# SUGESTÕES PARA LEITURA
# RESUMOS SELECIONADOS SOBRE AZITROMICINA E DST

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## Treatment of early syphilis with azithromycin

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An open, noncomparative study was performed to establish the efficacy of azithromycin in the treatment of early syphilis. Sixteen patients were treated with oral azithromycin: 1g the first day and then 500 mg for the following 8 days. Two patients were excluded from the study, leaving 14 patients for the evaluation of the efficacy. Venereal Disease Research Laboratory (VDRL) negativity was observed in 3 out of 6 patients treated for primary syphilis after 3 months and in all patients after 6 months. Two of 8 patients treated for manifest or early latent secondary syphilis had VDRL negativity after 3 months and 4 patients after 6 months. This study demonstrates that azithromycin is effective in the treatment of early syphilis. Two patients experienced gastrointestinal side effects which did not require treatment interruption.

## Azithromicin compared with penicilin G benzathine for treatment of incubating syphilis

***Ann Intern Med 1999 Sep 21;131(6):434-7***
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BACKGROUND: Preventive therapy is an important element of **syphilis** control efforts. No currently recommended, single-dose alternatives to penicillin G-benzathine are available for treatment of incubating **syphilis.** OBJECTIVE: To evaluate the use of a single 1.0-g dose of **azithromicyin** for treatment of persons recently exposed to sexual partners with infectious syphilis. DESIGN: Single-center, open-label, randomized pilot study to compare **azithromicin** with penicilin G benzathine therapy. Participants were evaluated serologically for 3 months. SETTING: Sexually transmitted disease clinic in Birmingham, Alabama. PARTICIPANTS: 96 participants who in the preceding 30 days had been exposed to partners with infectious **syphilis** though sexual intercourse. MEASUREMENTS: **Syphilis** prevention, as indicated by nonreactive serologic tests (rapid plasma reagin and fluorescent treponemal anti-body-absorbed), throughout the 3-month follow-up. RESULTS: Among 96 participants anrolled, none of 40 evaluable persons in the **azithromycin** group and none of 23 evaluable persons in the penicillin group developed evidence of **syphilis.** Significantly more penicillin-treated participants (21 of 44 [48%]) than **azithromicin**-treated participants (12 of 52 [23%]) became nonevaluable during follow-up (P = 0,01). CONCLUSION: A single 1,0 g dose of **azithromicin** seems to be efficacious for prevention of **syphilis** in persons exposed to infected sexual partners.

## Treatment of syphilis with azithromycin

***Int J STD AIDS 1996;7 Suppl 1:13-5***
Mashkilleyson AL; Gomberg MA; Mashkilleyson N; Kutin SA
Semashko Moscow Medical School, Russia

The efficacy of oral azithromycin (500 mg daily for 10 days or 500 mg on alternate days for 11 days) in 100 patients with seropositive syphilis was studied. Clinical manifestations regressed more rapidly in azithromycin-treated patients compared with patients who received erythromycin or penicillin, and there was also a more rapid reduction in serum antibody levels. In 90.3% of patients, the complete resolution of classic serological tests was observed within 4 months of completion of the azithromycin treatment. The immobilization (TPI) test and absorbed fluorescent treponema antibody tests became negative 12 months after treatment in 40% of patients. After 4 years of follow-up, no symptoms of neurosyphilis or syphilitic changes of visceral organs were observed.

## Pilot study of azithromycin for treatment of primary and secondary syphilis

***Clin Infect Dis 1994 Sep;19(3):486-8***
Verdon MS; Handsfield HH; Johnson RB
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Washington

Azithromycin has in vitro activity against Treponema pallidum and is effective against experimental syphilis in rabbits. We undertook an open, noncomparative pilot study of oral azithromycin (500 mg once daily for 10 days) to treat 16 patients with primary or secondary syphilis who were seronegative for human immunodeficiency virus. Cure was documented for 11 of 13 patients observed > or = 3 months; three patients were lost to follow-up. The serological response of one patient with secondary syphilis was indeterminate, and one patient with primary syphilis had either relapse or reinfection. Four patients had mild gastrointestinal side effects, and another patient had an episode of nausea and vomiting; all side effects occurred in the first 3 days and resolved spontaneously as treatment continued. Azithromycin shows promise as an alternative agent for treatment of early syphilis; controlled trials and assessment of other dosage regimens are indicated.

## Azithromycin in the treatment of syphilis

Azitromitsin v lechenii sifilisa
***Antibiot Khimioter 1994 Jun;39(6):36-8***
Mashkilleison AL
Department of Medicine, University of Washington, Seattle.

