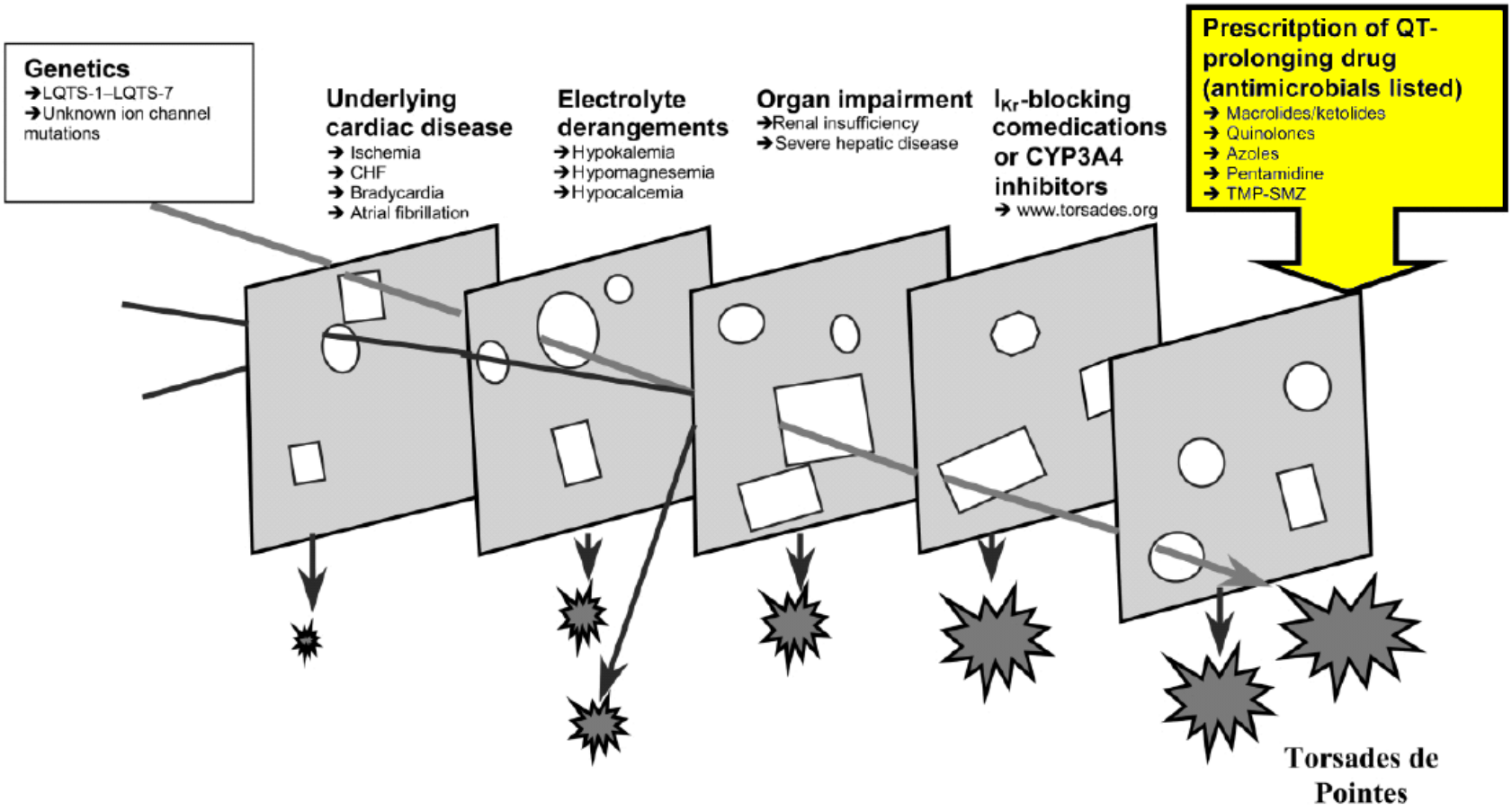
QTc prolongation
and associated risk
of Torsade de pointes



Moxifloxacin is used as a positive control for QTc effect(s) in Phase I studies because it offers a positive signal without risk of clinically meaningful adverse effect !



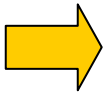
QTc prolongation & torsades de pointes



Owens & Ambrose, Clin. Infect. Dis. (2005) 41:S144-157

Cardiac toxicity

Antibiotic	TdP for 10,000,000 prescriptions
moxifloxacin	0 (0-26)
levofloxacin	5.4 (2.9-9.3)
gatifloxacin	27 (12-53)
cefuroxime	0.2 –1
erythromycin	0.7 -1.1
clarithromycin	1.8-3.4
azithromycin	0.6 –1



not on the market

* FDA reporting rate (spontaneous reports)

Van Bambeke & Tulkens, Drug Saf. (2009) 32:359-378

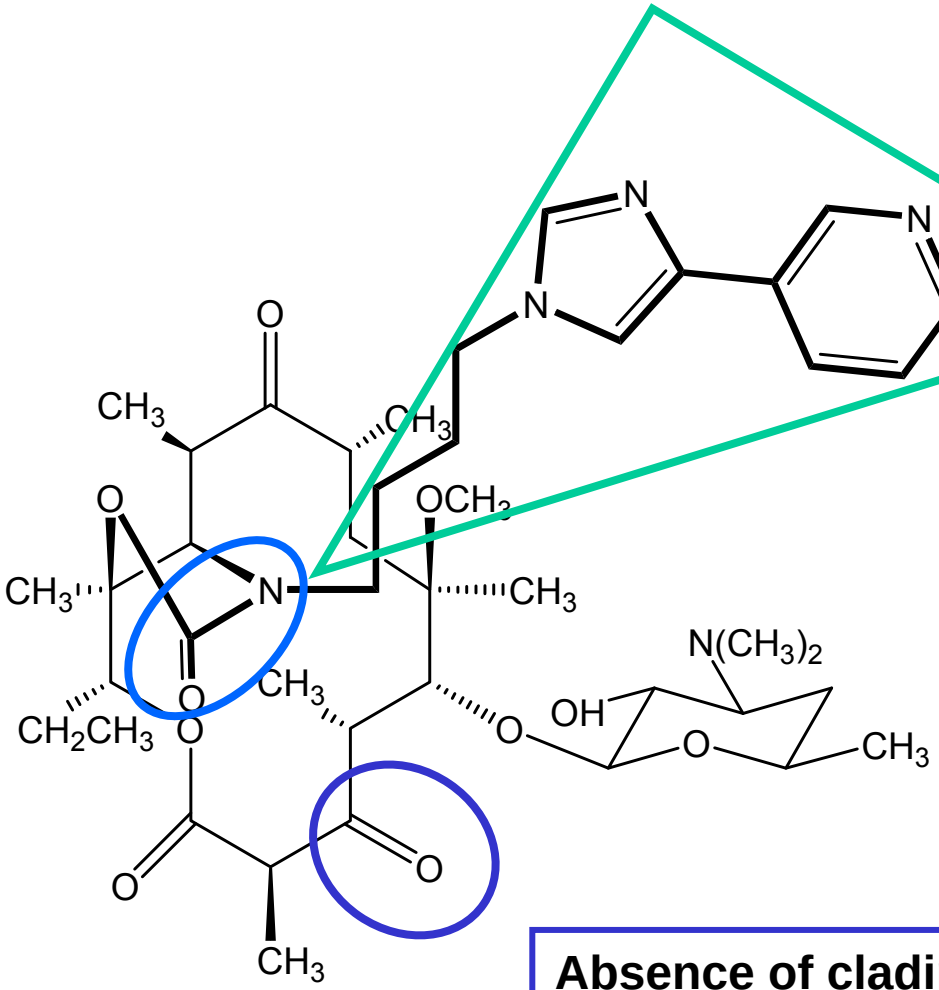
How can toxicity profile affect antibiotic usage ?

