

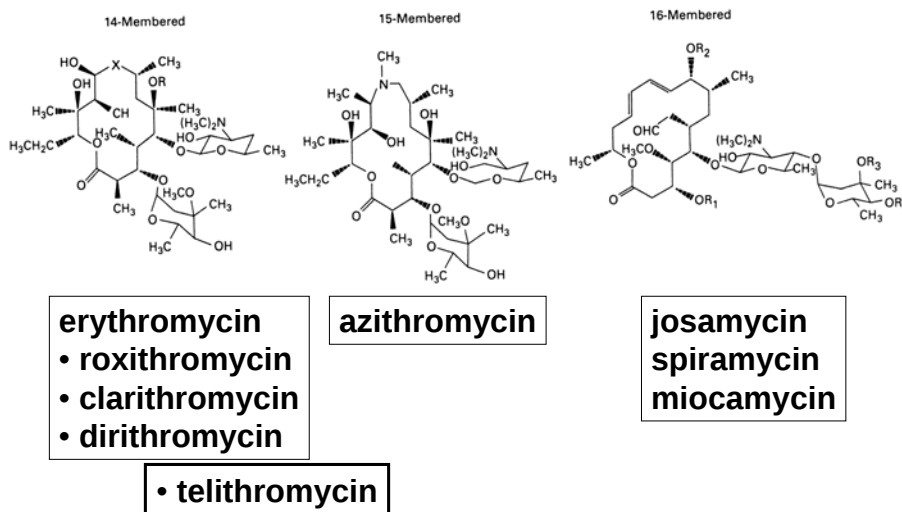
Macrolides

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The macrolide family ...



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Erythromycin: activity

Erythromycin A : mostly Gram (+) organisms

Plus:

- *Legionella p.*
- *Chlamydia spp.*
- *Mycoplasma spp.*
- *Mycobacterium avium*

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Erythromycin - MIC distributions of isolates that lack resistance mechanisms

Mg/L	.004	.008	.016	.032	.064	.125	.25	.5	1	2	4	8	16	32	≥64
<i>S.aureus</i>					•	•	•	•							
Coag-neg staph				•	•	•									
<i>S.saprophyticus</i>				•	•	•									
<i>Streptococcus_A</i>				•	•	•									
<i>Streptococcus_B</i>				•	•	•									
Pneumococci				•	•	•									
Strept misc			•	•	•	•									
Enterococcus						•	•	•	•	•					
Listeria						•	•	•							
Corynebacteria				•	•	•									
<i>Bacillus spp</i>				•	•	•									
<i>H.influenzae</i>								•	•	•	•	•			AST
<i>M.catarrhalis</i>					•	•	•								
<i>B.pertussis</i>						•	•	•	•						
<i>P.multocida</i>											•	•	•		
<i>L. pneumophila</i>						•	•	•	•						
Camp. jejuni						•	•	•							
<i>N.gonorrhoeae</i>			•	•	•	•									
<i>N.meningitidis</i>					•	•	•	•							
<i>M.pneumoniae</i>	•	•	•	•											
<i>Borr. burgdorferi</i>				•	•	•									

SRGA and SRGA- M, 1998-04-13, 2001-11-11
G Kahlmeter & B.Olsson-Liljequist

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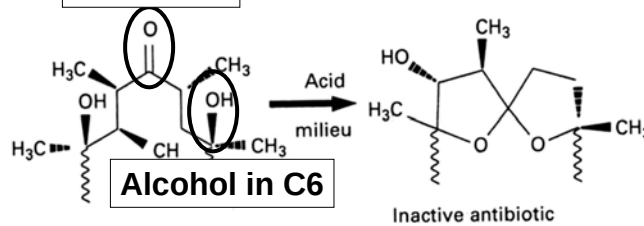
Erythromycin: the problems

