



Azalides revisited: Why the single dose ?

The pharmacologist's answer ...

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www.facm.ucl.ac.be



www.isap.org

The patient's views ...

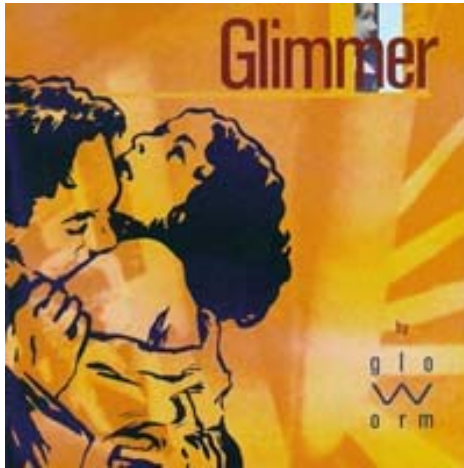
- Once daily makes it easier for me, Doc...
 - Enoxaparin ... (Thromb Res. 2004;114(3):149-53)
 - Doxazosin ... (Expert Opin Pharmacother. 2004 Sep;5(9):1957-64).
 - HAART ... (HIV Clin Trials. 2003 May-Jun;4(3):193-201)
 - β_2 -agonists ... (Eur J Clin Pharmacol. 2002 Jul;58(4):S1-21)
 - Aminoglycosides ... (Br J Clin Pharmacol. 1995 Jun;39(6):597-603)
 - ...



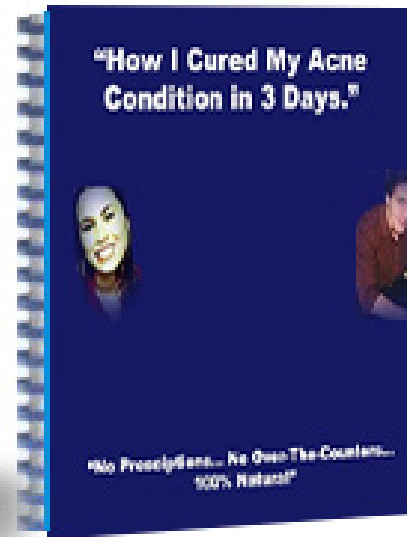
The patient's views ...

- A short treatment of my infections is what I want ...if it works ...
 - 3 days is (clinically) similar to 5-10 days for UTI
(Cochrane Database Syst Rev. 2005 Apr 18;(2):CD004682.)
 - Ultrashort (4 days) eradication of *H. pylori*
(Rev Gastroenterol Peru. 2005 Jan-Mar;25(1):23-41.)
 - 5 days for acute sinusitis ...
(Treat Respir Med. 2004;3(5):269-77.)
 - Less than 7 days for community-acquired pneumonia.
(Clin Infect Dis. 2004 Sep 1;39 Suppl 3:S159-64).

They can't be all wrong either...



You are better soon..



Yes, 3 days are enough...

The doctor's view ...

- Compliance is inversely proportional to the number of takes (and drugs) per day ...
 - Type-2 diabetes mellitus
(Clin Ther. 2004 Dec;26(12):2066-75)
 - Once-daily didanosine
(Antivir Ther. 2004 Jun;9(3):335-42)
 - Valproate and control of epilepsy ...
(Epilepsy Behav. 2003 Dec;4(6):710-6)
 - β -blocker and chronic glaucoma
(J Fr Ophtalmol. 2003 Sep;26(7):668-74).

The pharmacologist's key question ...

- What do you need for "once-daily" ?
 - long serum half-life ?
 - high, sustained tissue levels ?
 - Some sort of pharmacodynamic parameter ???

Hint: do aminoglycosides have the two first properties ?

Second hint: what if you have all three properties ?

Pharmacodynamic properties of antibiotics

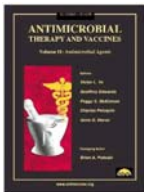
Available antibiotic can be divided in 3 groups

- time - dependent ($T > MIC$)
- AUC / MIC - dependent
- both AUC / MIC AND peak / MIC -dependent

Azithromycin has an long serum half-life ...