- restriction of indications
- limitation in treatment duration
- additional preregistration studies

Niagara Falls

3 examples with new drugs …

Telithromycin : a promizing ketolide …



Lateral chain:
- binding to domain II
- binding to methylated ribosomes
- no recognition by efflux pumps from *S. pneumoniae*
- improved PK profile

Absence of cladinose:
- stability in acidic medium
- no induction ~ MLS_B

Carbamate:
- increased activity

Van Bambeke et al., Exp.Op.Pharmacother. (2008) 9:267-283

Telithromycin : a promizing ketolide …

…for respiratory tract infections

Species and resistance genotype	Erythromycin	Telithromycin
S. pyogenes (WT)	0.03	0.08
(*ermB* ind.)	>64	0.5 - 1
(*ermB* const.)	>64	8
(*mef*)	8	0.5
S. pneumoniae (WT)	0,03	0.008
(*ermB* const.)	>64	0.06
(*mef*)	2	0.125

Van Bambeke et al., Exp.Op.Pharmacother. (2008) 9:267-283

Telithromycin : original indications (SmPC)

INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.

Rev. March 2004

Telithromycin : restriction of indications

Annals of Internal Medicine | ARTICLE

Brief Communication: Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review

Kimberly D. Clay, MD, MPH; John S. Hanson, MD; Scott D. Pope, PharmD; Richard W. Rissmiller, MD; Preston P. Purdum III, MD; and Peter M. Banks, MD

Background: Telithromycin is a ketolide antibiotic approved by the U.S. Food and Drug Administration for acute bacterial infections causing sinusitis, bronchitis, and community-acquired pneumonia.

Objective: To describe 3 cases of severe hepatotoxicity in patients receiving telithromycin.

Design: Case reports.

Setting: A tertiary care medical center.

Patients: 3 previously healthy patients who had recently taken telithromycin and took no other prescription medications.

Measurements: Serologic, histologic, and liver function tests.

Results: Within a few days of receiving telithromycin, the patients presented with acute hepatitis. All had jaundice and markedly abnormal results on liver function tests. Results of viral serologic tests were negative. One patient spontaneously recovered, 1 required orthotopic liver transplantation, and 1 died. Histologic examination in the latter 2 patients showed massive hepatic necrosis.

Limitations: Two patients had some history of alcohol use. The frequency of severe telithromycin-related hepatotoxicity cannot be established with case reports.

Conclusions: Telithromycin can cause severe hepatotoxicity. Caution is advised in prescribing this drug pending additional postmarketing surveillance data.

Ann Intern Med. 2006;144:415-420.
For author affiliations, see end of text.

FDA Advisory Panel: Ketek Side Effects Risks Outweigh Benefits For Bronchitis And Sinusitis; Urges Patient Medication Guide When Used For Pneumonia

In mid-December 2006, after two days of hearings, an FDA advisory panel recommended that the antibiotic Ketek should not be used as treatment for acute bacterial exacerbation of chronic bronchitis nor acute bacterial sinusitis. The same FDA panel, which included drug-safety experts and infectious-disease specialists, voted in favor of allowing Ketek to continue to be prescribed for community-acquired pneumonia, a more serious medical condition.

http://www.fda.gov/cder/drug/infopage/telithromycin/default.htm
Van Bambeke et al., Exp.Op.Pharmacother. (2008) 9:267-283

Telithromycin : restriction of indications (SmPc)

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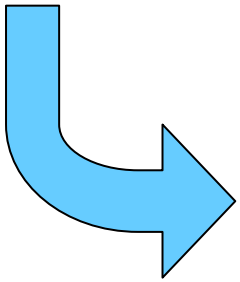
Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.

Rev. March 2004



INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae,* or *Mycoplasma pneumoniae,* for patients 18 years old and above.

Rev. February 2007a

Telithromycin : new warnings (SmPc)

WARNINGS

Hepatotoxicity

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK. (See **ADVERSE REACTIONS**.)

Visual disturbances*

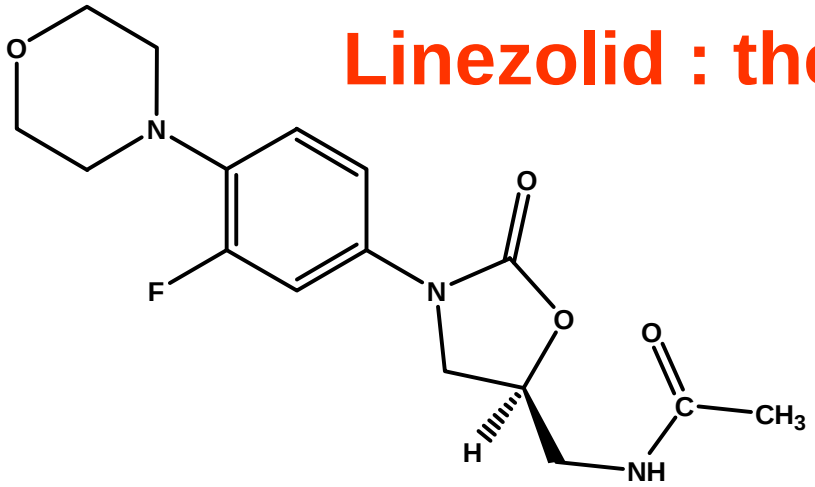
KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported.

Loss of Consciousness*

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome.

Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek. (See **CONTRAINDICATIONS**.)