Erythromycin A

14 atoms

Instability in acid media

Keto in C9

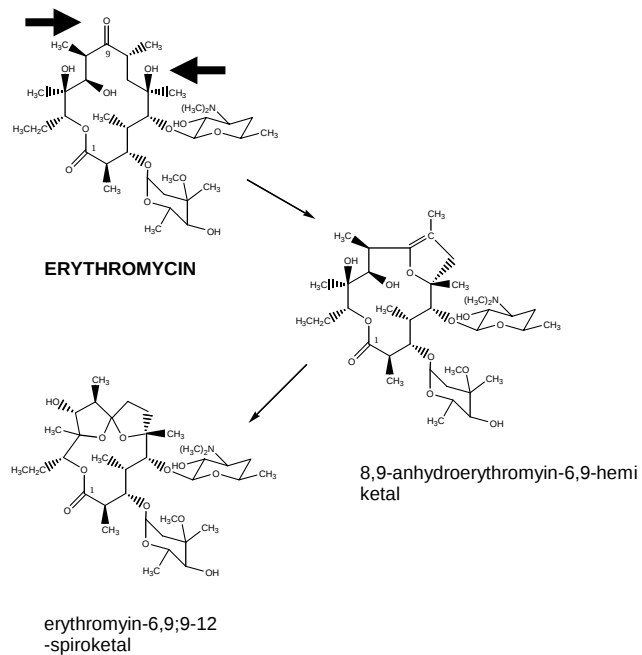


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Erythromycin: details of acid the degradation

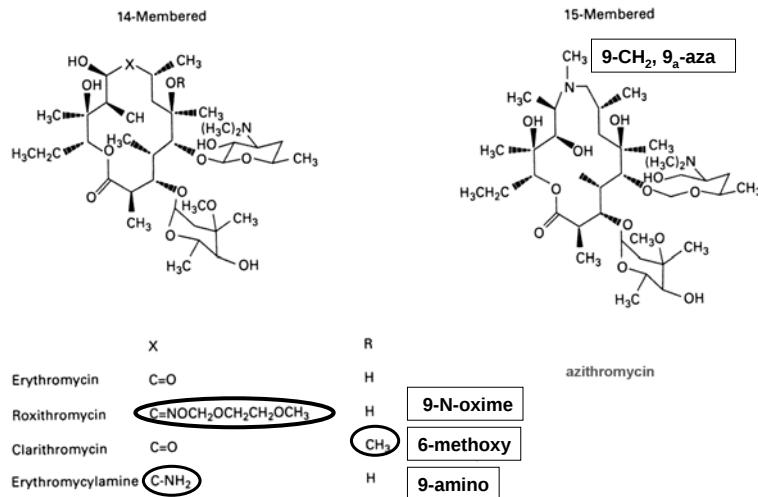


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What have the chemists done to avoid acid-instability ?

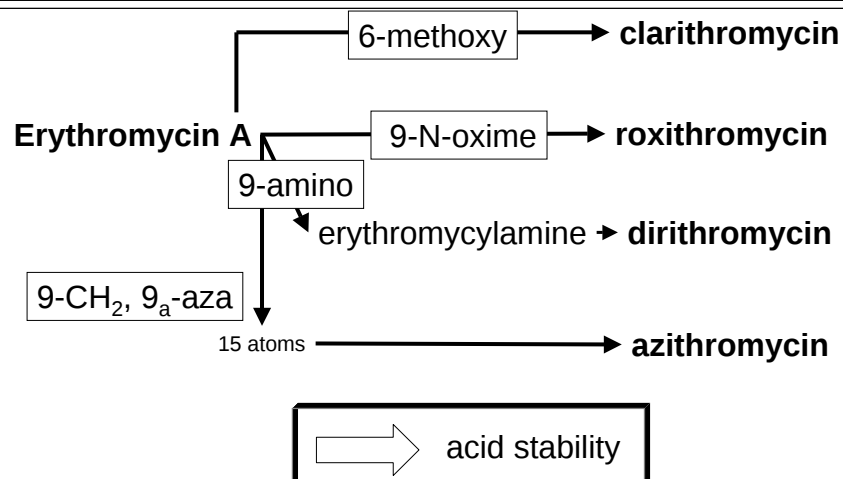


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What have the chemists done to avoid acid-instability ?