The results of the use of azithromycin (sumamed) in the treatment of 100 patients with fresh syphilis were analyzed. The antibiotic was used in accordance with two treatment schemes: 500 mg daily for 10 days and 500 mg every two days. The total course dose was 5 g in both the cases. The results of the treatment with azithromycin were compared with those of the treatment with erythromycin (30 g) and penicillin (300,000 U every 3 hours for 16-28 days depending on the disease stage). The results were estimated by the rate of the elimination of Treponema pallidum and syphilids as well as by the time course of the seroreactions. The analysis provided a conclusion that the therapeutic efficacy of sumamed in the treatment of patients with fresh manifest syphilis was high: by comparison with penicillin and erythromycin it more rapidly eliminated the clinical signs of syphilis and in the majority of the cases induced negativation of the cutaneous serological reactions within the first 4 months of the treatment. Azithromycin was shown to be as effective as standard benzathine penicillin and erythromycin in the therapy of active syphilis in the rabbit model. Following production of primary chancres by intradermal inoculation of 10(6) Treponema pallidum, groups of six rabbits were treated with benzathine penicillin (200,000 units im weekly for two weeks), erythromycin base (30 mg/kg/day orally four times daily for 15 days) or azithromycin (30 mg/kg/day given orally once or twice daily for 15 days); one group was untreated. Daily darkfield (DF) microscopic examinations

of chancre aspirates were conducted to identify motile organisms. Although all treated animals became DF negative prior to completion of therapy, the median time to DF negativity was longer in animals given azithromycin once daily, compared with animals receiving benzathine penicillin (P less than 0.01); no difference was seen in comparison with animals receiving erythromycin. Untreated animals remained DF positive for greater than 15 days. The mean maximum lesion diameters for all treated animals were similar and were significantly smaller than in untreated rabbits; fewer lesions ulcerated in treated than in untreated animals. Subsequent dose-ranging studies indicated that administration of lower doses of azithromycin (15 mg/kg/day given orally either once or twice daily, or 7.5 mg/kg/day given once daily) was as effective as benzathine penicillin for therapy of active syphilis in this model, though the median time to darkfield negativity was significantly longer in the azithromycin-treated animals (P less than 0.01). Persistent infection was demonstrable in lymph nodes of untreated animals, but no evidence of virulent T. pallidum was found three months following transfer of tissue from any animal treated with penicillin, erythromycin, or azithromycin.

## Concentration of azithromycin in human prostatic tissue

***EurJ Clin Microbiol Infect Dis 1991 Oct;10(10):868-71***
Foulds G; Madsen P; Cox C; Shepard R; Johnson R

Prostatic tissue was obtained from 36 patients at two study locations and assayed for **azithromycin** by HPLC or bioassay. The mean concentration of **azithromycin** in human prostatic tissue (2,54 micrograms/ml) 14 h after 500 mg oral dosing (two 250 mg doses 12 h apart) was much greater than plasma concentrations (less than or equal to 0,1 microrganisms/ml) **Azithromycin** was slowly eliminated from prostatic tissue (half-life 60 h) and a mean concentration of 0,62 microrgams/ml remained 137 h after dosing.

## Efficacy of azithromycin for therapy of active syphilis in the rabbit model.

***J Antimicrob Chemother 1990 Jan;25 Suppl A:91-9***
**J Antimicrob Chemother**
Lukehart SA; Fohn MJ; Baker-Zander SA
Department of Medicine, University of Washington, Seattle.

**Azithromycin** was shown to be as effective as standard benzathine penicillin and erythromycin in the therapy of active syphilis in the rabbit model. Following production of primary chancres by intradermal inoculation of 10(6) *Treponema pallidum*, groups of six rabbits were treated with benzathine penicillin (200,000 units im weekly for two weeks), erythromycin base (30 mg/kg/day orally four times daily for 15 days) or azithromycin (30 mg/kg/day given orally once or twice daily for 15 days); one group was untreated. Daily darkfield (DF) microscopic examinations of chancre aspirates were conducted to identify motile organisms. Although all treated animals became DF negative prior to completion of therapy, the median time to DF negativity was longer in animals given azithromycin once daily, compared with animals receiving benzathine penicillin (P less than 0.01); no difference was seen in comparison with animals receiving erythromycin. Untreated animals remained DF positive for greater than 15 days. The mean maximum lesion diameters for all treated animals were similar and were significantly smaller than in untreated rabbits; fewer lesions ulcerated in treated than in untreated animals. Subsequent dose-ranging studies indicated that administration of lower doses of **azithromycin** (15 mg/kg/day given orally either once or twice daily, or 7.5 mg/kg/day given once daily) was as effective as benzathine penicillin for therapy of active **syphilis** in this model, though the median time to darkfield negativity was significantly longer in the **azithromycin**-treated animals (P less than 0.01). Persistent infection was demonstrable in lymph nodes of untreated animals, but no evidence of virulent T. pallidum was found three months following transfer of tissue from any animal treated with penicillin, erythromycin, or **azithromycin.**

