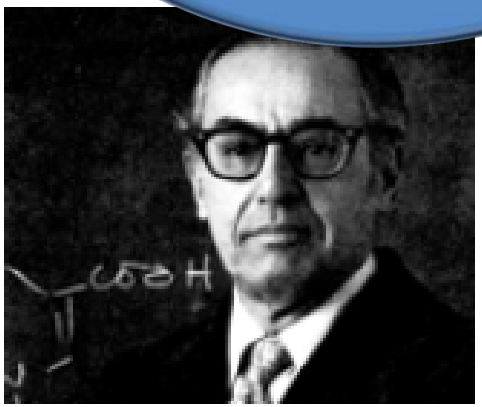
# Chinolonici in pediatria: quando e dove?

Elena Chiappini

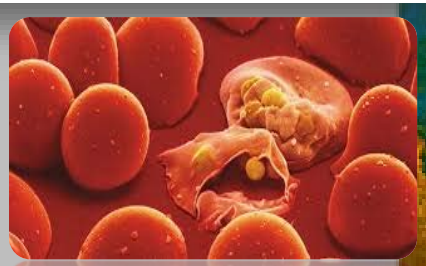
Dipartimento di Scienze della Salute, Università di Firenze

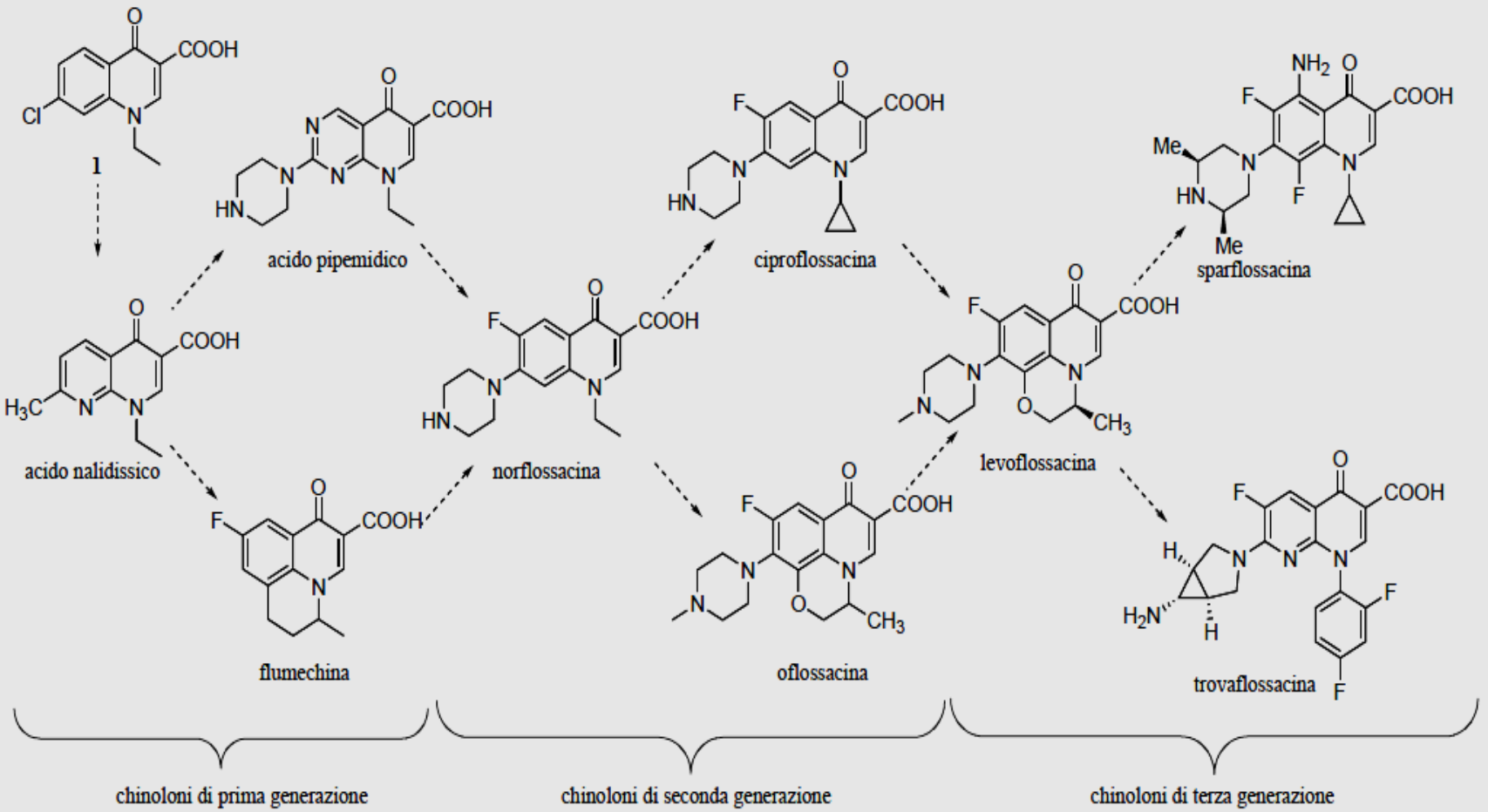
# I chinolonici non sono antibiotici ma chemoterapici antibatterici di sintesi



George Y. Lesher

The area of quinolones began with the introduction of nalidixic acid in 1962 for treatment of kidney infections in humans. The substance was discovered by George Lesher and coworkers in a distillate during chloroquine synthesis. Nalidixic acid, predecessor of all members of the family of topoisomerase inhibitors, is thus a by-product of antimalarial research. Due to modest serum and tissue kinetics, a consequence of high protein binding, and unfavourable antibacterial activity, the benefits of therapy with nalidixic acid were limited to Gram-negative infections of the urinary tract in humans.