Table 3. Main Pharmacokinetic Properties of Macrolide Antibiotics

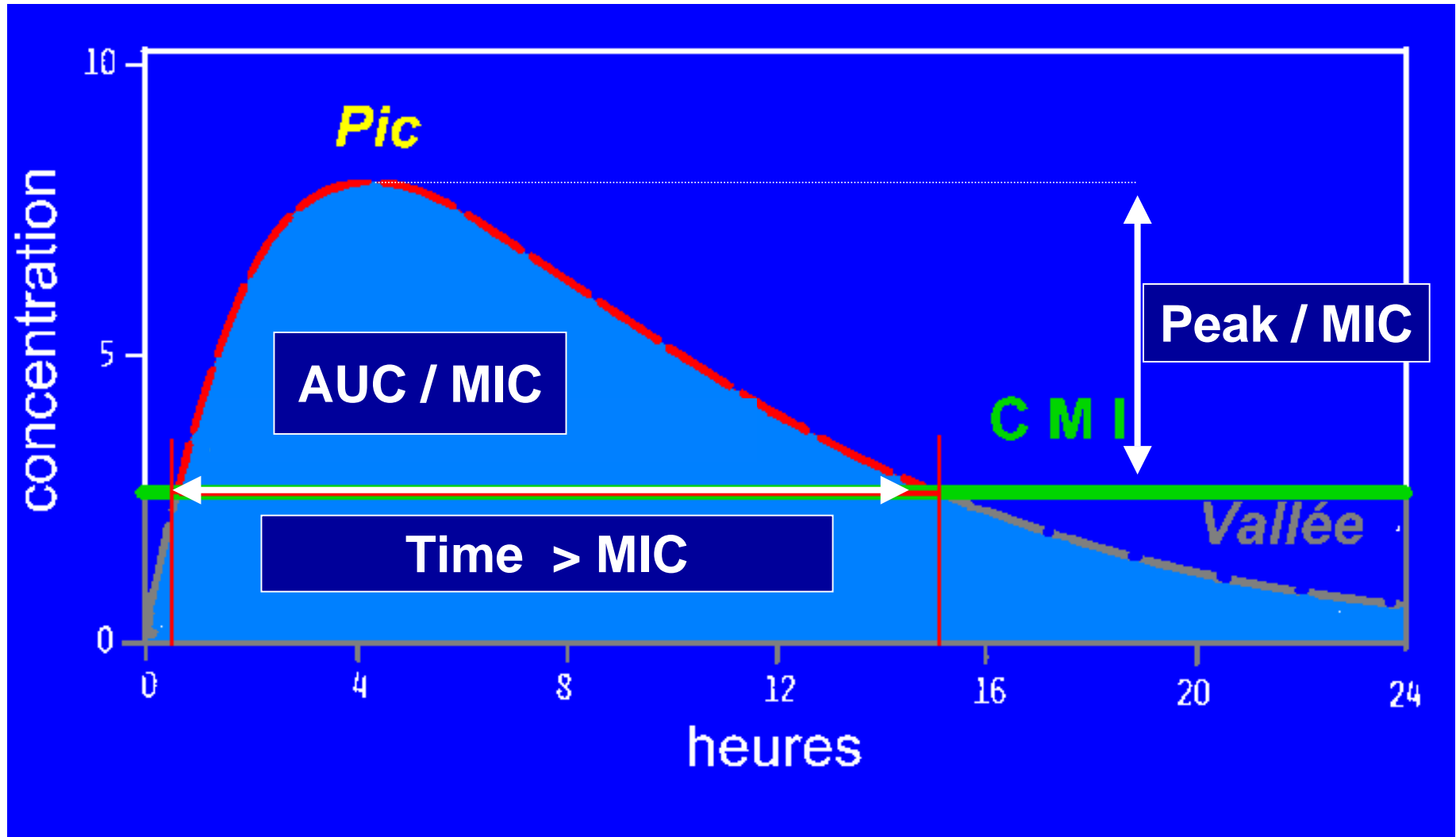
Pharmacokinetic parameter	<i>Erythromycin</i> (500 mg bid) (45)	<i>Roxithromycin</i> (150 mg qd) (349)	<i>Clarithromycin</i> (250 mg qd) (338, 339, 410)	<i>Dirithromycin</i> (500 mg qd) (45, 463)	<i>Azithromycin</i> (500 mg qd) (136, 338, 339)
C _{max} (mg/l)	3	6.8	6.8	0.2-0.6	0.4
T _{max} (h)	1.9-4.4	2	2.7	3-5	2.5
T _½ (h)	2	8-13	4.4	42	35-40



Mulazimoglu, Tulkens, and Van Bambeke: **Macrolides.**

In: Antimicrobial Therapy and Vaccines (Volume II) Editors: Victor L. Yu, Rainer Weber & Didier Raoult
<http://www.antimicrobe.org>

Pharmacokinetic parameters



Antibiotics Group # 2

(after W.A. Craig, 2000; revised 2003)

Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects

AB	PK/PD parameter	Goal
glycopeptides tetracyclines macrolides azalides fluconazole	24h AUC / MIC ratio	Optimize the quantity of AB administered

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000;
revised accord. to Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003

PK/PD vs. efficacy

Table 4. Pharmacodynamics of azithromycin versus macrolide-susceptible and -resistant *S. pneumoniae* (AUC₀₋₂₄/MIC)

Isolate/MIC	Serum (free drug)		ELF (free drug)		MEF (free drug)	
	AUC ₀₋₂₄ /MIC	outcome	AUC ₀₋₂₄ /MIC	outcome	AUC ₀₋₂₄ /MIC	outcome
11771/0.06	36.7	E	153	E	153	E
11888/0.06	36.7	E	153	E	153	E
12808/2.0	1.1	R	4.6	↓0.2	4.6	↓0.5
3860/4.0	0.6	R	2.3	R	2.3	R
12629/8.0	0.3	R	1.2	R	1.2	R
3910/16.0	0.14	R	0.6	R	0.6	R
1217/32.0	0.07	R	0.3	R	0.3	R
2670/256	0.002	R	0.07	R	0.07	R

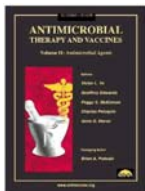
Assumption made that protein binding in ELF and MEF was the same as serum (fraction unbound 0.5). E, eradicated; R, regrowth; ↓0.2, 0.2 log₁₀ cfu/mL decrease; ↓0.5, 0.5 log₁₀ cfu/mL decrease.

Zhanel et al., Journal of Antimicrobial Chemotherapy (2003) 52, 83–88

Pharmacokinetics and beyond ...