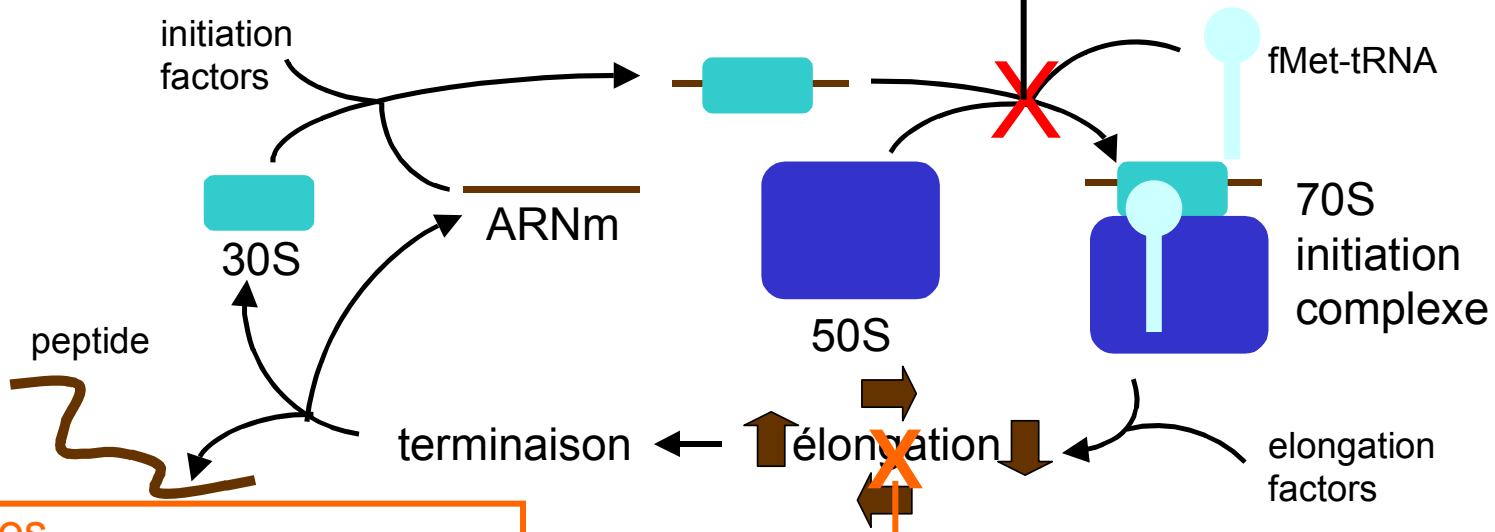
Linezolid : the first oxazolidinone



new target

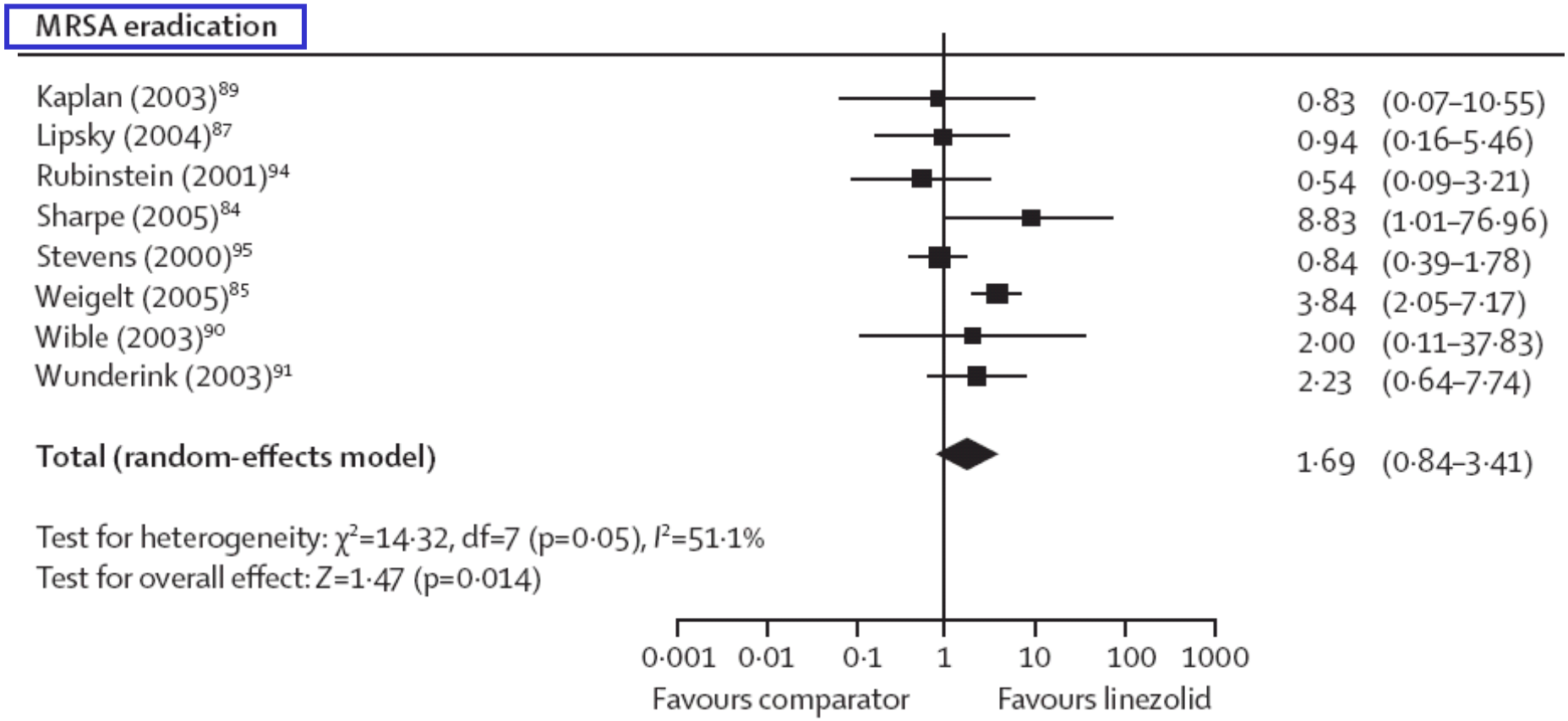
➡ no
- antagonism
- cross-resistance

Inhibition of the formation of the initiation complex



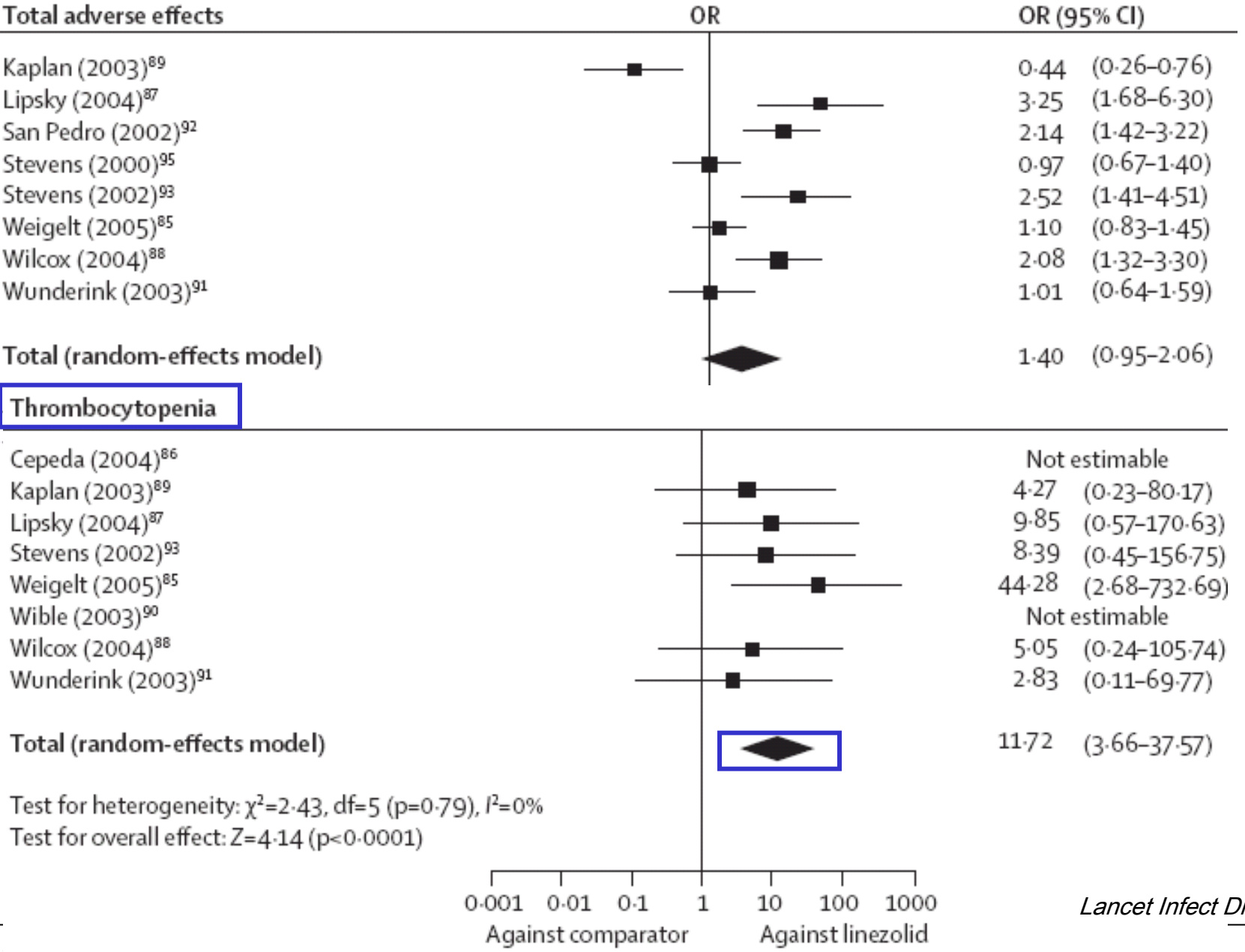
Tsuji et al. (2005) In Antimicrobial therapy and vaccines, ed. Yu, 223-42

Linezolid : the first oxazolidinone (anti-MRSA)