Diparti la
Salute, e

International Journal of Antimicrobial Agents

Available online 7 February 2015

In Press, Corrected Proof — Note to users

Review

# Appropriate use of fluoroquinolones in children

Nicola Principi, Susanna Esposito

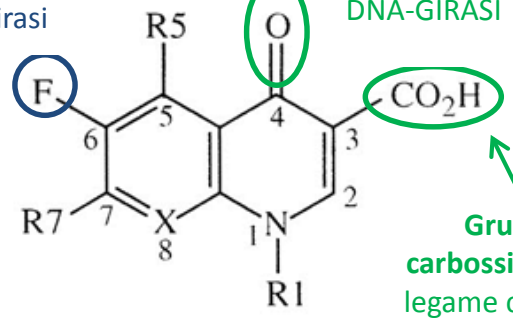
- BATTERICIDA
- AMPIO SPETTRO D'AZIONE
- OTTIMA DISPONIBILITÀ PER VIA ORALE
- OTTIMA PENETRAZIONE IN MOLTI TESSUTI E BUONA DIFFUSIONE INTRACELLULARE
- BUONA TOLLERABILITÀ

Dipartimento di Scienze della Salute, Università di Firenze

**Owens R C. Clin Infect Dis 2005;41:S144-S157**

aumentata affinità per la DNA-girasi

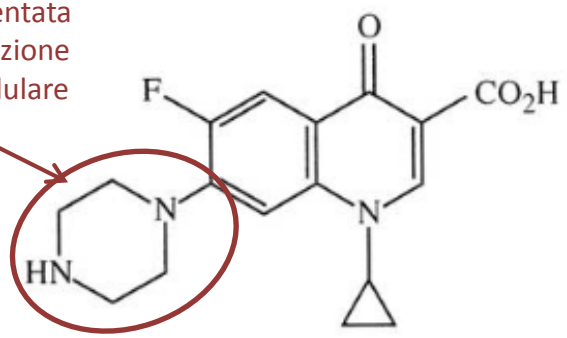
**Gruppo 4-carbonile:** media il legame con la DNA-GIRASI