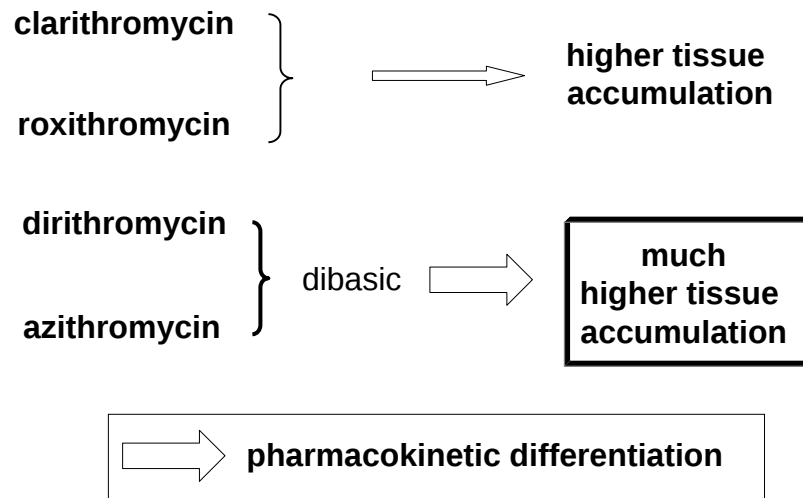


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Did these modifications change anything else in PK ?



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Did these modifications change anything else ?

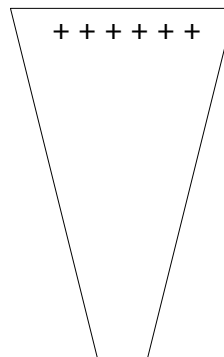
Cytochrome P₄₅₀ interactions

erythromycin A

clarithromycin
roxithromycin

dirithromycin

azithromycin



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Drug interactions with macrolides

- The main problem due to interactions between some macrolides and the cytochrome P 450 system, especially the CYP3A subclass of enzymes
- Finally results in lowered metabolism of CYP3A-dependent drugs

drug	azi	clari	diri	ery	josa	mid	roxi	spira
théophyllin	0	0	0	++	+	ND	0/+	0
ciclosporin	ND	ND	ND	+++	+++	+++	+	0
carbamazepin	ND	0/+	ND	+++	+	+	0/+	0/+
midazolam	0	++	ND	++	ND	ND	+	ND
warfarin	0	ND	ND	+	ND	ND	0	ND
terfenadin	0	++	ND	+++	0/+	ND	0	ND
cisapride	ND	++	ND	++	++	ND	ND	0

From Petitjean et al.

N=undocumented

Mainly considered as a class-effect, resulting from what is known for erythromycin, except for spira and azithromycin

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Basic indications of (classical) macrolides in a world of no resistance

erythromycin

clarithromycin

roxithromycin

dirithromycin

azithromycin

Respiratory tract infections

- pharyngitis
- otitis
- sinusitis
- acute exacerbations of chronic bronchitis
- community acquired pneumonia
- legionellosis
- *C. pneumoniae*
- *Mycobacterium avium* (AIDS)

Genital/Ocular infections

- chlamydiosis (*C. trachomatis*)
- syphilis
- donovanosis
- gonorrhea

Gastric ulcer (*H. pylori*)

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Which (who ...) is the best ?

erythromycin
clarithromycin
roxithromycin
dirithromycin
azithromycin



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But what has been the problem ?

erythromycin
clarithromycin
roxithromycin
dirithromycin
azithromycin

Emergence of resistance

Target modification: erm

Efflux: Mef

All are similarly affected

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Mechanisms of macrolide resistance