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T _{max} (h)	1.9-4.4	2	2.7	3-5	2.5
T _½ (h)	2	8-13	4.4	42	35-40
Vd (l/kg)	0.64		3-4	11	23-31
Bioavailability	25-60 %	72-85 %	55 %	6-14%	37%
Protein binding	65-90	73-96	40-70	15-30	12-40
Tissue/serum concentration	0.5	1-2	3-8	20-30	50-1150
AUC (mg.h/l)	4.4-14	70	4.1	3.8	2-3.4



Mulazimoglu, Tulkens, and Van Bambeke: **Macrolides.**

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<http://www.antimicrobe.org>

Accumulation of azithromycin in cells

TABLE 1. Uptake of azithromycin and erythromycin by various phagocytic cells

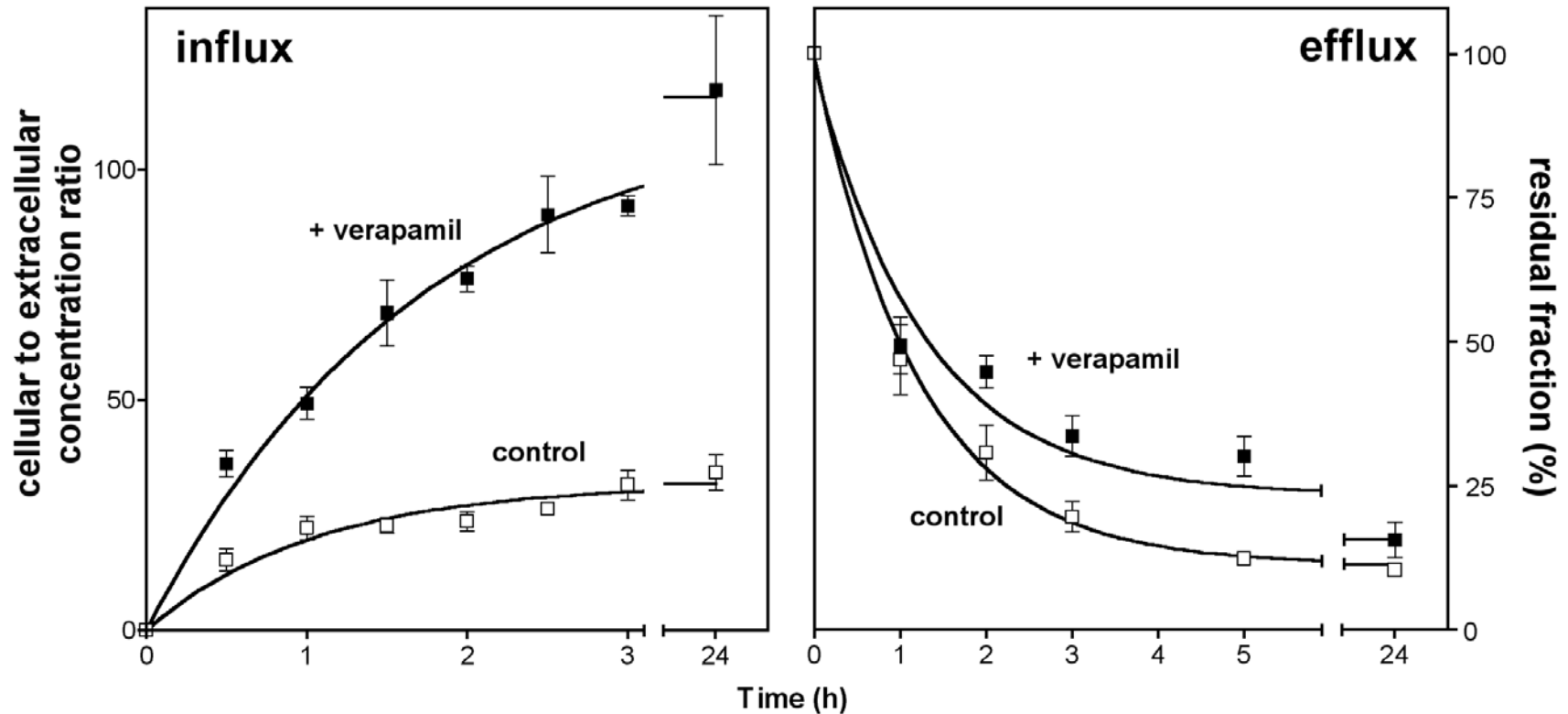
Cell type	Antibiotic ^a	Differential ^b	Antibiotic uptake	
			I/E	μg/10 ⁷ cells
Human PMNs	Azithromycin	4.9	79	1.58
	Erythromycin		16	0.32
Murine PMNs	Azithromycin	3.9	39	0.78
	Erythromycin		10	0.20
Murine alveolar macrophages	Azithromycin	5.9	170	18.66
	Erythromycin		29	3.18
Rat alveolar macrophages	Azithromycin	5.5	60	6.58
	Erythromycin		11	1.21
Murine resident peritoneal macrophages	Azithromycin	15.5	62	6.81
	Erythromycin		4	0.43

^a Cells were incubated for 2 h with 10 μg of the antibiotic per ml.

^b Ratio of azithromycin uptake to erythromycin uptake. All values are statistically significant.