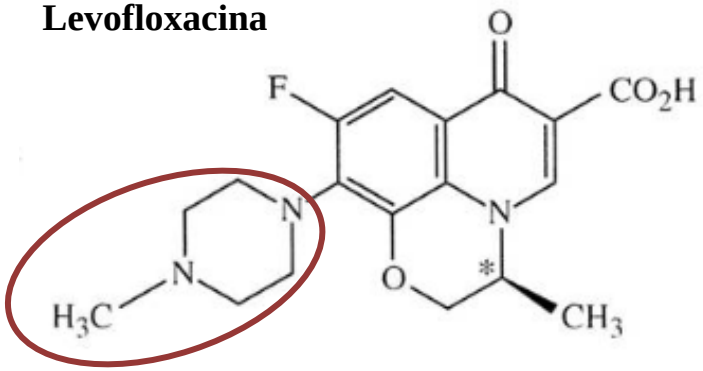

**Gruppo 3-carbossile:** media il legame con la DNA-GIRASI

**Ciprofloxacina**

**Anello piperazinico in posizione 7**: incrementata penetrazione intracellulare



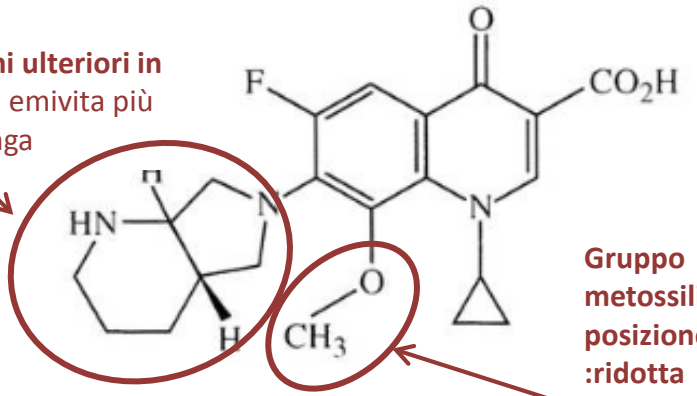

**Levofloxacina**




**Modificazioni ulteriori in posizione 7**: maggiore attività verso Gram+

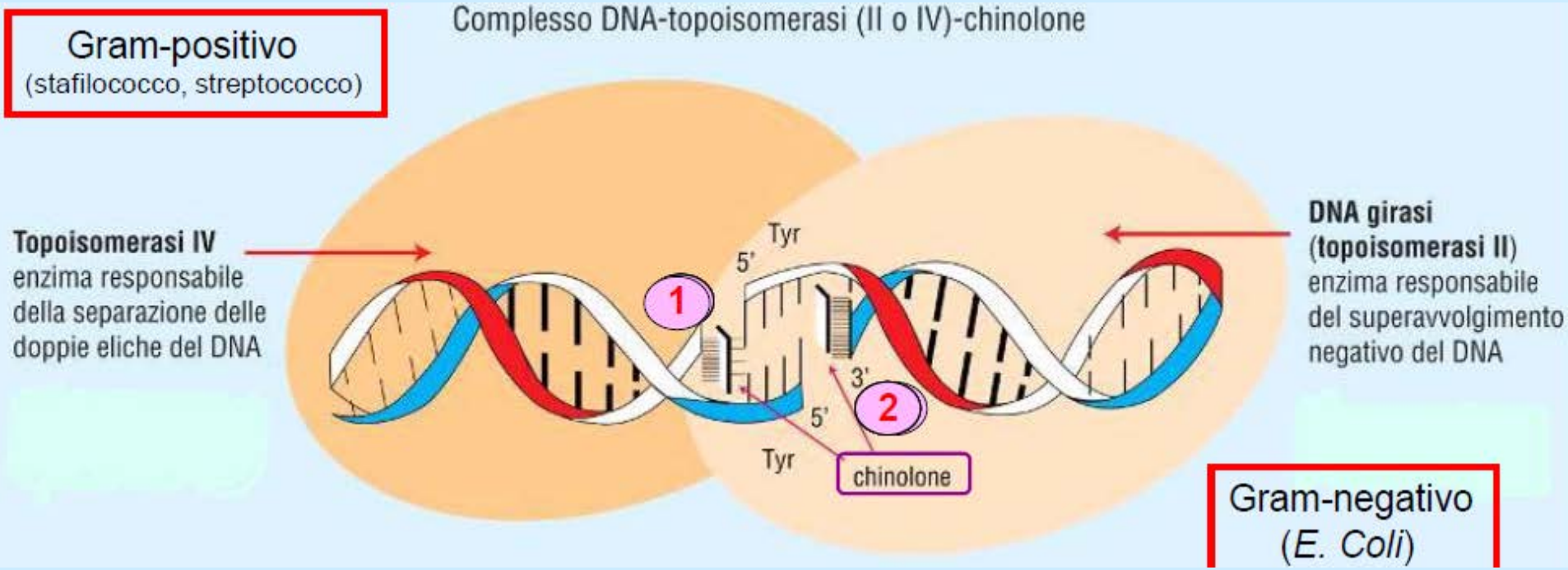
**Moxifloxacina**

**Modificazioni ulteriori in posizione 7**: emivita più lunga




**Gruppo metossilico in posizione 8 :ridotta fototossicità**

**Owens R C. Clin Infect Dis 2005;41:S144-S157**

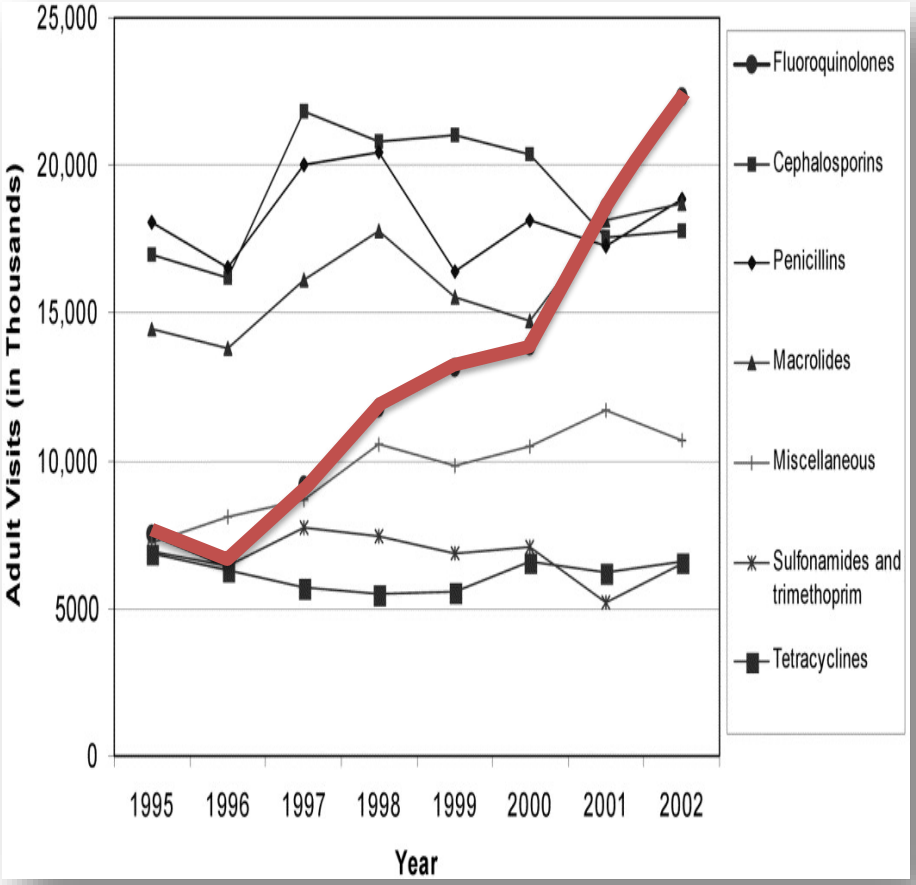


Sparfloxacina : fototossicità e allungamento QT
Gatifloxacina: alterazioni metabolismo glicidico
Trovafloxacina: epatotossicità
Temafloxacina: emolisi , TV, epatotossiticà
Grepafloxacina: prolungamento QT