Falagas et al, Lancet Infect Dis. (2008) 8:53-66

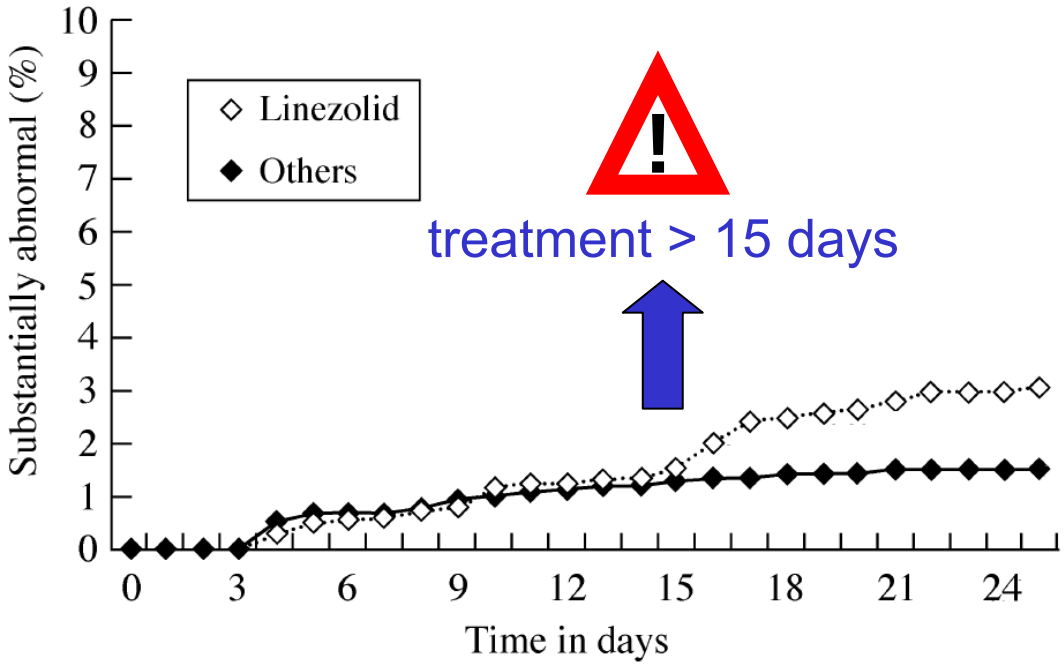
Linezolid : the first oxazolidinone (anti-MRSA)



Falagas et al,
Lancet Infect Dis. (2008) 8:53-66

Linezolid : avoiding prolonged treatment

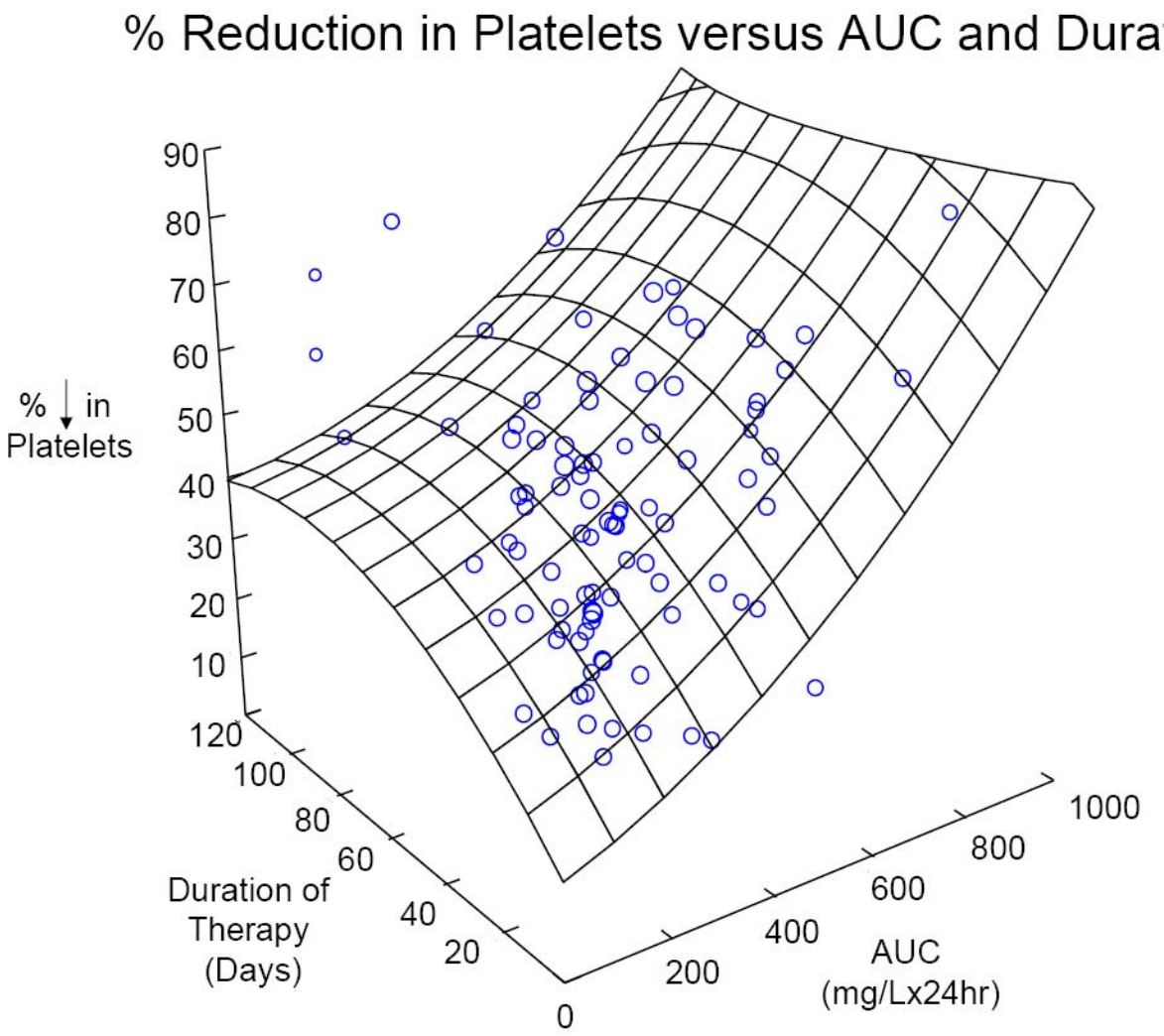
Thrombocytopenia:
2046 "linezolid" patients versus 2001 "comparator" patients - phase III



Phase III comparator-controlled trials: cumulative percentage of patients with at least one substantially low platelet count (<75% of lower limit of normal and/or baseline).

Gerson et al., Antimicrob.Ag.Chemother. (2002) 46:2723-6

Linezolid : avoiding prolonged treatment



Forrest et al, ICAAC (2000) abstract 283

Linezolid : avoiding prolonged treatment

Neuropathy - case reports

Review of reported cases of linezolid-associated neuropathy

Infection (n)	Months of therapy	Side-effect	Linezolid discontinued	Resolution (follow-up, months)
MRSA (1)	6	SLPPN	Yes	No (2)
*(3)	Mean 3·2	PN NOS	2 of 3	*(*)
MRSA (1)	6	SLPPN/ON	Yes	ON yes, PN no (5)
MRSA (2)	10	ON	Yes	1 yes (9), 1 partial (6)
Nocardia (1)	4	PN NOS	Yes	Yes (*)
NTM/nocardia (5)	Mean 6·4	SLPPN	2 of 5	1 of 5 (*)
MDR TB (1)	*	*	No	*(17)
Nocardia farcinica (1)	4	ON	Yes	Yes (8)
Actinomyces odontolyticus	6	SLPPN	Yes	No
NTM (1)	*	PPN NOS	Yes	No (?)
NTM (1)	7	PN NOS	*	*
Nocardia (1)	6	PPN NOS	*	*
MRSA (1)	12	PN, ataxia	No	No (*)
MRSA (1)	3	PN NOS	*	*

*Data not provided. MRSA=meticillin-re[illegible]nt *Staphylococcus aureus*, NTM=non-tuberculous mycobacteria, SLPPN=stocking-like painful peripheral neuropathy, PN NOS=peripheral neuropathy not otherwise specified, ON[illegible]otic neuropathy, PPN NOS=painful peripheral neuropathy location not specified.

treatment > 28 days

Bressler et al., Lancet Infect. Dis (2004) 4:528-31

Linezolid : avoiding prolonged treatment (SmPC)