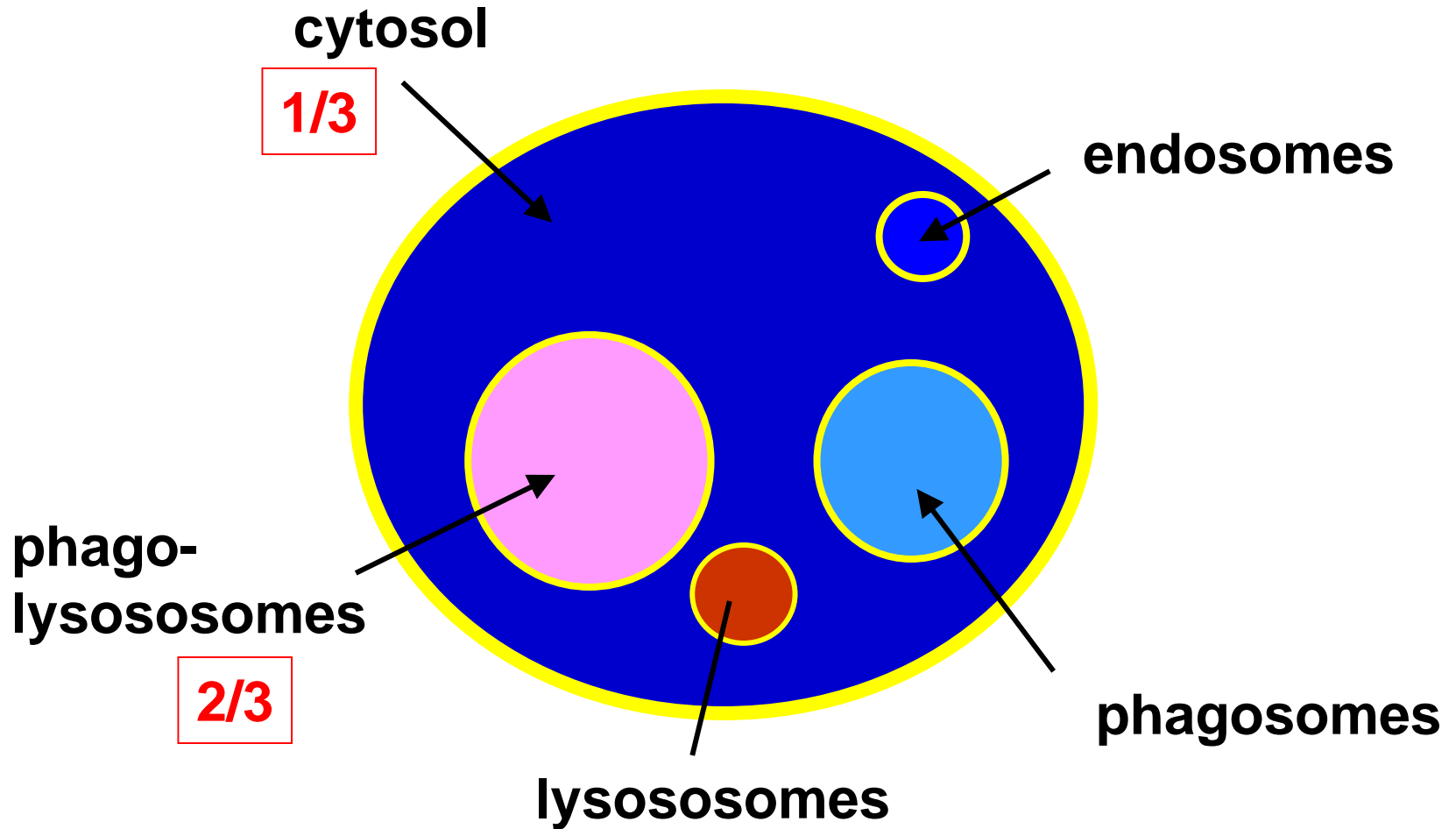
Gladue et al.,
AAC 33:277-82, 1989

Azithromycin is subject to P-gp-mediated efflux from macrophages...