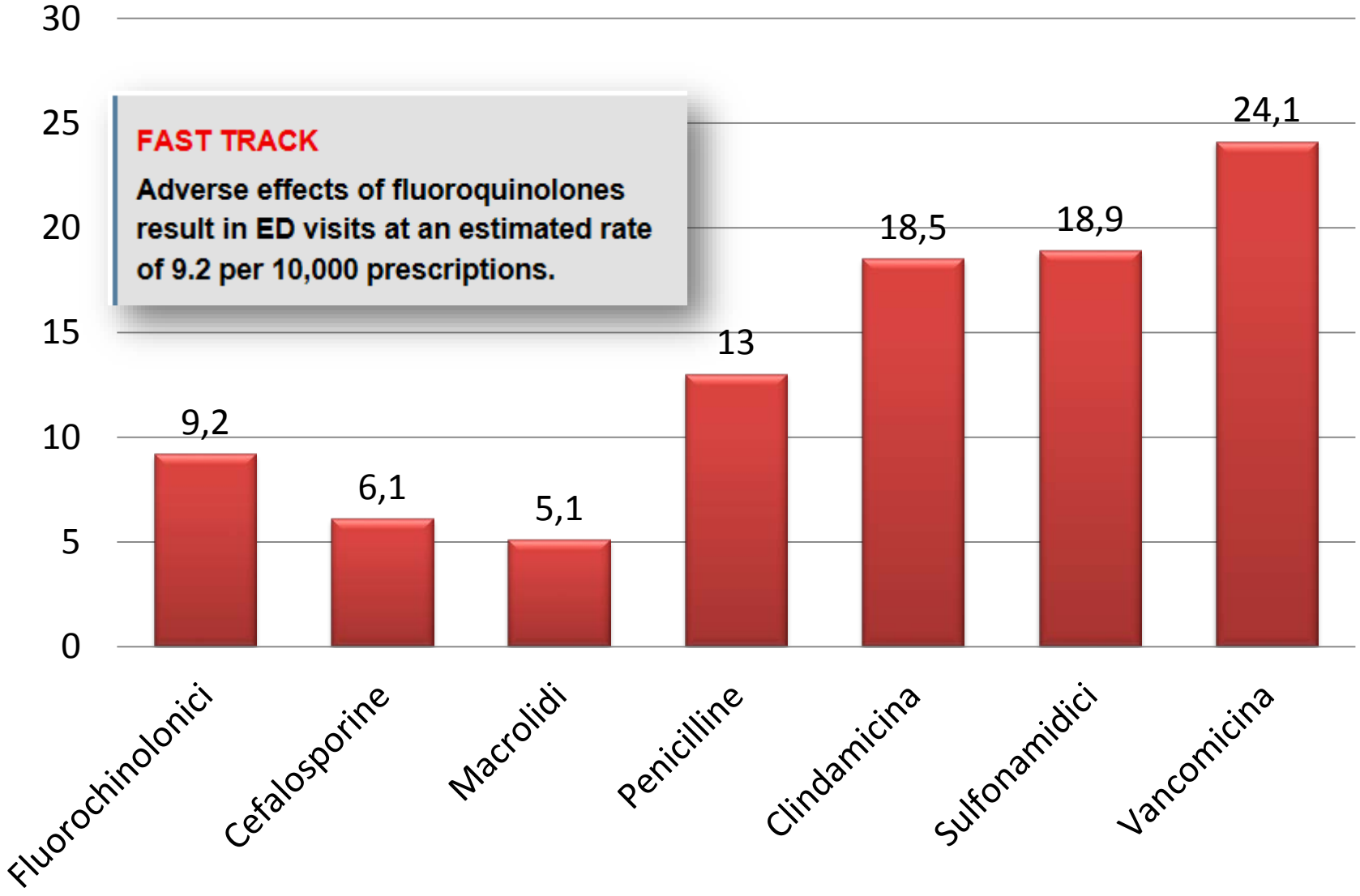
**Between 1995 and 2002, fluoroquinolone prescribing tripled, making fluoroquinolones the class of antibiotics most commonly prescribed to adults in the United States.**
*Linder JA. Am J Med 2005; 118:259-268.*

Fluoroquinolone prescribing increased as
- a proportion of overall antibiotic prescribing (**from 10% to 24%;** *P*=0.0001)

42% of fluoroquinolone prescriptions were for nonapproved diagnoses.



# Eventi avversi per 10.000 prescrizioni: report dei CDC



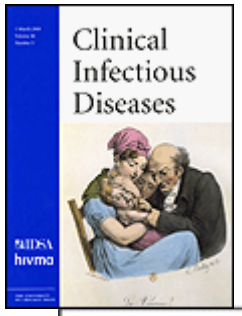


Shehab N. *Clin Infect Dis.* 2008;47:735-743.

Heidelbaugh JJ. *Fam Pract* 2013;62:191-7

## *Stahlmann R. Expert Opinion on Drug Safety 2013.;2:497-505*

| | |
|---|---|
| **Cardiovascular**<br>• Hypotension<br>• Torsades de pointes | **Immunologic**<br>• Anaphylactoid reaction<br>• Hypersensitivity reaction |
| **Dermatologic**<br>• Eruption (angioedema, pruritus, rash, urticaria) | **Musculoskeletal**<br>• Arthralgias<br>• Myalgias<br>• Polyarthritis<br>• Tendinopathies |
| **Drug-drug interactions**<br>• Antacids (calcium carbonate, histamine-2 receptor antagonists)<br>• Antiarrhythmics<br>• Digoxin<br>• Ferrous sulfate<br>• Phenytoin<br>• Sucralfate<br>• Theophylline<br>• Warfarin+ | **Neurologic**<br>• Confusion<br>• Dizziness<br>• Drowsiness<br>• Hallucinations<br>• Headaches<br>• Seizures |
| **Endocrine/Metabolic**<br>• Glycosuria<br>• Hyper- and hypoglycemia | **Ocular**<br>• Diplopia<br>• Halos/hazy vision<br>• Photophobia<br>• Visual hallucinations |
| **Gastrointestinal**<br>• Diarrhea<br>• Hepatotoxicity<br>• Nausea/Vomiting | **Psychiatric**<br>• Psychoses<br>• Suicidal ideation |
| **Hematologic**<br>• Anemia<br>• Leukopenia<br>• Thrombocytopenia | **Respiratory**<br>• Dyspnea |