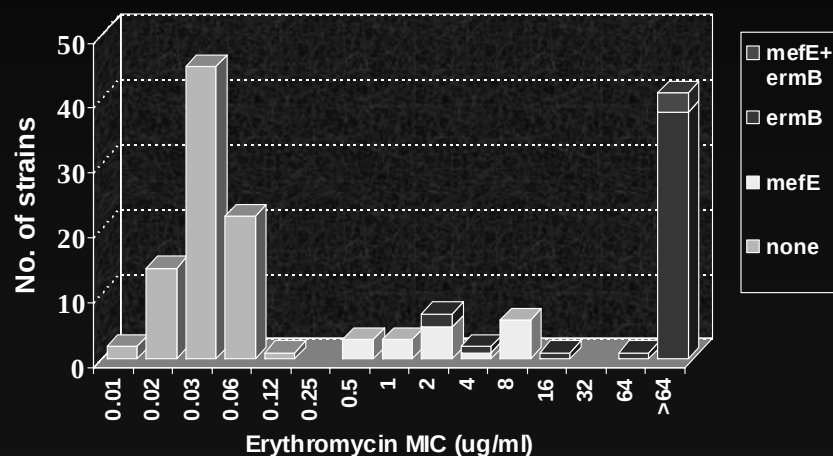
- **Ribosomal modification by methylase (*erm* genes)**
 - *S. pneumoniae*: *erm*(B) 75-100% of Ery-R strains in Europe
 - *S. pyogenes*: *erm*(B) generally <50% of Ery-R strains
erm(A)
- **Ribosomal modification by mutation (rRNA, proteins)**
 - Occasional in Ery-R *S. pneumoniae*
 - Rare in Ery-R *S. pyogenes* (up to 18% in Eastern Europe)
 - The only mechanism or highly prevalent in *H. pylori*, *Campylobacter*, *M. avium*
- **Drug efflux (*mef* genes)**
 - <25% in Ery-R *S. pneumoniae*
 - >50% in Ery-R *S. pyogenes* (up to 95%)

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Correlation between erythromycin MICs and resistance mechanisms



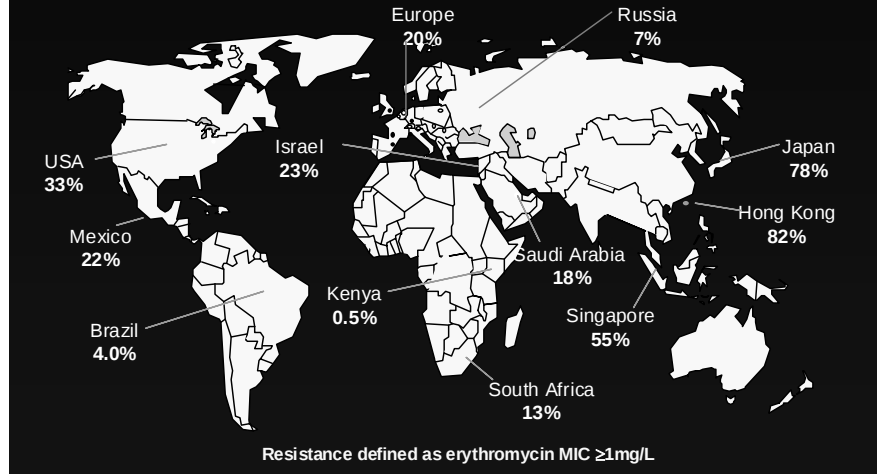
Nagai ICAAC 2000, abstr # 892

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The Alexander Project 1999: *S. pneumoniae*, Macrolide Resistance