WARNINGS

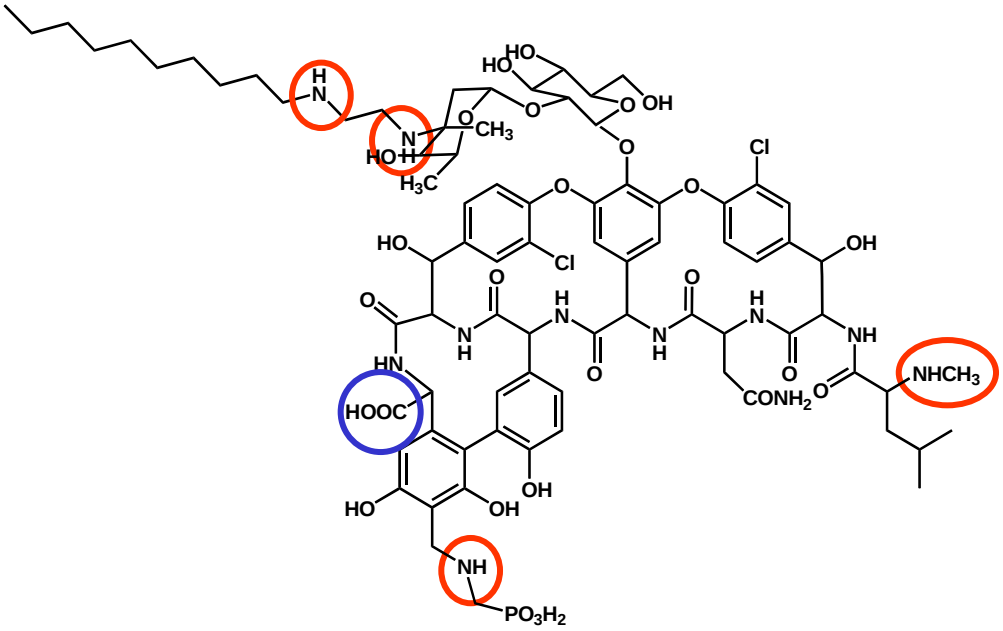
Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

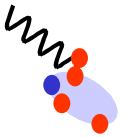
Peripheral and Optic Neuropathy

Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days.

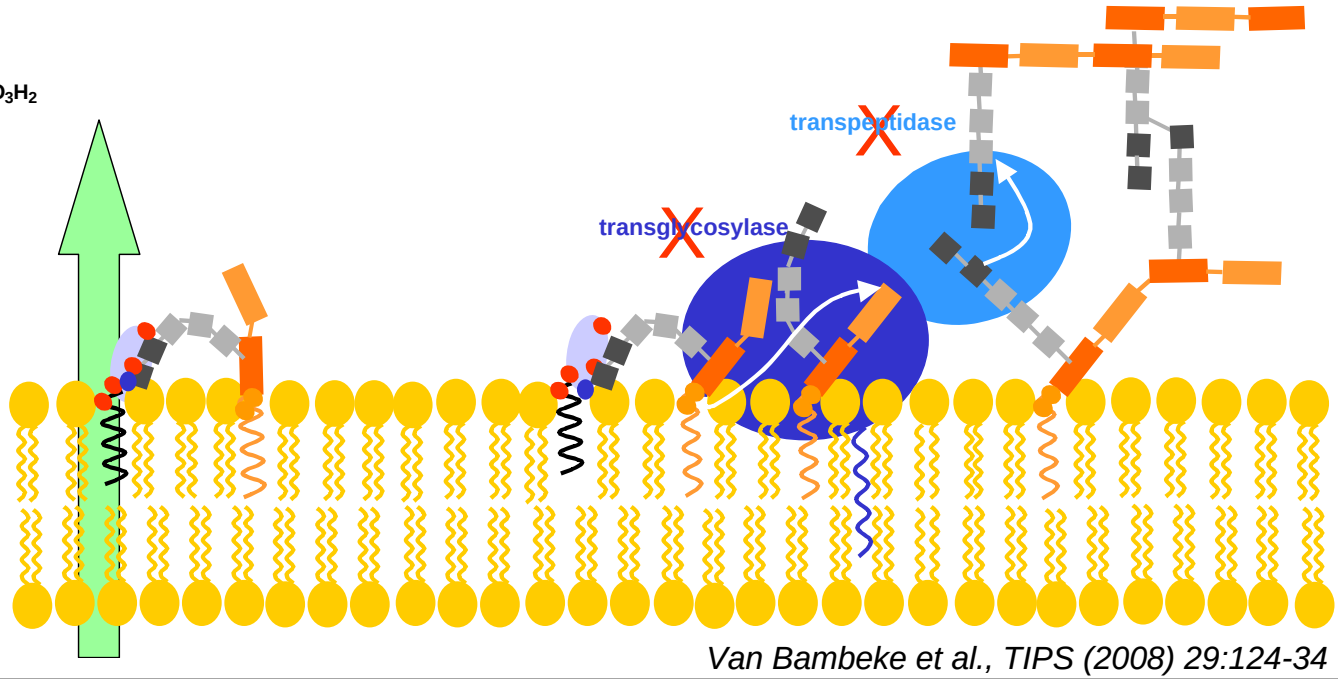
Revised July 2008

Telavancin : a rapidly bactericidal lipoglycopeptide





telavancin



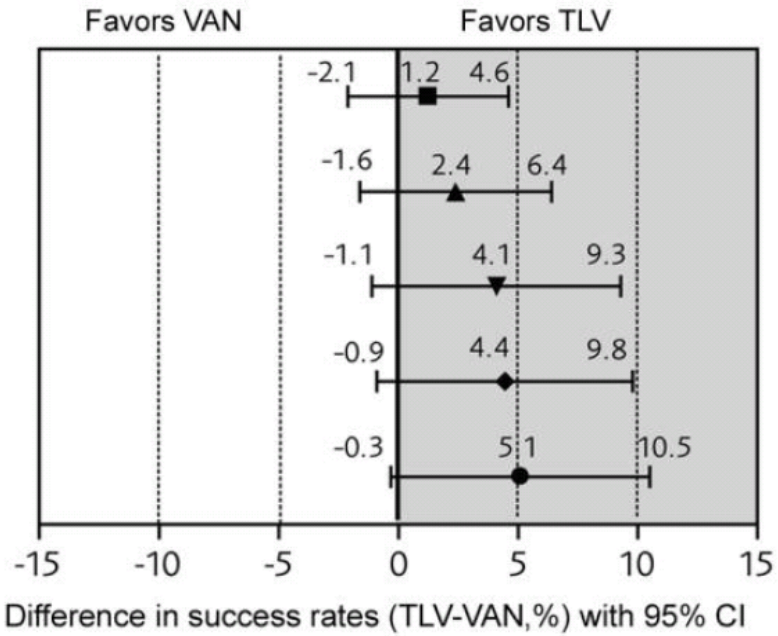
Van Bambeke et al., TIPS (2008) 29:124-34

Telavancin : delay to re-submission to EMEA

Phase 3 - Skin and skin structure infections

TLV 10 mg/kg q24h vs VAN 1 g q12h ; 7-14 days

Clinical outcome



	TLV % success (N)	VAN % success (N)
Clinical cure in CE patients	88.3% (745)	87.1% (744)
Overall therapeutic response[a] in ME patients	88.6% (527)	86.2% (536)
Clinical cure in ME patients with MRSA infection	90.6% (278)	86.4% (301)
Microbiological eradication in ME patients with MRSA infection	89.9% (278)	85.4% (301)
Overall therapeutic response[a] in ME patients with MRSA infection	89.9% (278)	84.7% (301)

Stryjewski et al., Clin.Infect.Dis. (2008) 46:1683-93

Telavancin : delay to re-submission to EMEA

Safety profile

Adverse events reported in ⩾3% of patients in any group in the all-treated population: pooled analysis (studies 0017 and 0018).