**Multifactorial risks contributing to increased host susceptibility to Torsades de Pointes.** *Owens RC. Clin Infect Dis 2005;41:S144-S157*

FQs prolong the QT interval by **blocking voltage-gated potassium channels**

**Genetics**
- LQTS-1–LQTS-7
- Unknown ion channel mutations

**Underlying cardiac disease**
- Ischemia
- CHF
- Bradycardia
- Atrial fibrillation

**Electrolyte derangements**
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

**Organ impairment**
- Renal insufficiency
- Severe hepatic disease

**$I_{Kr}$-blocking comedications or CYP3A4 inhibitors**
- www.torsades.org

**Prescritption of QT-prolonging drug (antimicrobials listed)**
- Macrolides/ketolides
- Quinolones
- Azoles
- Pentamidine
- TMP-SMZ

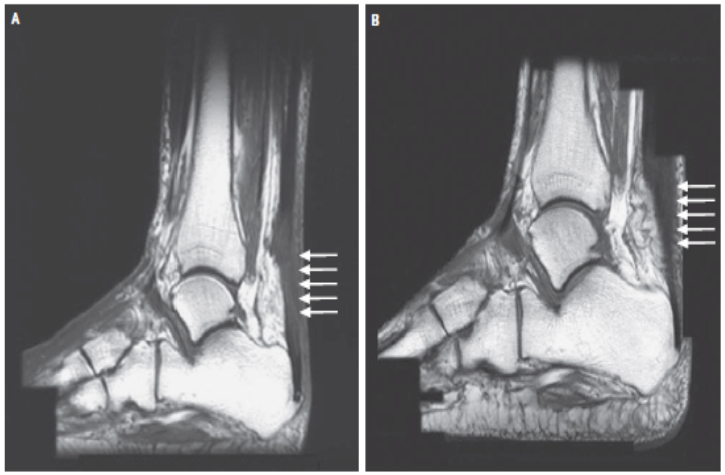
**abnormal baseline QT prolongation** (>440 ms in men; >460 ms in women)
class Ia (eg, procainamide, quinidine) or class III (eg, amiodarone, sotalol) antiarrhythmics. **warfarin** because FQ may potentiate the anticoagulant.
**An electrocardiogram is advisable, as well**

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

# Quinolone-Associated Rupture of the Achilles' Tendon




AN 81-YEAR-OLD WOMAN WITH RHEUMATOID ARTHRITIS, SJÖGREN'S SYNdrome, and hypertension presented with swelling and pain in the area of the left heel, which had developed suddenly a week after a short course of levofloxacin for acute bronchitis. She reported neither trauma to the area nor any excessive physical activity before the pain began. Examination revealed an ecchymotic area around the left posterior heel and a moderately swollen calf. A defect was palpable in the lateral side of the Achilles' tendon; the medial side was still intact. Movement of the ankle was limited by severe pain. Magnetic resonance imaging (MRI) of the ankle revealed a near-full-thickness rupture of the Achilles' tendon (Panel A, arrows). The patient's ankle was immobilized in a short leg cast for 2 months. After removal of the cast, a repeat MRI scan showed nearly complete healing of the ruptured tendon (Panel B, arrows), and since then, the patient has been walking without limitation. Quinolones may facilitate the enhanced expression of matrix metalloproteinases in tissue, which in turn causes tendon injury and is most common in the elderly and in persons taking corticosteroids.

Harsha Vyas, M.D.
Guha Krishnaswamy, M.D.

Wake Forest University School of Medicine
Winston-Salem, NC 27157-1082
dr_harshavyas@yahoo.com

Copyright © 2007 Massachusetts Medical Society.

PM&R

Volume 3, Issue 2, February 2011, Pages 132–142

Clinical review: Current concept

# Musculoskeletal Complications of Fluoroquinolones: Guidelines and Precautions for Usage in the Athletic Population

Mederic M. Hall, MD[a], Jonathan T. Finnoff, DO[b], Jay Smith, MD[c]

Show more

Table 1.

Clinical musculoskeletal conditions associated with fluoroquinolones

| Area Affected | Conditions |
|---|---|
| Tendon | Tendinitis, tendinosis, tendon rupture |
| Cartilage/bone | Arthralgia, impaired fracture healing, cartilage lesions |
| Muscle | Myalgia, rhabdomyolysis |