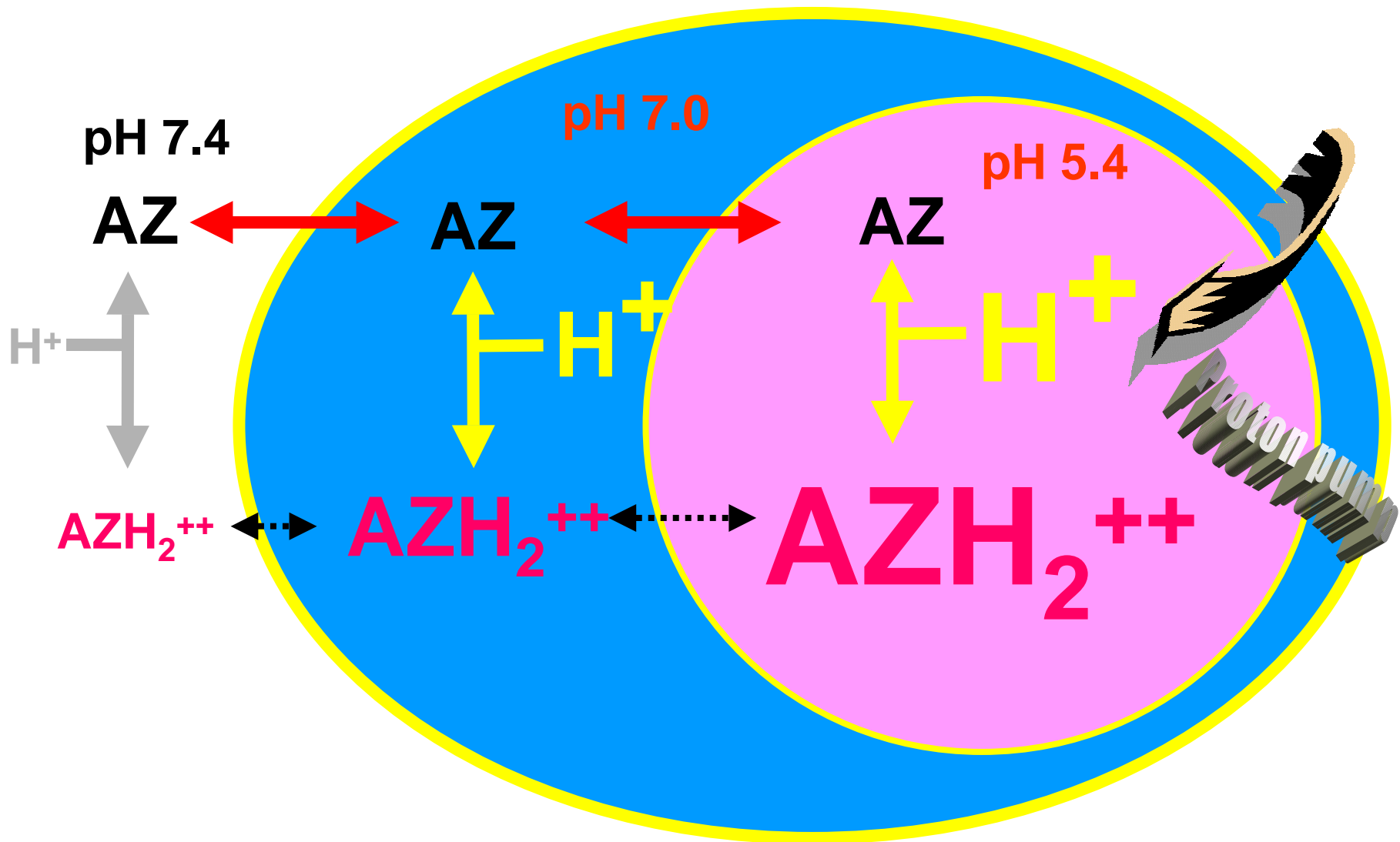


Kinetics of uptake (A) and release (B) of azithromycin in J774 murine macrophages with (open squares) or without (closed squares) 20 μ M verapamil.

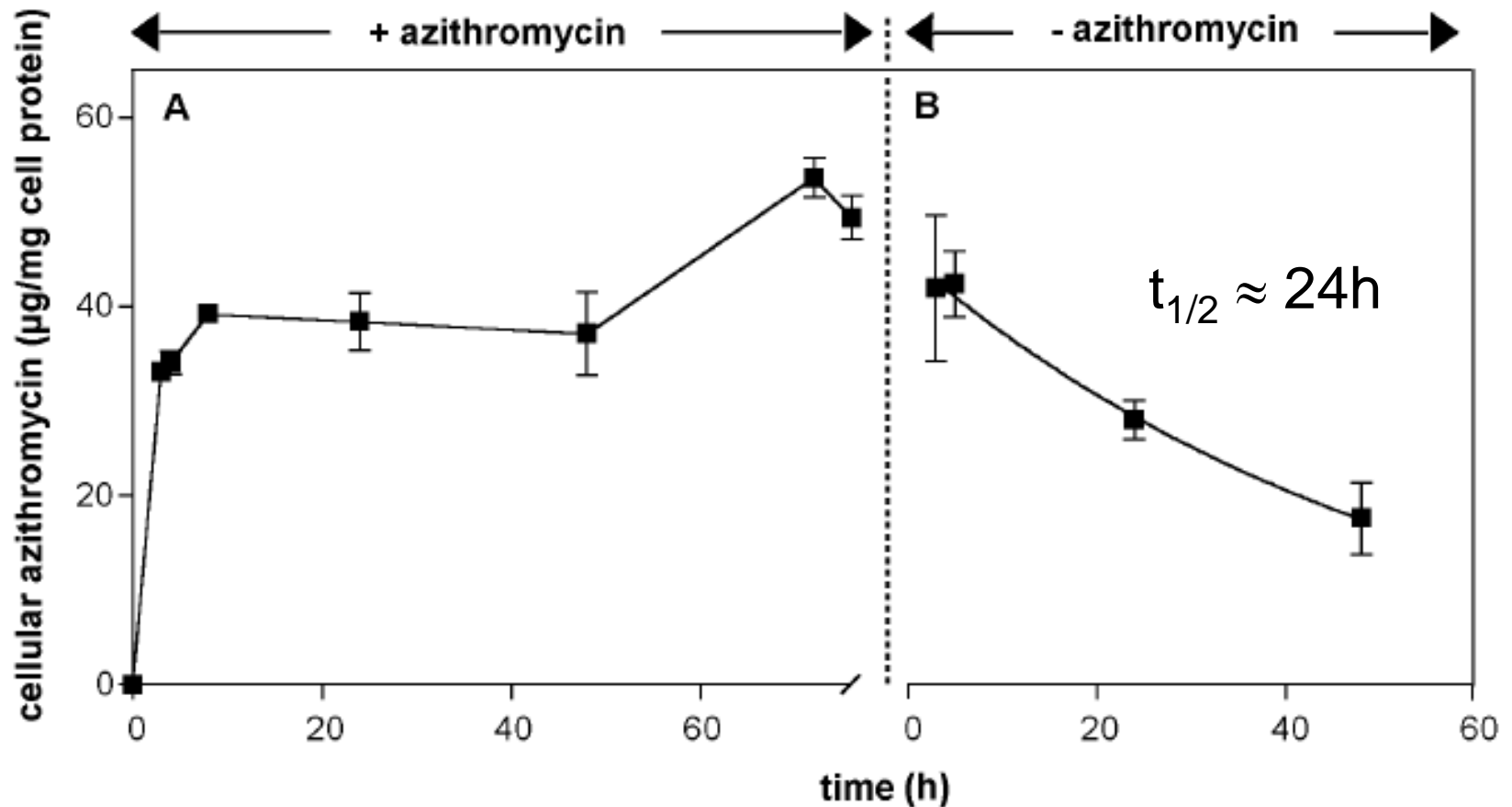
Intracellular localization of azithromycin



Mechanism of accumulation...