## The pharmacokinetics of azithromycin in human serum and tissues

***J Antimicrob Chemother 1990 Jan;25 Suppl A:73-82***
Foulds G; Shepard RM; Johnson RB.
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The pharmacokinetics of azithromycin, a new azalide antibiotic, were examined in man. Approximately 37% of a single oral dose of 500 mg was bioavailable and produced a peak serum concentration of 0.4 mg/l. Multiple dose regimens (two doses of 500 mg separated by 12 h and followed by 500 mg qds for five days, or two doses of 250 mg separated by 12 h and followed by 250 mg qds for nine days) produced only slight increases in peak serum concentrations. The serum protein binding of azithromycin declined from about 50% at 0.02 mg/l to 12% at 0.5 mg/l. Tissue concentrations of azithromycin were much higher than serum concentrations. After two 250 mg doses 12 h apart, peak azithromycin concentrations exceeded 3 mg/kg in prostate, tonsil and many other tissues. Concentrations in tissues declined with apparent half-lives of 2.3 days in prostate and 3.2 days in tonsil. The high tissue concentrations suggest that proposed standard dosage regimens of 500 mg qds on day 1 followed by 250 mg qds for four days, or three daily dosages of 500 mg, will produce tissue concentrations above 3 mg/kg in a variety of tissues. Since these tissue concentrations exceed the MICs of relevant pathogens, these dosage regimens should be effective against respiratory tract and soft-tissue infections. A single 1 g dose may be effective in the treatment of many sexually transmitted diseases.

## Gynaecological tissue levels of azithromycin.

***Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):864-8***
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In an open study the concentrations of azithromycin in plasma, urine, peritoneal fluid and gynaecological tissue in 20 patients undergoing elective gynaecological surgery were compared. Patients were allocated to one of four groups and all patients received a single 500 mg oral dose of azithromycin prior to surgery. In Group I, the dose was administered 24 h before surgery. In Groups II, III and IV it was administered 48, 72 and 96 h, respectively, prior to surgery. A total of 19 patients completed the study; one patient had peri-operative complications and did not proceed to surgery. High concentrations of azithromycin were found in gynaecological tissue up to 96 h after administration. The mean maximum observed concentration 24 h after administration was 1.44 +/- 0.22 micrograms/g. Using all data, the depletion rate constant was 0.0104 h-1, equivalent to a half-life of approximately 67 h. The mean concentration of drug in peritoneal fluid was approximately 9% of the mean concentration in gynaecological tissue. Tissue and peritoneal fluid azithromycin concentrations were much higher than plasma levels at the time of surgery. Detectable plasma levels were only found in four patients from Groups I and II. Six percent of the total dose was excreted in the urine during the seven-day period after drug administration. The single dose of azithromycin was well tolerated by all the patients in this study and no treatment-related side effects or laboratory test abnormalities were seen. It is concluded that a single 500 mg oral dose of azithromycin produces high and sustained levels in gynaecological tissue up to 96 h after administration.

## Phagocyte uptake and transport of azithromycin.

*Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):828-33*
McDonald PJ; Pruul H
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Azithromycin achieves high concentrations in phagocytic cells and in fibroblasts. The newer macrolides also have this property but the intracellular penetration of azithromycin in relation to extracellular concentration is particularly notable. As a weak base, azithromycin is thought to concentrate in lysosomes of phagocytes and fibroblasts but many in vitro factors such as pH and temperature also affect the uptake process. Uptake of azithromycin by polymorphonuclear leucocytes results in an intracellular/extracellular concentration ratio of approximately 40 after one hour of incubation. Intraphagocytic antimicrobial activity has been demonstrated but is rather less than might be anticipated from the intracellular concentrations that are reached. Importantly, the high antibiotic levels found intracellularly do not appear to disrupt normal phagocyte function. Although azithromycin levels in the blood are low soon after administration, tissue concentrations are high and sustained. It appears that fibroblasts serve as a reservoir of drug in tissue, allowing activity against organisms and possibly transferring antibiotic to phagocytic cells for activity against intracellular pathogens and delivery to infection sites.

## Tissue-directed pharmacokinetics

*Am J Med 1991 Sep 12;91(3A):5S-11S*
Schentag JJ; Ballow CH
State University of New York, Buffalo 14209

Azalide antibiotics demonstrate pharmacokinetics distinct from all antibacterial agents in common use. Following oral absorption, conventional oral antibiotics diffuse through serum and interstitial compartments and are eliminated rapidly. A minimal to moderate degree of intracellular penetration may be observed. The pharmacokinetics of azithromycin, the first azalide, are characterized by a rapid and extensive movement of the drug from the serum into intracellular compartments. A dynamic equilibrium exists between the intracellular, interstitial, and serum compartments, with predominant flux into tissue sites. Azithromycin is concentrated to a high degree within phagocytes and transported by chemotactic mechanisms to the site of infection. High concentrations of azithromycin are found in pulmonary, genital, and lymphatic tissues. Azithromycin's serum levels decline in a polyphasic manner with a terminal half-life of approximately 60 hours. These kinetics allow azithromy!cin to be administered once daily. It is predicted that after drug administration for 5 days, therapeutic levels of azithromycin will be maintained at the tissue sites of infection for an additional 4-7 days. Consideration of the extravascular pharmacodynamics of azithromycin is necessary when making predictions regarding its therapeutic application.