# A black box warning of tendinopathies

Heidelbaugh JJ. *Fam Pract* 2013;62:191-7

**How common is this adverse effect?**

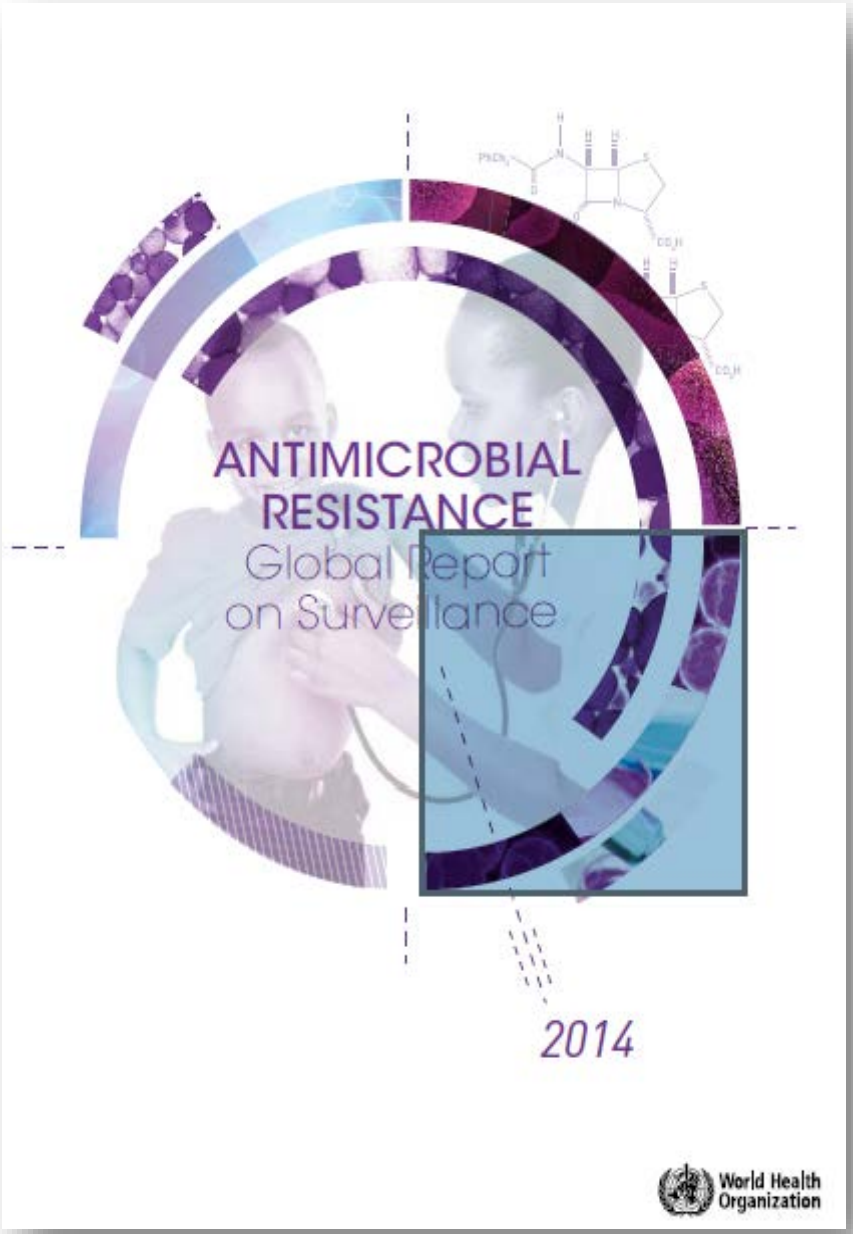
A case-control study **of 22,194 patients** with a diagnosis of **nontraumatic tendiopathy** determined that FQ use resulted in a more than a **4-fold risk of rupture of the Achilles tendon. One Achilles tendon rupture would occur for every 5958 patients treated with FQs,** the researchers estimated.

**MECHANISM**

- **1) Decrease in the synthesis of type I collagen, elastin, fibronectin, and beta (1)-integrin**
- **2) Increase of cellular apoptosis**
- **3) Decreased cell proliferation and fibroblast metabolism of tissue exposed to FQs, which may impede tissue healing**

**AT RISK**

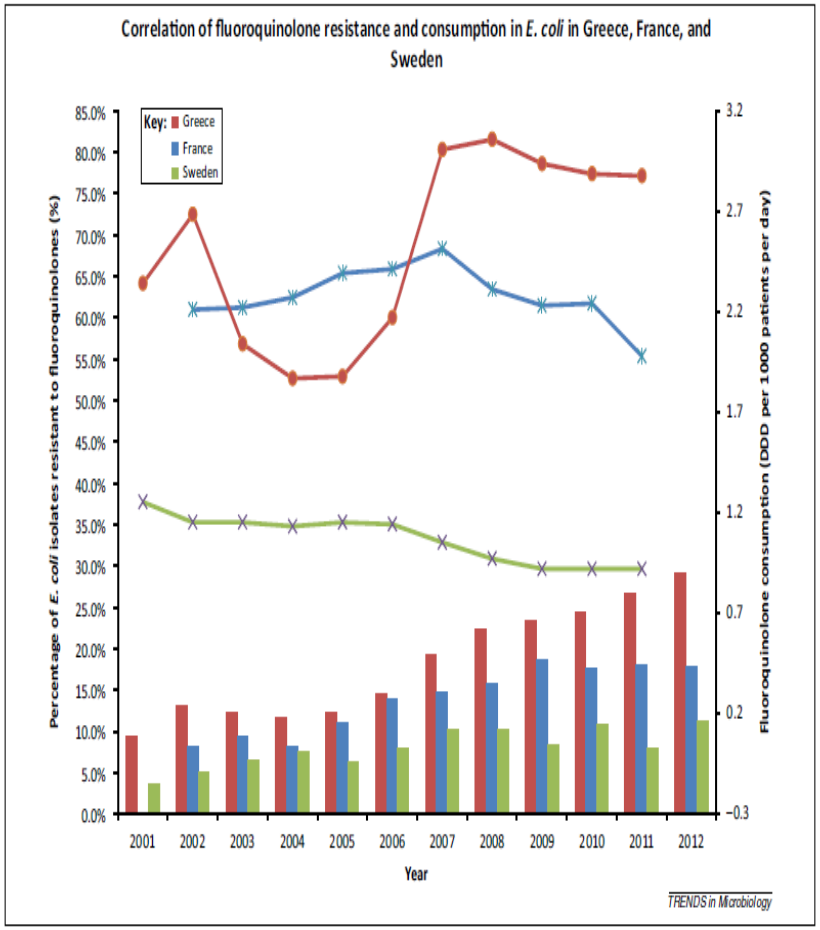
- **older than 60 years**
- **in kidney, heart, and lung transplant recipients**
- **in patients with concomitant corticosteroid therapy**
- **decreased renal clearance of the medication**