Variable	No. (%) of patients	
	Telavancin treatment arm (n = 929)	Vancomycin treatment arm (n = 938)
Any adverse event	735 (79)	676 (72)
Serious adverse event	69 (7)	42 (4)
Discontinued treatment because of an adverse event	73 (8)	53 (6)
Adverse event term		
Taste disturbance	311 (33)	62 (7)
Nausea	249 (27)	142 (15)
Headache	130 (14)	120 (13)
Vomiting	127 (14)	69 (7)
Urine abnormality (foamy urine)	122 (13)	27 (3)
Insomnia	90 (10)	86 (9)
Constipation	96 (10)	61 (7)
Diarrhea	67 (7)	76 (8)
Dizziness	55 (6)	53 (6)
Rash	35 (4)	43 (5)
Infusion site pain	41 (4)	40 (4)
Fatigue	41 (4)	31 (3)
Chills	41 (4)	21 (2)
Generalized pruritus	28 (3)	60 (6)
Infusion site erythema	24 (3)	24 (3)
Decreased appetite	25 (3)	19 (2)
Anxiety	26 (3)	22 (2)
Renal dysfunction	27 (3)	10 (1)
Abdominal pain	17 (2)	26 (3)

Stryjewski et al., Clin.Infect.Dis. (2008) 46:1683-93

Telavancin : delay to re-submission to EMEA

astellas
Leading Light for Life

Attn Dr. Abadie
European Medicines Agency
7 Westferry Circus
Canary Wharf
London
E14 4HB
UNITED KINGDOM

Direct line +31(0)71 545 5527
Direct fax +31(0)71 545 58 40
Our ref. NH/IV/08-02106
Your ref.
Date 20 October 2008

Subject: Withdrawal of Vibativ®, (telavancin), 15 mg/ml, powder for concentrate for solution for infusion - EMEA/H/C/000864//0000

Dear Dr. Abadie,

I would like to inform you that, at this point of time, Astellas Pharma Europe B.V. has taken the decision to withdraw the application for Marketing Authorisation of Vibativ®, (telavancin), 15 mg/ml, powder for concentrate for solution for infusion, which was intended to be used for the treatment of complicated skin and soft tissue infections in adults.

This withdrawal is based on the following reason:

Astellas has taken this decision based on the CHMP's communication that the data provided are not sufficient to allow the Committee to conclude a positive benefit-risk balance for Vibativ for the applied indication at this time. Astellas currently intends to prepare a new marketing authorisation application (MAA) to include new and expanded clinical trial data in patients with Hospital Acquired Pneumonia, not available at the time of the initial application.

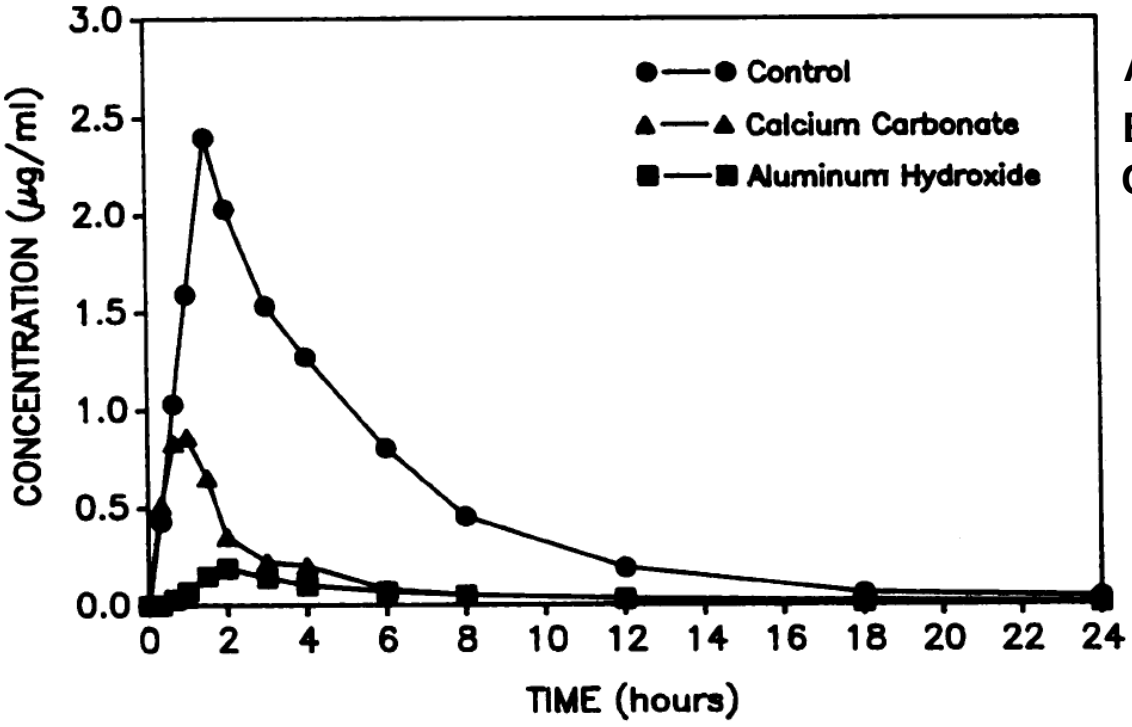
Drug interactions with antibiotics

CN tower, Toronto

Reduction in antibiotic exposure

⇨reduction in AUC ⇨ increased risk of { therapeutic failure / selection of resistance }

Fluoroquinolones / tetracyclines and cations …



A. Cipro 750 mg

B. + 850 mg $CaCO_3$

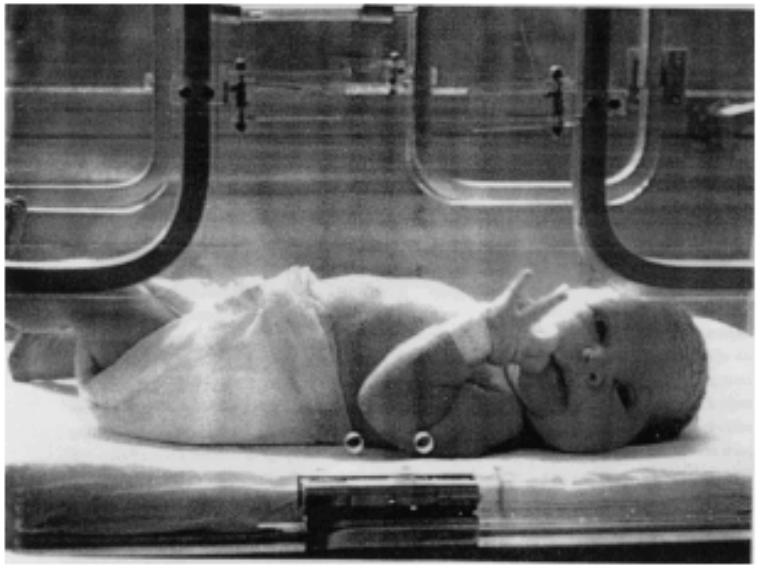
C. + 600 mg $Al(OH)_3$

Treatment[a]	C_{max} (µg/ml)	AUC_{0-t} (µg/h/ml)
A	3.18 ± 1.29	13.50 ± 4.61
B	1.69 ± 0.48	7.82 ± 3.09
C	0.60 ± 0.58	2.08 ± 1.20