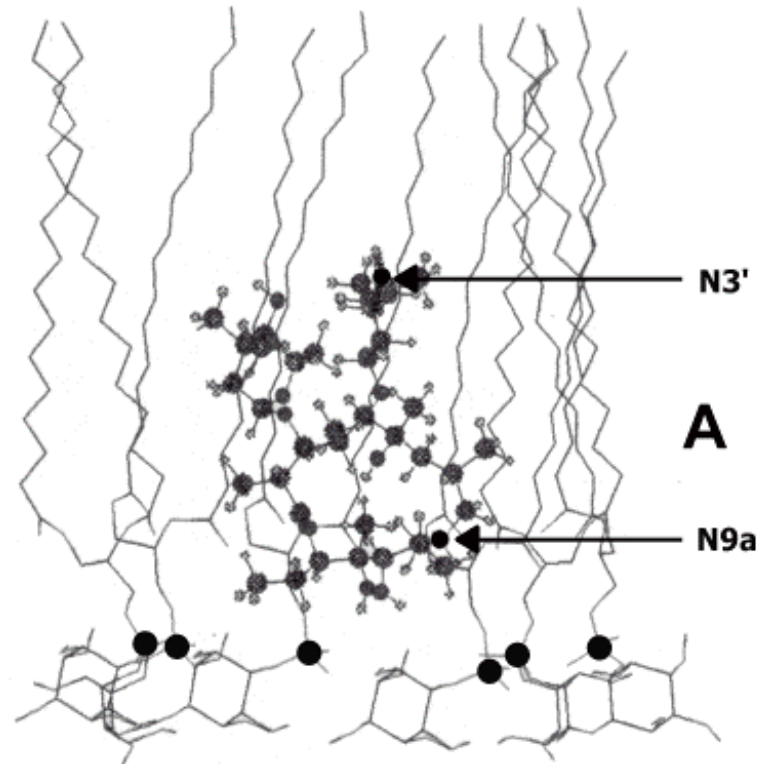
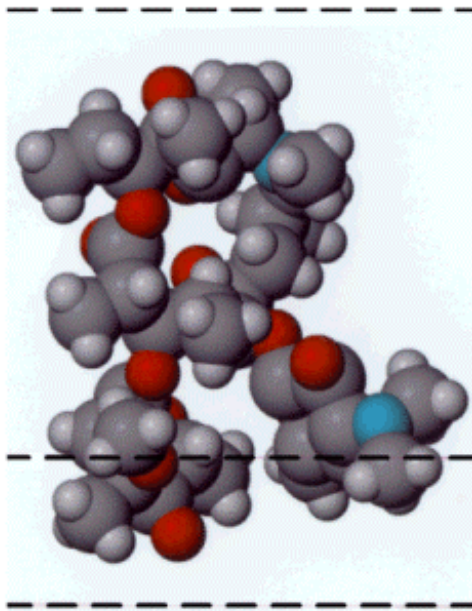


3-days exposure of cells to azithromycin is associated with slower release...



Tyteca et al., Eur. J. Cell Biol. 80:466-478, 2001

Azithromycin binds to (and is released from) phospholipids ...



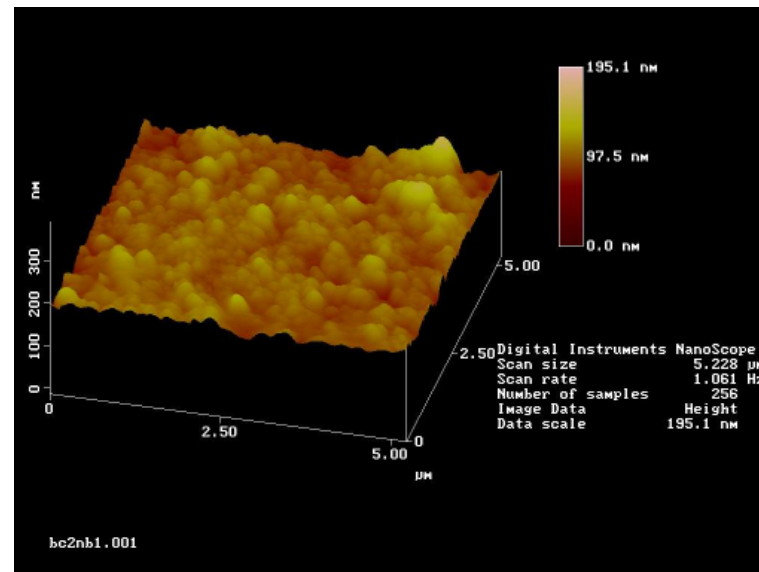
Montenez et al., Toxicol Appl Pharmacol. 1999 Apr 15;156(2):129-40.
Chanteux et al., Pharm Res. 2003 Apr;20(4):624-31.

Azithromycin interaction with phospholipids is visible



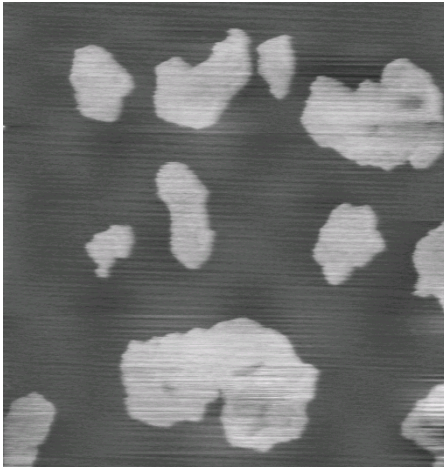
Atomic force microscopy
allows to probe the surface of
bilayers

Marti et al., Science. 1988 Jan 1;239(4835):50-2.