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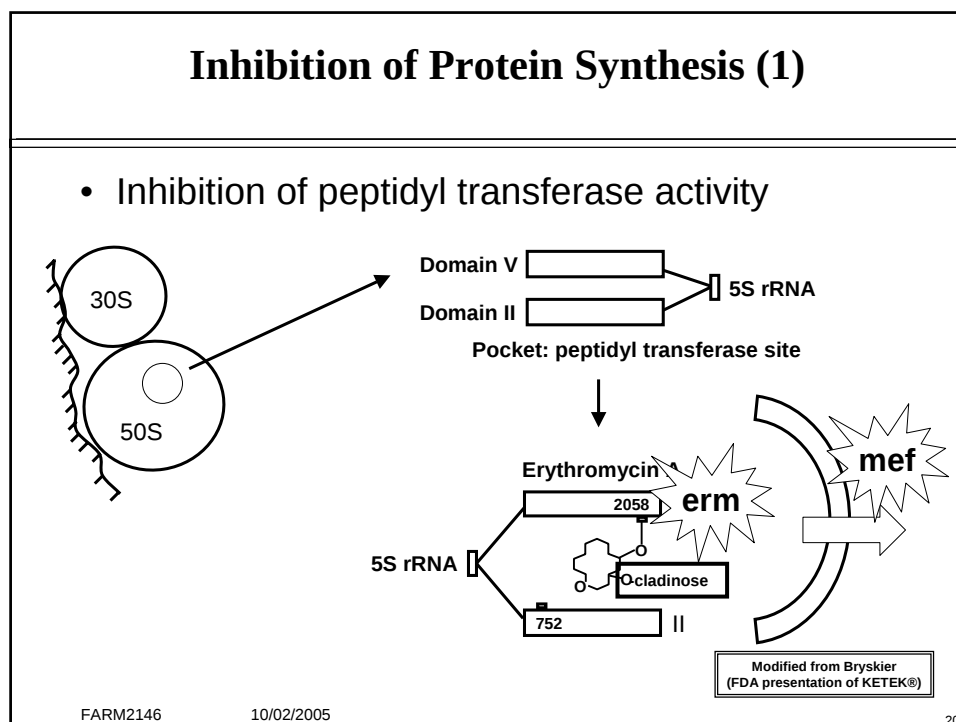
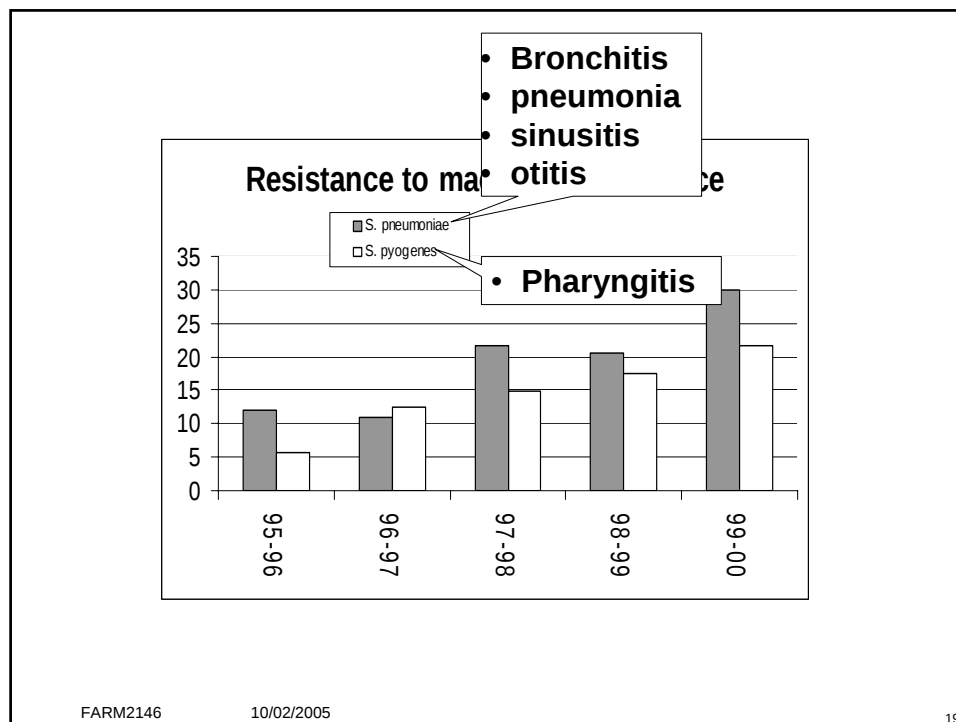
Distribution of erythromycin-resistance phenotypes among pneumococci from 8 different European countries (1998-2000)