## Clinical toleration and safety of azithromycin

*Am J Med 1991 Sep 12;91(3A):40S-45S*
Hopkins S

The toleration and safety profile of the azalide antibiotic, azithromycin, has been assessed in 3,995 patients aged 2-94 (mean, 36) years, comprising 1,644 females and 2,351 males. Patients with infections of the respiratory tract or skin/skin structure received 1.5 g azithromycin over 5 days; patients with urethritis/cervicitis caused by Chlamydia were treated with 1 g as a single dose. Assessments of side effects and laboratory safety test abnormalities were made pretreatment and approximately 7-14 and 30 days after the start of therapy. Twelve standard antibiotics have been used for comparison. Overall, side effects were recorded in 12.0% of patients, significantly less (p less than 0.05) than with comparative drugs (14.2%). The most common side effects were diarrhea (3.6%), abdominal pain (2.5%), and other gastrointestinal symptoms. Ninety-three percent of side effects were classed as mild or moderate, and only 0.7% of patients withdrew from treatment, significantly less (p less than 0.001) than with comparative agents (2.6%). The frequency of side effects was not affected by patient age. Azithromycin had no marked or consistent effect on laboratory safety parameters. Treatment-related laboratory abnormalities were rare, the most common being transient increases of ALT and AST in 1.7% and 1.5% of patients, respectively. Specific tests revealed no neurologic, audiometric, or ophthalmologic abnormalities, or evidence of phospholipidosis. There were no pharmacokinetic interactions observed with theophylline, warfarin, cimetidine, carbamazepine, or methylprednisolone, but coadministration with food altered the absorption of the drug. Coadministration with antacids decreased the peak serum concentration of azithromycin, but did not affect its overall absorption. Azithromycin was well tolerated in the presence of a wide variety of concurrent illnesses and medications.

## An open study to compare the pharmacokinetics, safety and tolerability of a multiple-dose regimen of azithromycin in young and elderly volunteers.

*Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):850-2*
Coates P; Daniel R; Houston AC; Antrobus JH; Taylor T

An open, parallel study was conducted to compare the pharmacokinetics of oral azithromycin in young and elderly healthy volunteers. A total of 12 young subjects (six males, six females) with a mean age of 29 (range 22-39) years and another 12 elderly subjects (six males, six females) with a mean age of 72 (range 67-80) years were given a standard five-day therapeutic regimen of azithromycin (500 mg single dose on day 1 and 250 mg once daily on days 2-5). Pharmacokinetic results indicated that Cmax, Cmin and urinary excretion were similar in the two age groups. Mean AUC0-24 was significantly greater (2.7 micrograms.h/ml) at day 5 in the elderly subjects compared with the younger age group (AUC0-24 = 2.1 micrograms.h/ml) (p = 0.041). Similarly, tmax values on days 1 and 5 were significantly greater in the elderly subjects; 3.8 h compared with 2.5 h in young subjects (p = 0.005) on day 1 and 4.4 h, compared with 3.2 h (p = 0.047) on day 5. There was also evidence of an inverse relationship between creatinine clearance and AUC0-24 (p less than 0.01) but not urinary excretion or Cmax. Despite these observations, it is concluded that the differences between the two age groups were of insufficient magnitude to warrant a dose modification in elderly subjects with only mild renal impairment. Side effects, chiefly headache and gastrointestinal symptoms, were reported by seven subjects in each group. No subject, however, was withdrawn from the study and there were no treatment-related abnormalities in any of the laboratory parameters measured.

## Azithromycin in the treatment of sexually transmitted disease

*Journal of Antimicrobial Chemotherapy (1990) 25, Suppl A, 109-114*
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**One hundred** and eighty-two patients were enrolled in a rendomized third-party blinded study to assess the efficacy and safety of azithromycin in the treatment of sexually transmitted diseases. Three regimens of azithromycin, including a single oral dose, were compared with a standard treat-

ment with doxycycline. The patients were followed for four weeks. Efficacy was evaluated in 168 patients (113 azithromycin, 55 doxycycline). Fourteen patients had negative cultures or did not come for all follow-up visits. Of the 168, 138 were infected with *Chlamydia trachomatis* , 43 with *Neisseria gonorrhoeae* , and 45 with *Ureaplasma urealyticum* . Ninety-six per cent of the patients with chlamydial infections and 92% of those with gonorrhoea were cured with azithromycin . Two patients infected with *N. gonorrhoeae*, four with *C. trachomatis* and six with *U. urealyticum* had positive cultures on follow-up visits after receiving azithromycin . Of these 11 patients with positive cultures on follow-up visits , seven (five with *U. urealyticum* and two with *C. trachomatis*) violated the protocol by having intercourse with infected individuals during the study . Azithromycin was very well tolerated ; one patient complained of mild abdominal pain shortly after receiving the drug , seven patients had mild diarrhoea.