Frost et al, Antimicrob.Ag. Chemother. (1992) 36:830-2

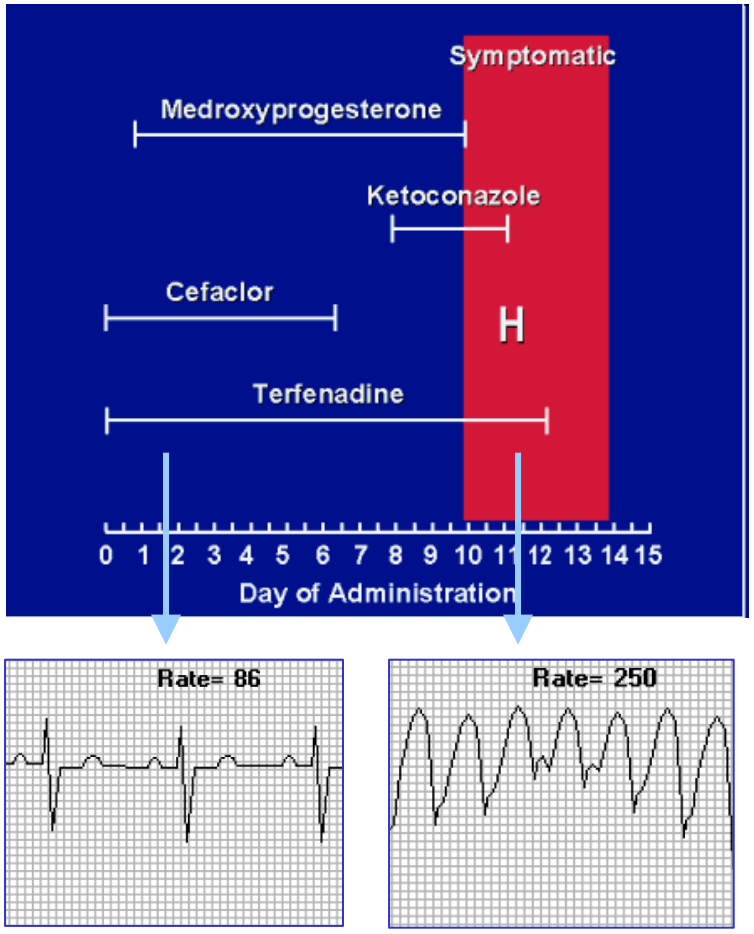
Alteration of hepatic metabolism

⇨ increased metabolism
⇨ loss of efficacy

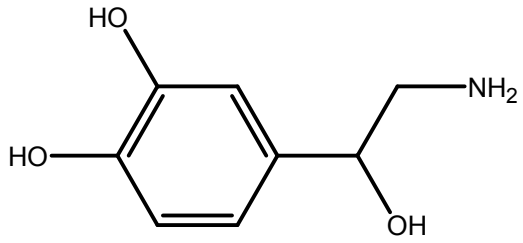


Parmi les nombreux exemples d'effets indésirables de médicaments, on cite souvent celui de la perte d'effet de la pilule contraceptive en présence d'un antibiotique, la rifampicine. C'est ainsi que sont nés des enfants « rifampicine », nés de mères soignées avec un médicament qui a réduit leur protection contraceptive…

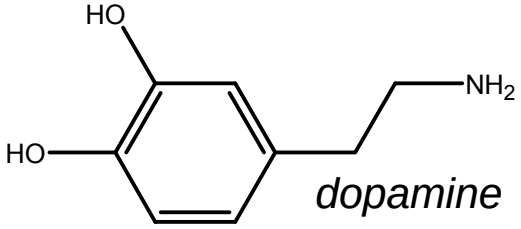
⇨ decreased metabolism
⇨ increased risk of ADR



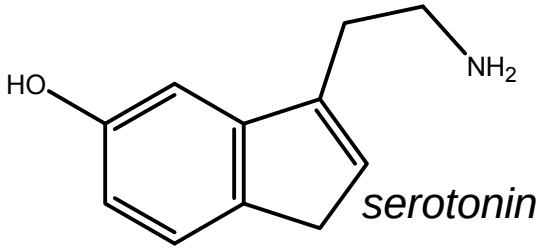
Alteration of other metabolic pathways



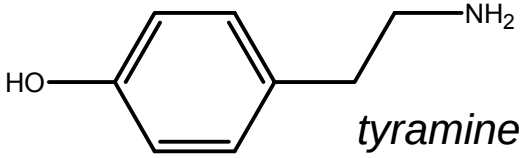
noradrenalin



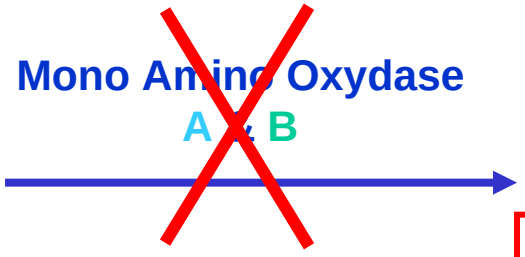
dopamine

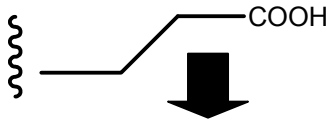


serotonin



tyramine





SEROTONINERGIC syndrome

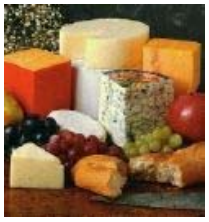
Association with drugs

- ↗ synthesis
- ↗ release
- ↘ metabolism
- ↘ reuptake

for neurotransmitters

- agonists of receptors

(< 100 mg de tyramine / meal)



50 mg/100 g aged cheese

28 mg/100 g smoked meat

42 mg/33 cl beer

5 mg/spoon Soja sauce

6 mg/20 cl red wine

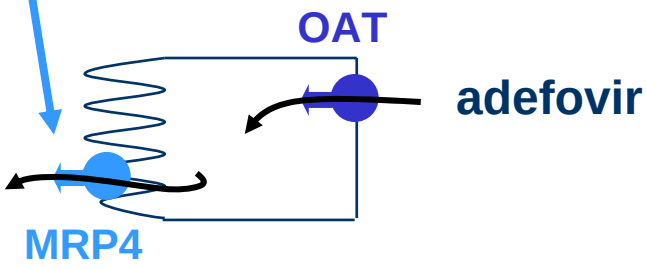
Taylor et al., Clin. Infect. Dis (2006) 43:180-7

Increased risk of ADR

Adefovir:
drug interactions and nephrotoxicity

Targeting the same organ	Competition for transport
• cyclosporin A	• NSAID
• aminoglycosides	• methotrexate
• vancomycin	• tenofovir/cidofovir
• amphothericin B	•…
• foscarnet	
• …	

Many anti-infective agents !
remember patients at risk
for HBV …



Need more information ?

Toronto University

Useful databases: ADR ...

http://sideeffects.embl.de/

SIDER Side Effect Resource

type your search terms...

http://sideeffects.embl.de

Trovafloxacin

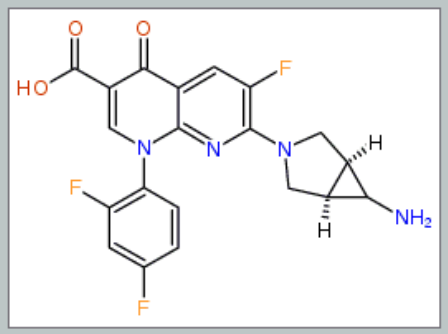
Side effects and indications

Whenever possible, frequency information about the side effects was extracted from the labels. Aggregated frequency information for the drug and, if available, placebo is shown. To the right, you can click on shaded boxes to be taken to mentions of the side effect on the label. (In some cases, the side effect cannot be highlighted due to conversion problems.) Information about indications was extracted from the indications and usage sections of the labels.