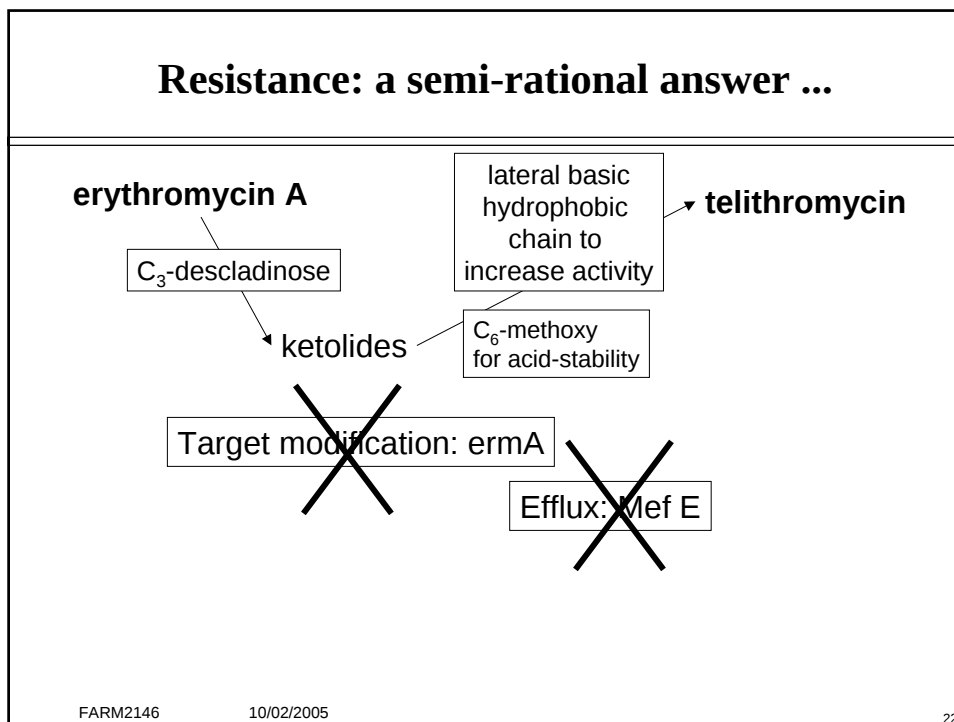
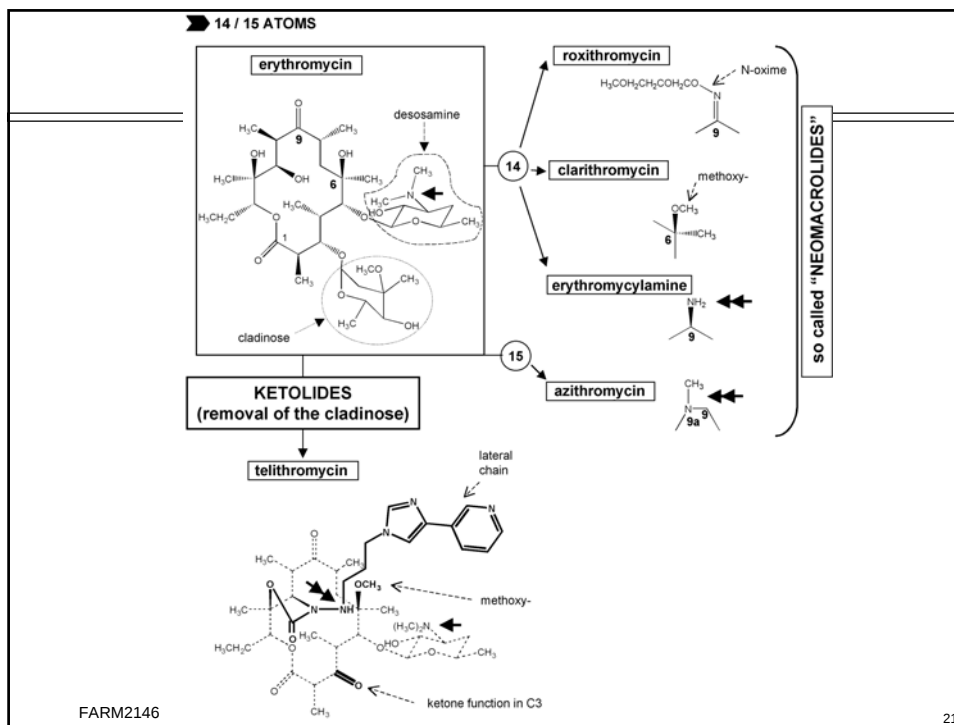
Country (total No of isolates)	ref	overall % of erythromycin-resistance	distribution of resistance phenotype		
			MLS _B	M	other
Belgium (59)	1	31	91.5	8.5	0
Finland (651)	2	11.2	71	21	11.2
France (48)	3	53	100	0	0
Germany (102)	4	10.6	74	22.5	3.5
Greece (140)	5	18	67.9	29.2	3.6
Italy (85)	6	31.7	76.5	23.5	0
Norway (8)	7	4.5	75	25	0
Spain (109)	8	36.1	84	15	1