## Single dose azithromycin for the treatment of chancroid: a randomized comparison with erythromycin

***Sexually Transmited Diseases, July-August, 1994***
Mark W. Tyndall , MD , Elizabeth Agoki , RN , Francis A. Plummer, MD , Bch , Jo , Ndinya-Achola , MD, Bch , and Allan R. Ronald , MD.

**Background and Objectives** : Chancroid is endemic in sub-Saharan Africa and enhances the sexual transmission of the human immunodeficiency virus Type1 (HIV-1). Azithromycin is na orally , absorbed macrolide antibiotic that is active against *Haemophilus ducreyi* , the causative agent of chancroid , and has pharmacokinetic properties that are suitable for single dosing . Study Desing : In a randomized single-blinded study of 127 men presenting to a referral STD clinic with culture proven chancroid, we compared the efficacy of azithromycin 500mg given 4 times daily for 7 days . **Results :** Cure rates were 89% (73 of 82) in the azithromycin group and 91% (41 of 45) in the erythromycin group . A failure to respond to treatment was associated with HIV-1 seropositivity and a lack of circumcision . Both regimens were well tolerated. **Conclusions:** Azithromycin , given as a single 1g oral dose , is na effective treatment for chancroid in men , and offers major prescribing advantages over erythromycin .

## Pilot study of azithromycin in the treatment of genital donovanosis

***Genitourin Med 1996;72:17-19***
*Francis J Bowden , Jackie Mein , Catherine Plunkett , Ivan Bastian*

**Objectives :** To determine the effectiveness of azithromycin , an azalide antibiotic with long tissue half-life , in a pilot study of patients wiyh genital donovanosis in the Northern Territory , Australia . **Design :** Patients with histologically confirmed donovanosis were randomised to receive one of two open-label azithromycin dosage regimens: Regimen A-10g once weekly for 4 weeks ; or Regimen B-500 mg daily for 7 days . Patients were assessed at 6 weeks and classified as either "cured", "improved" or "failed". **Results :** Seven patients received regimens A and 4 received regimens B . six weeks after commencing treatment the genital ulcers of four pacients receiving regimen A and one pacient receiving regimen B had healed ; the lesions of the other six patients (3 in each regimen) were "improved". No patients failed to respond and no significant adverse reaction was recognise . The eleven patients were reviewed after completing the six-week trial ; all lesions had re-epithelialised wiyhout further antibiotic treatment , no relapses had occurred , the longest follow-up period being seven months . A futher 17 patients with donovanosis who were unable to meet the entry criteria were also treated successfully with azithromycin during the study period . **Conclusions :** This is the first time that azithromycin has been shown to have clinical activity against donovanosis . Poor compliance with prolonged courses of antibiotics is one of the major barriers to control of the disease . Intermittent or short-course therapy , made possible by the long tissue half-life of the drug , could facilitate control of donovanois in endemic populations if the high cost of medication can be addressed .

## Azithromycin and erythromycin in the treatment of cervical chlamydial infection during pregnancy

***Obstet Gynecol 1994;84:61-3***
Mark R Bush,MD, and Cesar Rosa, MD

**Objective:** To compare azithromycin and erythromycin in regard to side effects, intolerance, and cure rate in a pregnant population with chlamydial cervicitis. **Methods:** Thirty women were randomized to receive either erythromycin, 500 mg orally four times a day for 7 days, or azithromycin, 1 g orally as one dose. All subjects completed questionnaires identifying the incidence of nausea, vomiting, diarrhea, abdominal pain, and anorexia. Post-treament cultures were taken from all subjects. **Results:** All subjects receiving erythromycin reported two or more gastrointestinal side effects, versus none in the azithromycin group ($P < .001$). Five of 15 subjects in the erythromycin treatment arm were intolerant to the 500-mg dose given four times a day, compared to none in the azithromycin group ($P < .025$), so the dosage was lowered to 250 mg four times a day to complete the course. Repeat cervical testing demonstrated similar cure rates for both medications: 100 and 93% (14 of 15) for azithromycin and erythromycin, respectively.Conclusion: These data suggest that azithromycin is a valid treatment option in pregnant patients who cannot tolerate erythromycin because of side effects.

## A azitromicina no tratamento de Doenças Sexualmente Transmissíveis

***Rev. Contemp. Pharmacother. 1994, 5: 367-372***
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A azitromicina tem um espectro de atividade *in vitro* semelhante ao da eritromicina contra uma série de organismos sexualmente transmissíveis. A azitromicina é melhor absorvida que a eritromicina no aparelho gastrointestinal e provoca menos efeitos colaterais gastrointestinais. Sua prolongada meia vida tissular, com elevadas concentrações intracelulares, permite a administração de uma única dose diária, o que melhora a adesão dos pacientes ao tratamento. Estudos realizados *in vitro* sugerem que a azitromicina é muito eficaz contra *Chlamydia trachomatis* e *Haemophilus ducreyi*, além de Ter algum efeito contra *Treponema pallidum*, *Neisseria gonorhoeae*, *Ureaplasma urealyticum* e *Gardnerella vaginallis*. Estudos clínicos demonstraram que a azitromicina é um tratamento eficaz nas infecções por clamídia, em uma única dose, e ensaios clínicos sugerem que poderá ser um agente útil no tratamento do cancro mole e da sífilis.