Review
CellPress

# Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success

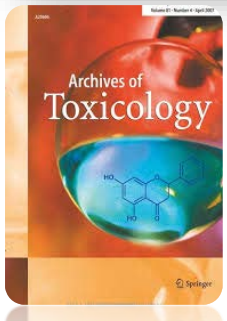
Liam S. Redgrave*, Sam B. Sutton*, Mark A. Webber, and Laura J.V. Piddock*,†



# Gastrointestinal (GI) disturbances are common in patients taking FQs, and typically occur more frequently in children and older adults, and in those taking higher doses.

Heidelbaugh JJ. *Fam Pract* 2013;62:191-7

| Reactions attributable to ciprofloxacin, for example, include | | |
|---|---|---|
| | Adults | Children |
| nausea | 1.4%-4% | 2.7% |
| vomiting | 1%-2% | 4.8% |
| diarrhea | 1%-2% | 4.8% |
| abdominal pain or discomfort | <1%-1.7% | 3.3% |




**Effects of ciprofloxacin on joint cartilage in immature dogs.**

*von Keutz E.*
*Arch Toxicol*
*2004;78: 418–424*

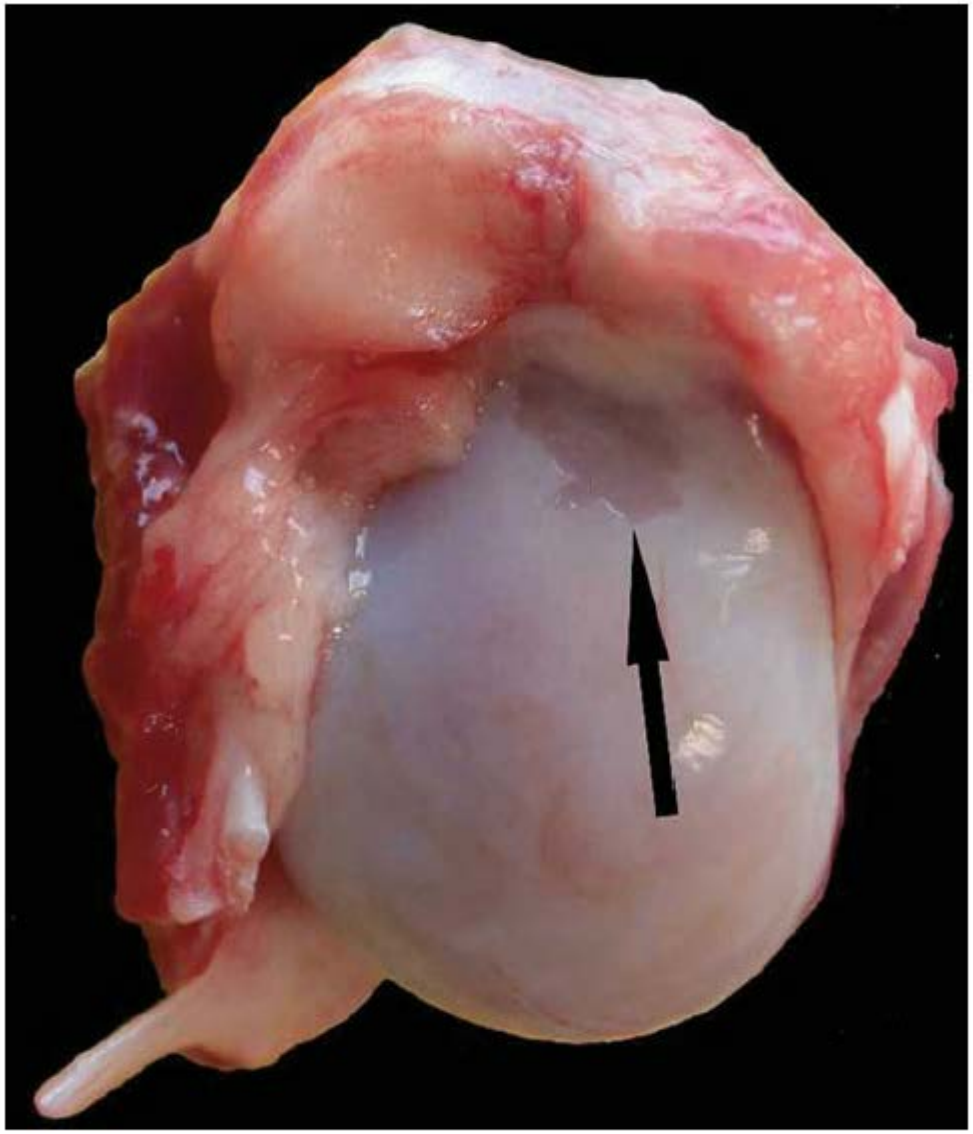
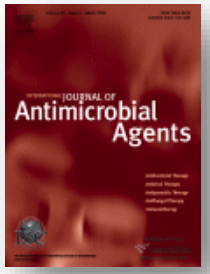
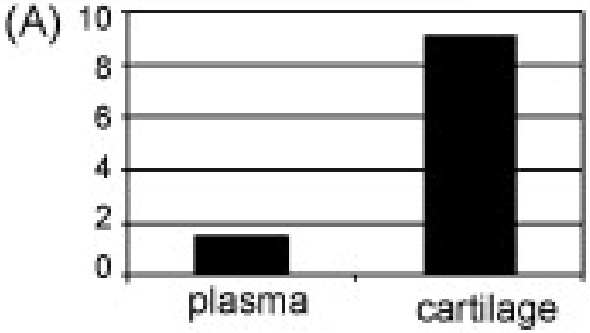