Azithromycin interaction with phospholipids is visible

AFM on DOPC:DPPC 1:1 bilayers :



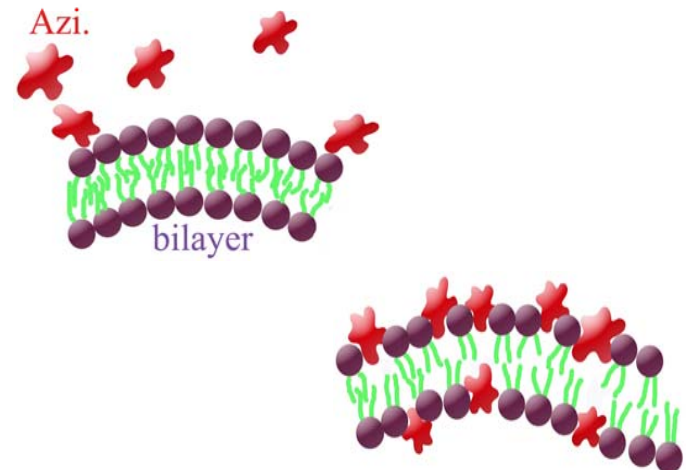
DPPC gel domains (white) in DOPC fluid matrix (dark) ; eight difference: 1.10 ± 0.05 nm



Addition of azithromycin + 60 mn : only one uniform fluid phase visible

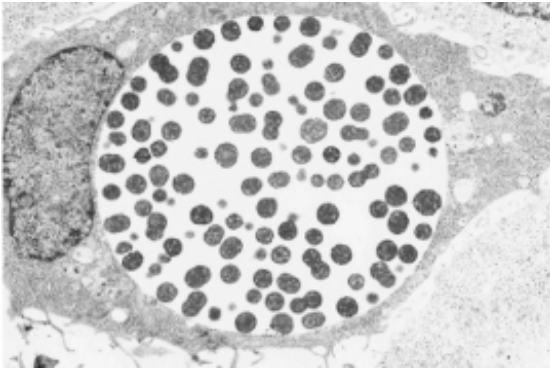
Actions of the azithromycin on bilayers :

- interaction of azithromycin with polar head groups
- fluidification of DPPC at the DOPC-DPPC interface
- decrease of the enthalpy associated to the gel-fluid phase transition
- enhancement of the fluctuations of the bilayers by mechanical effect of the insertion of azithromycin molecules between the polar head of DOPC molecules,



Berquand et al. Pharm Res. 2005 Mar;22(3):465-75.

Intracellular infection ...