## Presence of azithromycin milk concentrations: a case report

***Am J Obstet Gynecol 1994;170:1375-6***
Julie J. Kelsey, PharmD, Lynette R. Moser, PharmD,
Jenifer C. Jennings, PharmD, and Mark A. Munger, PharmD

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We describe a case of breast milk concentrations of azithromycin, na azalide antibiotic, in a woman with postpartum bilateral tubal ligation incisional cellulitis. Azithromycin appears to demonstrate a tirne-dependent versus time-accumulation profile in breast milk.

## Azithromycin levels in plasma and gastric tissue, juice and mucus.

***Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):862-4***
Harrison JD; Jones JA
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Azithromycin is the first member of a new class called the azalides. Its distribution in gastric tissues was studied in 27 patients (mean age 66 years) with proven gastric cancer due to be resected. Five groups of patients received a single 500 mg oral dose of azithromycin 24, 48, 72, 96 or 120 h pre-operatively. Samples of blood, gastric juice, mucus and gastric tissue were taken and azithromycin assayed by high performance liquid chromatography. There was an increase in the level of azithromycin in gastric juice up to the 73-96 h period reaching a median peak of 0.20 micrograms/ml. There were higher levels of azithromycin in gastric mucus (approximately double the maximum attained in gastric juice) at each of the time periods to 120 h after the dose of azithromycin. Much higher levels were seen in the gastric tissue (median peak of 4.6 micrograms/g), which were statistically significant compared with gastric juice for the first two time periods (24-48 h, $p = 0.005$; 49-72 h, $p = 0.012$). Concentrations seen in the gastric tissue specimens were between five- and 10-fold greater than those seen in gastric mucus, and approximately 20-fold greater than the levels seen in gastric juice at each of the time periods after dosing. It is concluded that remarkably high levels of azithromycin are found in gastric tissue within 24 h of a 500 mg oral dose and that these levels persist over a five-day period. There exists a significant concentration gradient from gastric tissue to gastric juice. Such levels may be advantageous in the therapy of Helicobacter pylori infections.

## High and prolonged pulmonary tissue concentrations of azithromycin following a single oral dose.

***Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):859-61***
Morris DL; De Souza A; Jones JA; Morgan WE
Department of Surgery, University Hospital, Nottingham, UK

Antibiotic concentrations in pulmonary tissue samples and plasma were studied in this open investigation. Twenty-nine patients scheduled for elective pulmonary surgery received a single oral dose of 500 mg azithromycin 24, 72, 96 or 120 h prior to the operation; two patients received 250 mg b.i.d. Blood samples were taken before and at the time of resection, and tissue was obtained during surgery. Plasma and tissue concentrations of azithromycin were measured by high performance liquid chromatography (HPLC) and a microbiological bioassay. Only one patient had a detectable plasma concentration of azithromycin (0.13 micrograms/ml), measured 24 h post-dose by HPLC. However, high and sustained levels were found in lung tissue: mean concentrations measured by HPLC were 3.10 micrograms/g (SD +/- 2.17), 2.55 micrograms/g (SD +/- 1.36), 3.94 micrograms/g (SD +/- 2.40) and 3.13 micrograms/g (SD +/- 0.50) at 24, 72, 96 and 120 h, respectively. Bioassay results were similar to those for the HPLC assay. In summary, azithromycin levels in pulmonary tissue remained close to 3 micrograms/g for up to 5 days after a single oral 500 mg dose, in contrast to plasma levels which were much lower. The lung concentrations found are inhibitory for many sensitive respiratory pathogens and short-course azithromycin therapy is therefore a possibility.
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## Concentrations of azithromycin in human tonsillar tissue.

***Eur J Clin Microbiol Infect Dis 1991 Oct;10(10):853-6***
Foulds G;Chan KH; Johnson JT; Shepard RM; Johnson RB

Patients scheduled to undergo tonsillectomy were administered 500 mg oral azithromycin as two 250 mg capsules given 12 h apart. Between 9 h and one week after the second dose, tonsil samples were taken during surgery and assayed for azithromycin. Mean concentrations in tonsillar tissue, 12 and 24 h after the second of the two 250 mg doses given 12 h apart, were 4.5 and 3.9 micrograms/g, respectively. Concurrent mean serum concentrations were approximately 0.03 and 0.01 micrograms/g, respectively. The mean concentration in tonsillar tissue 7.5 days after the last dose was 0.93 micrograms/g. The apparent half-life of drug in the tissue was 76 h. The ratio of mean concentration in tissue to that in serum was greater than 150-fold for all time intervals. The presence of high azithromycin concentrations in tonsillar tissue suggests that a once-daily regimen over five days or less may be effective in treating tonsillo-pharyngitis.