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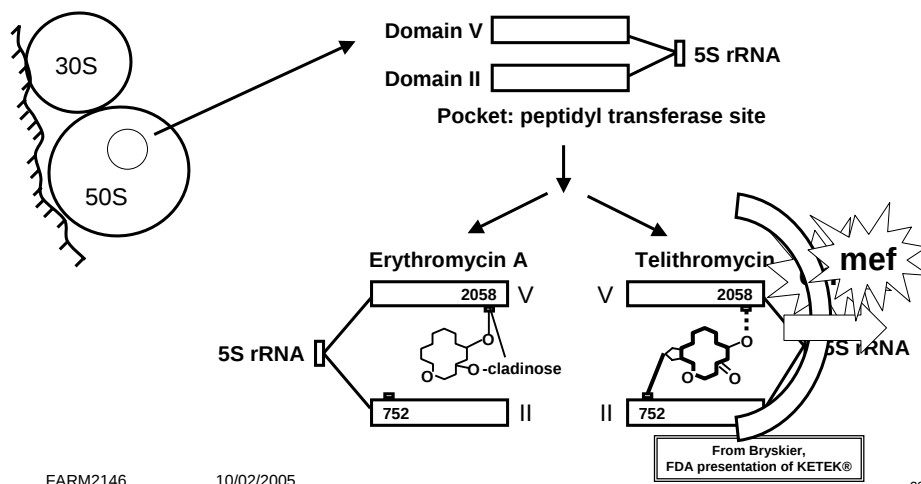
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Inhibition of Protein Synthesis (2)

- Inhibition of peptidyl transferase activity



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MIC₅₀ [µg/ml] of wild type and mutant strains

	Erythromycin	Telithromycin
<i>S. pyogenes</i> (WT)	0.03	0,08
(<i>ermTR</i> ind.)	4	0,06
(<i>ermTR</i> const.)	>64	0,25
(<i>ermB</i> ind.)	>64	0,5 - 1
(<i>ermB</i> const.)	>64	8
(<i>mef</i>)	8	0,5 ←
<i>S. pneumoniae</i> (WT)	0,03	0,008
(<i>ermB</i> const.)	>64	0,06
(<i>mef</i>)	2	0,125

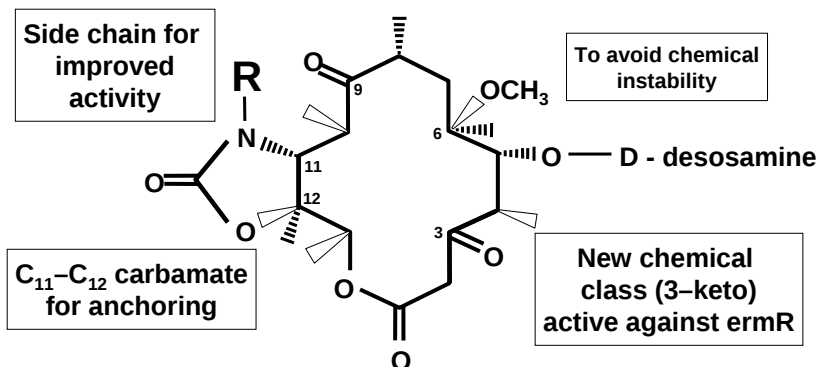
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Telithromycin

- Telithromycin, the first ketolide, was designed to overcome erythromycin A resistance within Gram (+) positive cocci and take advantage of PK improvements of clarithromycin



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Pharmacokinetics of telithromycin

(as submitted to the FDA; april 2001)