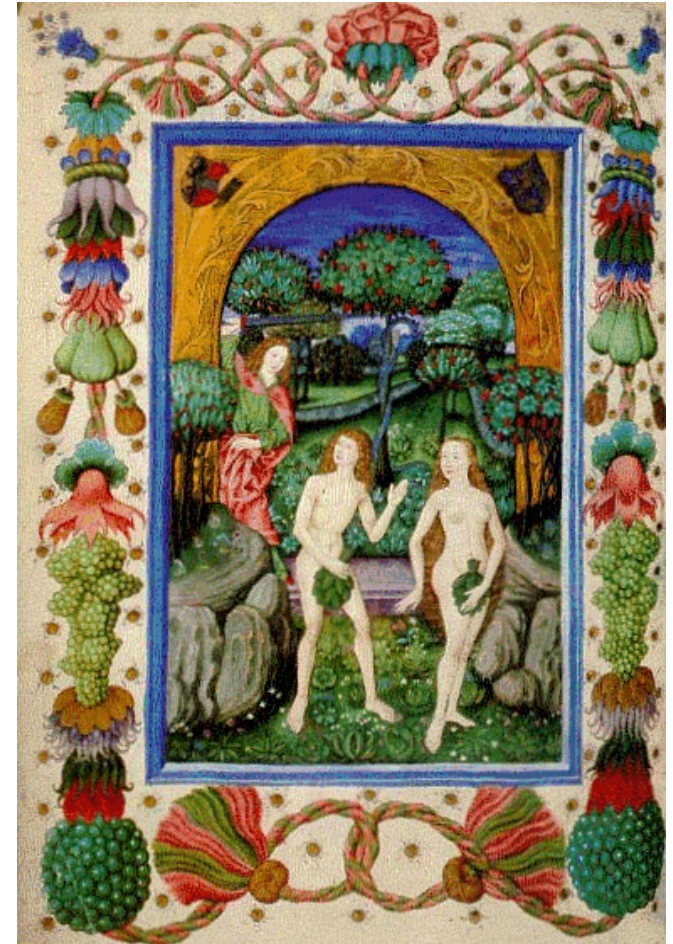


C. trachomatis:

- urethritis, cervicitis
- trachoma

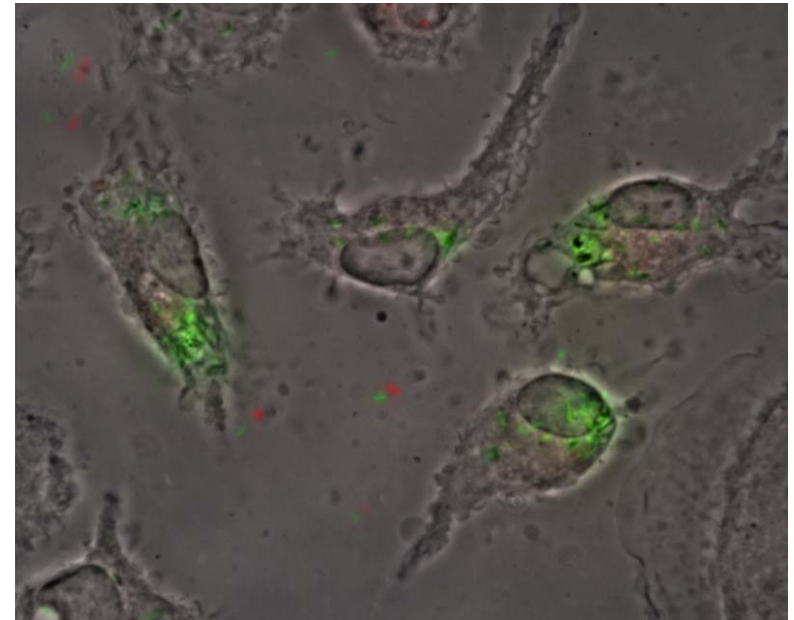
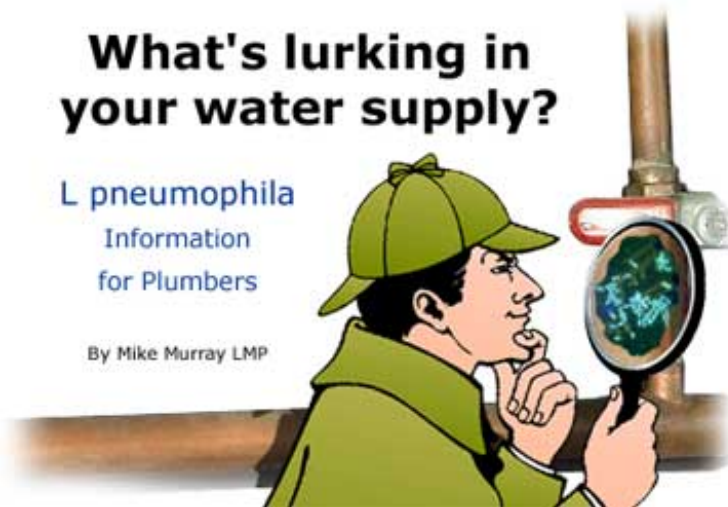
C. pneumoniae

- pneumonia



Intracellular infection ...

Legionella pneumophila...



Legionella infected macrophage (using legionella expressing green fluorescent protein; picture: Hubert Hilbi;

<http://www.ethlife.ethz.ch/e/articles/sciencelife/legionellenhilbi.html>

Azithromycin has pharmacological potentials ... and success in short treatments

□ 1: Treat Respir Med. 2005;4(1):31-9.

[Related Articles, Links](#)

Once-daily azithromycin for 3 days compared with clarithromycin for 10 days for acute exacerbation of chronic bronchitis: a multicenter, double-blind, randomized study.

Swanson RN, Lainez-Ventosilla A, De Salvo MC, Dunne MW, Amsden GW.

□ 1: Pediatr Infect Dis J. 2004 Feb;23(2 Suppl):S129-34.

[Related Articles, Links](#)



Defining the optimum treatment regimen for azithromycin in acute tonsillopharyngitis.

Cohen R.

□ 1: Antimicrob Agents Chemother. 2003 Sep;47(9):2770-4.

[Related Articles, Links](#)

Comment in:

♦ [J Fam Pract. 2004 Feb;53\(2\):98-101.](#)

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Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis.

Henry DC, Riffer E, Sokol WN, Chaudry NI, Swanson RN.

Azithromycin in single dose...

□ 1: *Pediatr Infect Dis J.* 2005 Feb;24(2):153-61.

[Related Articles, Links](#)



A randomized, multicenter, double blind, double dummy trial of single dose azithromycin versus high dose amoxicillin for treatment of uncomplicated acute otitis media.

Arguedas A, Emparanza P, Schwartz RH, Soley C, Guevara S, de Caprariis PJ, Espinoza G.

Azithromycin in single dose...

1: Arch Gynecol Obstet. 2005 Mar 19; [Epub ahead of print]

[Related Articles, Links](#)



The demographic and behavioural profile of women with cervicitis infected with *Chlamydia trachomatis*, *Mycoplasma hominis* and *Ureaplasma urealyticum* and the comparison of two medical regimens.

Guven MA, Gunyeli I, Dogan M, Ciragil P, Bakaris S, Gul M.

1: N Engl J Med. 2004 Nov 4;351(19):1962-71.

[Related Articles, Links](#)

Comment in:

- [N Engl J Med. 2004 Nov 4;351\(19\):2004-7.](#)
- [N Engl J Med. 2005 Jan 27;352\(4\):414-5; author reply 414-5.](#)

FREE full text article at
content.nejm.org

Mass treatment with single-dose azithromycin for trachoma.

Solomon AW, Holland MJ, Alexander ND, Massae PA, Aguirre A, Natividad-Sancho A, Molina S, Safari S, Shao JF, Courtright P, Peeling RW, West SK, Bailey RL, Foster A, Mabey DC.

Conclusions ...

- Azithromycin has the pharmacological potential of being a once-daily / single dose drug ...
- Clinical trials are encouraging ...
- This may be beneficial to
 - patients
 - public health
 - public economies ...



The Department of Defense Pharmacoeconomic Center
PEC UPDATE
Jun 2003, Vol. 03, Issue 6, www.pec.ha.osd.mil

What next ...

I simply throw ideas ...



Maybe, like those ones...