## Intracellular accumulation of azithromycin by cultured human fibroblasts [published erratum appears in Antimicrob Agents Chemother 1990 Oct; 34(10):2041

***Antimicrob Agents Chemother 1990 Jun;34(6):1056-60***
Gladue RP; Snider ME

Azithromycin was shown to achieve high concentrations in human skin fibroblasts. Intracellular penetration occurred rapidly (10 micrograms/mg of cellular protein after 3 h) and then increased progressively over a 3-day period; azithromycin accumulated up to 21 times more than erythromycin (61.1 versus 2.9 micrograms/mg of protein). Uptake was dependent on the extracellular concentration, was inhibited at 4 degrees C, did not occur in nonviable cells, and was reduced by a low pH. Intracellular accumulation was not affected by the metabolic inhibitor 2,4-dinitrophenol or sodium fluoride or by the nucleoside transport inhibitor 2-chloradenosine. Once concentrated in cells, azithromycin remained intracellular and was released slowly in the absence of extracellular drug, compared with erythromycin (17 versus 78% released after 1 h). After 48 h of incubation in drug-free medium, 27% of the initial amount of azithromycin remained cell associated. The release of azithromycin was not affected by various monokines reported to stimulate fibroblasts (interleukin-1 or tumor necrosis factor) or by exposure to bacteria. Incubation of azithromycin-loaded fibroblasts with human polymorphonuclear leukocytes resulted in a higher intracellular accumulation of azithromycin in polymorphonuclear leukocytes than in cells incubated with free nonintracellular azithromycin for the same time (8.3 versus 2.2 micrograms/ml after 2 h), suggesting a more efficient or rapid uptake through cell-to-cell interaction. The widespread distribution of fibroblasts in tissues suggests a potential for these cells, and possibly other lysosome-containing tissue cells, to serve as a reservoir for azithromycin, slowly releasing it for activity against extracellular organisms at sites of infection and passing it to phagocytes for activity against intracellular pathogens and potential transport to sites of infection.

## Relationship of high tissue concentrations of azithromycin to bactericidal activity and efficacy in vivo

***J Antimicrob Chemother 1990 Jan;25 Suppl A:83-9***
Retsema JA; Girard AE;Girard D; Milisen WB

Measurement of killing kinetics of azithromycin against strains of Streptococcus pneumoniae and Klebsiella pneumoniae in vitro showed that it had a limited bactericidal activity (greater than 90% kill) for the first eight hours of incubation, but developed complete bactericidal activity (greater than 99.9% kill) by 24 h incubation. Since high and sustained tissue levels of azithromycin occur in animals and humans, it was proposed that it might produce a bactericidal effect in vivo. This was demonstrated in a lung infection model in mice, designed to mimic the in-vitro killing studies. A 25 mg/kg dose of azithromycin given 24 h before intranasal challenge reduced the recoverable Str. pneumoniae population by greater than 99.9%, in comparison with untreated controls. Erythromycin did not produce a bactericidal effect at 100 mg/kg, and roxithromycin only reduced the viable count by 96%, at a dose of 50 mg/kg. Against a K. pneumoniae lung infection, a 50 mg/kg dose of azithromycin reduced the bacterial count by 99%. The bactericidal effect was correlated with lung tissue concentrations of azithromycin. In a proliferating Escherichia coli paper disc infection model, extravascular fluid concentrations of azithromycin were correlated with a 99.9% reduction in bacterial count, while corresponding serum concentrations were always less than the MIC. Dosing with azithromycin eradicated Haemophilus influenzae from the bulla (middle ear) of gerbils, as was not the case with erythromycin and roxithromycin. This effect was correlated with the antibiotic concentration in bulla lavage.