	800 mg (single dose)	800 mg (7 days)
C _{max} (mg/L)	1.9 (42)	2.3 (31)
C _{24h} (mg/L)	0.03 (45)	0.07 (72)
AUC _{24h} (mgxh/L)	8.3 (31)	12.5 (43)
t _{1/2} (h)	7.2 (39)	9.8 (20)

The company has declared that activity of telithromycin is driven by C_{max}/MIC and by AUC_{24h}/MIC ratios

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

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Pharmacodynamics of telithromycin
(as based on FDA submission; april 2001)

Organism	MIC ₉₀	C _{max} /MIC _{90max}	AUC _{24h} /MIC _{90max}
<i>S. pneumoniae</i>	< 0.008 - 0.25	7.6	33.2
<i>S. pyogenes</i>	< 0.015 - 0.06	31.6	138
<i>H. influenzae</i>	2.0 - 4.0	0.475	2.075
<i>M. catarrhalis</i>	0.12	15.8	69.1
<i>L. pneumophila</i>	0.03 - 0.12		
<i>C. pneumoniae</i>	0.03 - 2		
<i>M. pneumoniae</i>	0.25		

Activity will be good for
MIC ≤ 0.25 mg/L, but may
become problematic for
higher MICs

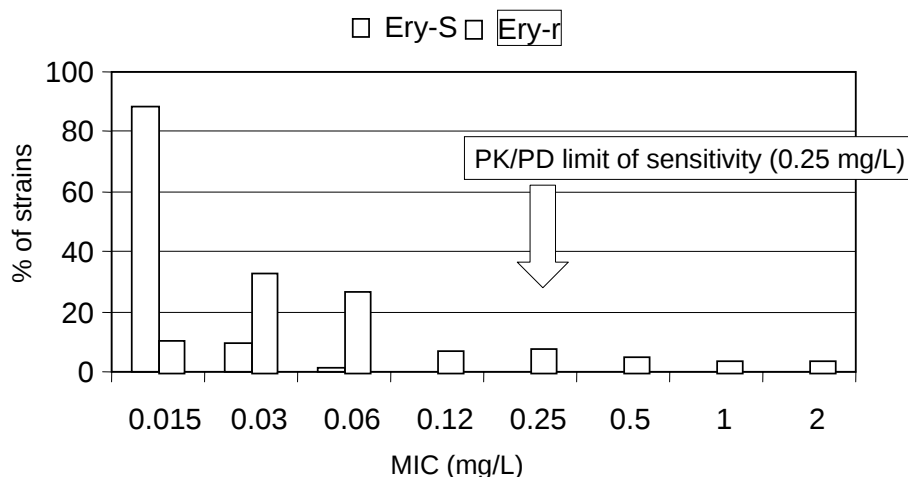
http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

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Which are the sensitivities of *S. pneumoniae* towards telithromycin
in Belgium in 2000 ?



MIC₉₀ for Ery-s strains: < 0.06 ...

But MIC₉₀ for Ery-r strains: 0.25-0.5 ...

Verhaegen & Verbist, Acta Clin. Belg. 2001, 56: 351

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Macrolides: the 16 atoms family

Erythromycin A

14 atoms

Instability in acid media

Carbomycin A / Spiramycins

16 atoms

**Intrinsically
acid-stables**

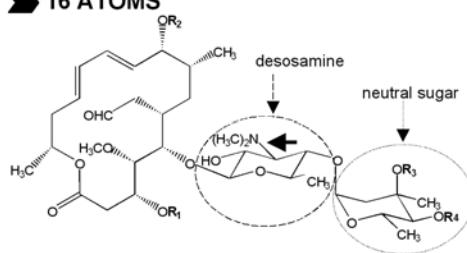
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Macrolides: the 16 atoms family

➤ 16 ATOMS



joramycin

$R1 = COCH_3 / R2 = H / R3 = H / R4 = COCH_2CH(CH_3)_2$

miocamycin

$R1 = COCH_2CH_3 / R2 = COCH_3 / R3 = COCH_3 / R4 = COCH_2CH_3$

spiramycin

$R1 = H / R2 = CO(CH_2)_2CHCHOHCH_3 / R3 = H / R4 = H$

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