Sort by: related terms – **frequency**

Side effect	Data for drug	Placebo Labels
		1
Dizziness def	2%, 11%	
Nausea def	4% — 8%	
Headache def	1%, 5%	
Lightheadedness	1% — 4%	
Vomiting def	1%, 3%	
Vaginitis def	1%, 2%	
Pruritus def	1%, 2%	
Diarrhea def	2%	
Exanthema def	1%, 2%	
Abdominal Pain def	0%, 1%	
Hepatic necrosis	postmarketing	
Aplastic Anemia def	postmarketing	
Eosinophilia def	postmarketing	
anaphylaxis def	postmarketing	
Hepatitis def	postmarketing	

Information



More information: STITCH, PubChem and possibly Wikipedia or Medpedia

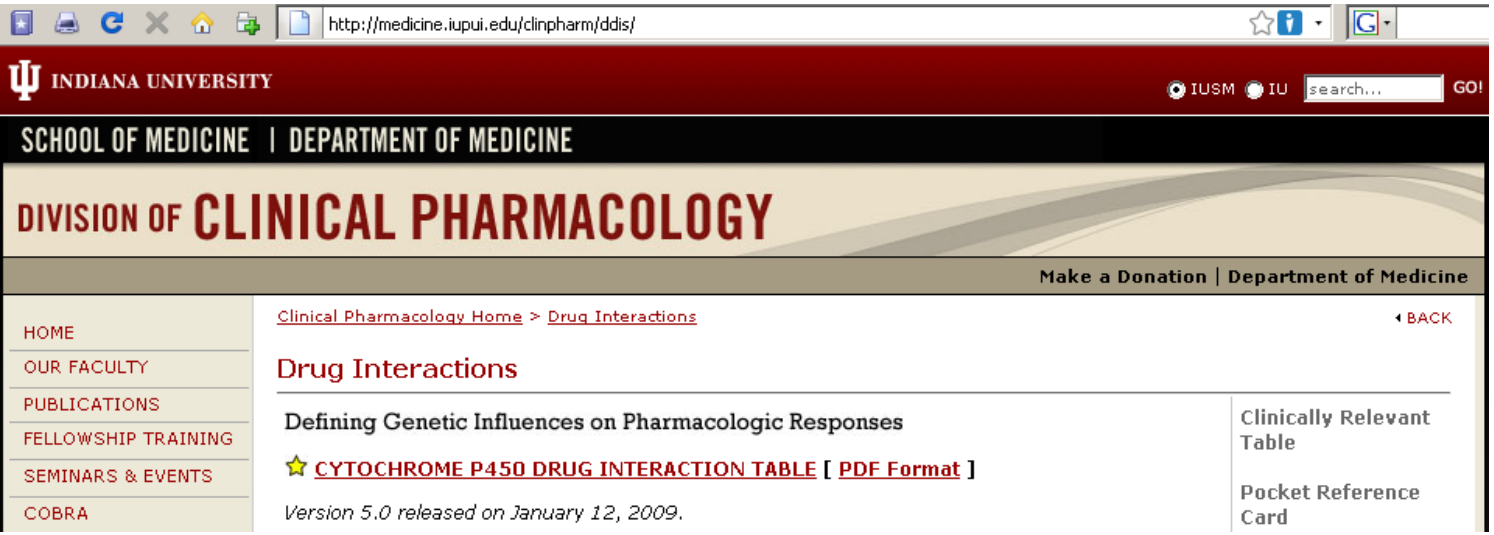
ATC Code: J01MA13

Legend

Color scheme: **standard** – alternative

100%	rare (<0.1%)
75%	postmarketing
50%	0%
10%	no frequency information
frequent (1% to 100%)	not found on label
infrequent (0.1% to 1%)	

Useful databases: drug interactions …

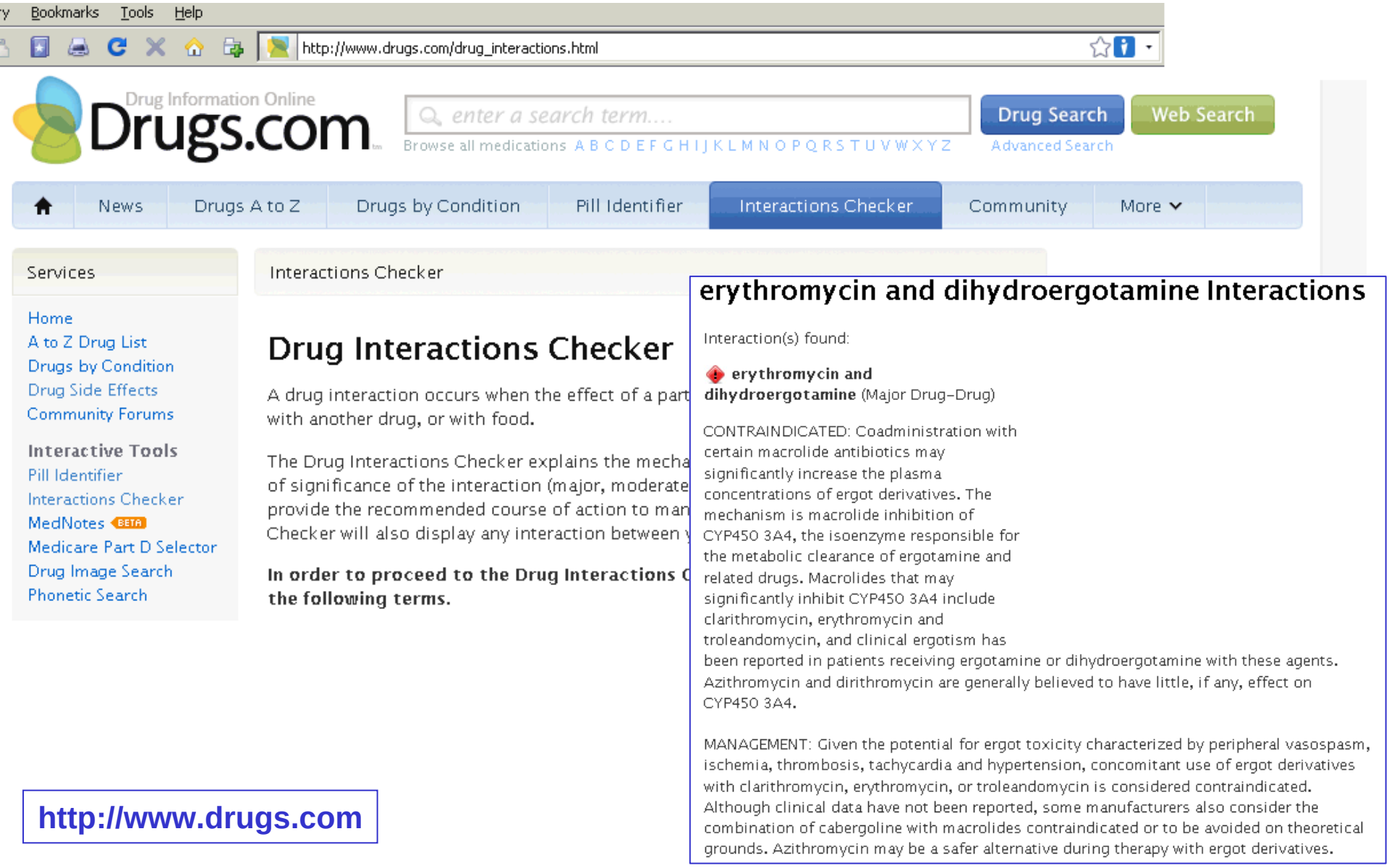


- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.
- All other inhibitors.

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
cimetidine	thiotepa	gemfibrozil	fluconazole2	fluoxetine	bupropion	disulfiram	**HIV Antivirals:**
	ticlopidine[2]		amiodarone	fluvoxamine	fluoxetine		indinavir
fluoroquinolones		montelukast1		ketoconazole	paroxetine		nelfinavir
fluvoxamine[1]			isoniazid	lansoprazole	quinidine1		ritonavir
ticlopidine				omeprazole			
				ticlopidine2	duloxetine		clarithromycin
							itraconazole
					amiodarone		ketoconazole
					cimetidine		nefazodone
					chlorpheniramine		erythromycin
					clomipramine		grapefruit juice
					doxepin		verapamil2
					haloperidol		diltiazem
					methadone		
					mibefradil		cimetidine
					ritonavir		

http://medicine.iupui.edu/clinpharm/ddis/

Useful databases: drug interactions …



http://www.drugs.com

Take home message …

Take home message …

- post-marketing surveillance are needed for detection of rare/severe ADR
  - careful examination of these cases to define link with drug and associated risk factors
- safety profile should contribute to define
  - indications
  - treatment duration
  - conditions of use and of monitoring
- drug interactions are important to take into account for :
  - PK/PD issues and associated risk of failure
  - increased risks of toxicity

Thank you for your attention

… and have a nice day !