J bras Doenças Sex Transm 13(3): 39-44, 2001

**Treatment of *Chlamydia trachomatis* during pregnancy – published trials during 1990 – 1998**

| Lead author & year | Antibiotics | Number enrolled | Results – Cure rates | Gastrointestinal side effects | Detection methodology | Remarks |
|---|---|---|---|---|---|---|
| Crombleholme, 1990 | Amoxicillin vs. erythromycin | 193 | 98% with amoxicillin and 95% with erythromycin | 13% of women in erythromycin group stopped therapy | Culture three weeks after therapy | Excluded from Cochrane Data Base secondary to methodology problems |
| Magat, 1993 | Amoxicillin vs. erythromycin | 143 | 86% witch amoxicilin and 94% with erythromycin | 23% of women in erythromycin group stopped therapy | Culture four weeks after therapy | Includes intent to treat analysis |
| Alary, 1994 | Amoxicillin vs. erythromycin | 210 | 98% witch amoxicilin and 88% with erythromycin | 13% of women in erythromycin group stopped therapy | Culture three weeks after therapy | Includes intent to treat analysis |
| Bush, 1994 | Azithromycin vs. erythromycin | 30 | 100% witch azithromycin and 93% with erythromycin | 33% of women in erythromycin group stopped therapy | Direct DNA assay (GenProbe) - 14 days after therapy | |
| Silverman, 1994 | Amoxicillin vs. erythromycin | 74 | 82% witch amoxicilin and 84% with erythromycin | 13% of women in erythromycin group stopped therapy | Culture three to four weeks after therapy | Failures were crossed over to other therapy |
| Turrentine, 1995 | Erythromycin vs. Amoxicillin vs. clindamycin | 174 | 96% with erythromycin 94% with amoxicillin and 98% with clindamycin | 15% of women in erythromycin group stopped therapy | Culture four weeks after therapy | Other trials of clindamycin show similar results – 10% of clindamycin group did not complete treatment |
| Rosenn, 1996 | Azithromycin vs. erythromycin | Unclear | 91% witch azithromycin and 77% with erythromycin | | Unclear | Published only as abstract |
| Adair, 1998 | Azithromycin vs. erythromycin | 106 | 88% witch azithromycin and 93% with erythromycin | 19% of women in erythromycin group stopped therapy | Direct DNA assay (GenProbe) three weeks after therapy | |

**Summary** – Erythromycin treatment for *Chlamydia* during pregnancy is characterized by severe gastrointestinal side effects. Thirteen to 33% of women will quit therapy due to these side effects. **Amoxicillin** has been studied in four prospective randomized trials. Cure rates ranged from 82 to 98%. All three studies used culture for *Chlamydia as a test of cure*. Since beta lactam antibiotics may cause persistence of infection, cure rates may be overstated. Few of the above studies have used the newer non-culture techniques available. ***Azithromycin*** was studied in three of the above studies. One has been published only as an abstract. The study by Bush is small with only thirty subjects. The study by Adair was published at the same time as the new CDC guidelines for the treatment of sexually transmitted diseases. Potentially advantages of azithromycin include a single dose therapy with a high cure rate. For these reasons, azithromycin should be considered as a safe and effective therapy for *Chlamydia* during pregnancy.

# DST RECIFE 2001

31 DE AGOSTO E 1º DE SETEMBRO DE 2001

**Promoção:** Cooperativa dos Médicos Ginecologistas e Obstetras de Pernambuco
Sociedade Brasileira de Doenças Sexualmente Transmissíveis
Real Hospital Português de Beneficiência de Pernambuco

**Local:** Auditório do Real Hospital Português de Pernambuco

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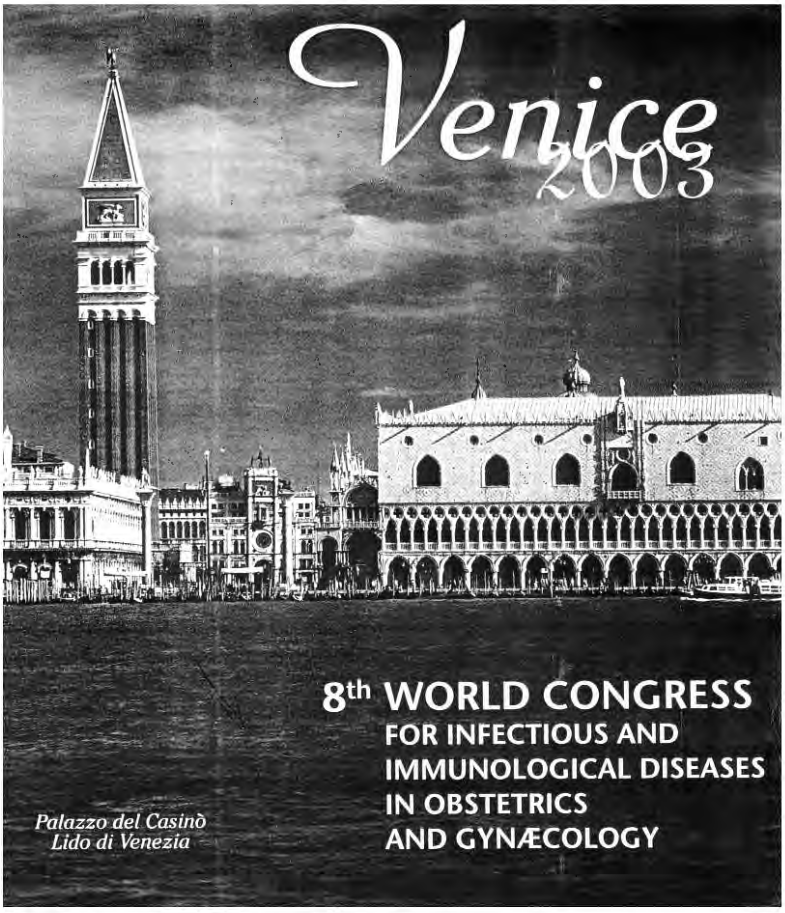


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