Fig. 2 Humeral head necropsy finding of a young beagle dog 5 months after treatment with 90 mg/kg ciprofloxacin per day for 2 weeks. A large erosion of articular cartilage (*arrow*) has developed




# Quinolone-induced chondrotoxicity.

*Sendzik J. Int J Antimicrob Ag 2009;33:194 - 200*




Quinolones reach high concentrations in cartilage and form chelate complexes with divalent cations

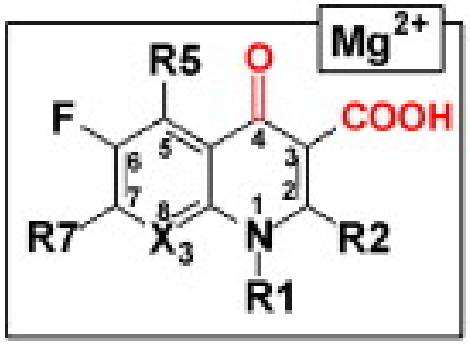
Deficit of functionally available magnesium and other tri- and/or divalent cations

Reduction of functionally available magnesium is not readily counterbalanced due to the poor supply of cartilage (no vascularisation)

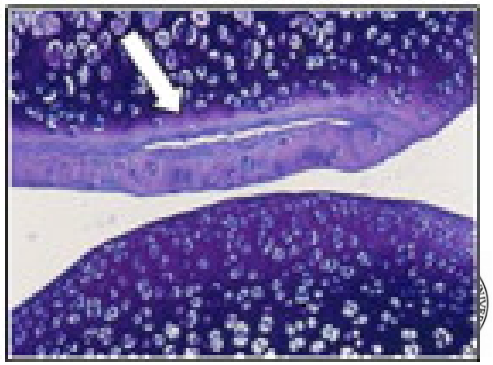
Impairment of integrin function (and other structures ?). disturbance of cell–matrix interaction

Radical formation, apoptosis, tissue damage

(B)




(C)



Archives of
DISEASE IN CHILDHOOD

# Ciprofloxacin safety in paediatrics: a systematic review. *Adefurin A. Arch Dis Child 2011;96:874–880.*

*16,184 children from 105 studies*

**258 musculoskeletal adverse events occurred in 232 pediatric patients** (estimated risk, 1.6; 95% CI, 0.9 to 2.6)

approximately 1 musculoskeletal adverse event for every 62.5 patients.

Arthralgia → 50%, most frequently of knee joint. median age, 10 years. reversible through conservative management, which included cessation of antibiotics.

pooled data from **23 controlled trials** → 57% increased risk of arthropathy in the patients receiving ciprofloxacin compared to controls *(OR, 1.57; 95% CI, 1.26 to 1.97)*

Dipartimento di Scienze della Salute, Università di Firenze

**Committee on Infectious Diseases; American Academy of Pediatrics. The use of systemic and topical fluoroquinolones**.
*Bradley JS. Pediatrics 2011;128:e1034–e1045*

**A large, prospective safety study conducted by Bayer**

**TABLE 2** Rate of FDA-Defined Arthropathy 6 Weeks and 1 Year After Treatment With Ciprofloxacin or a Comparator

| | Ciprofloxacin ($N = 335$) | | Comparator ($N = 349$) |
|---|---|---|---|
| Arthropathy rate at 6 wk of follow-up, *n* (%) | 31 (9.3) | | 21 (6.0) |
| 95% confidence interval[a] | | (−0.8 to 7.2) | |
| Cumulative arthropathy rate at 1 y of follow-up, *n* (%) | 46 (13.7) | | 33 (9.5) |
| 95% confidence interval[a] | | (−0.6 to 9.1) | |

intravenous ceftazidime with intravenous ciprofloxacin, permitting oral step-down therapy vs. oral ciprofloxacin with oral cefixime or trimethoprim-sulfamethoxazole for the treatment of **complicated urinary tract infections** in children aged 1-17 years.

The Pediatric Infectious Disease Journal

# Ciprofloxacin use in neonates:

*Kaguelidou F.*

*Pediatr Infect Dis J 2011;30:e29–e37*

utilizzato come terapia di salvataggio per sepsi da patogeni MDR o fallimento degli antibiotici di prima linea.

**5 studi di coorte →** 308 ciprofloxacin e 692 controlli
**27 case reports o serie di casi →** 143 ciprofloxacin

*No serious adverse events were observed*.

no significant relationship between ciprofloxacin use and the cartilage size of the right knee, as measured by ultrasound, and no height differences at 12 months corrected age

The Pediatric Infectious Disease Journal

**Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders.**
*Noel GJ. Pediatr Infect Dis J 2007;26:879-91.*

the safety profile of levofloxacin in 2,523 children using data from **3 multicenter efficacy trials**.

**Spontaneous reports** of musculoskeletal adverse events (arthritis, arthralgias, tendinopathy, or gait abnormality) were higher in levofloxacin-treated children than in those treated with non-FQ antibiotics at both

| | | |
|---|---|---|
| **2-month follow up** | **2.1% vs. 0.9%** | ***P*=0.04** |
| **12-month follow-up** | **3.4% vs. 1.8%** | ***P*=0.03** |

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

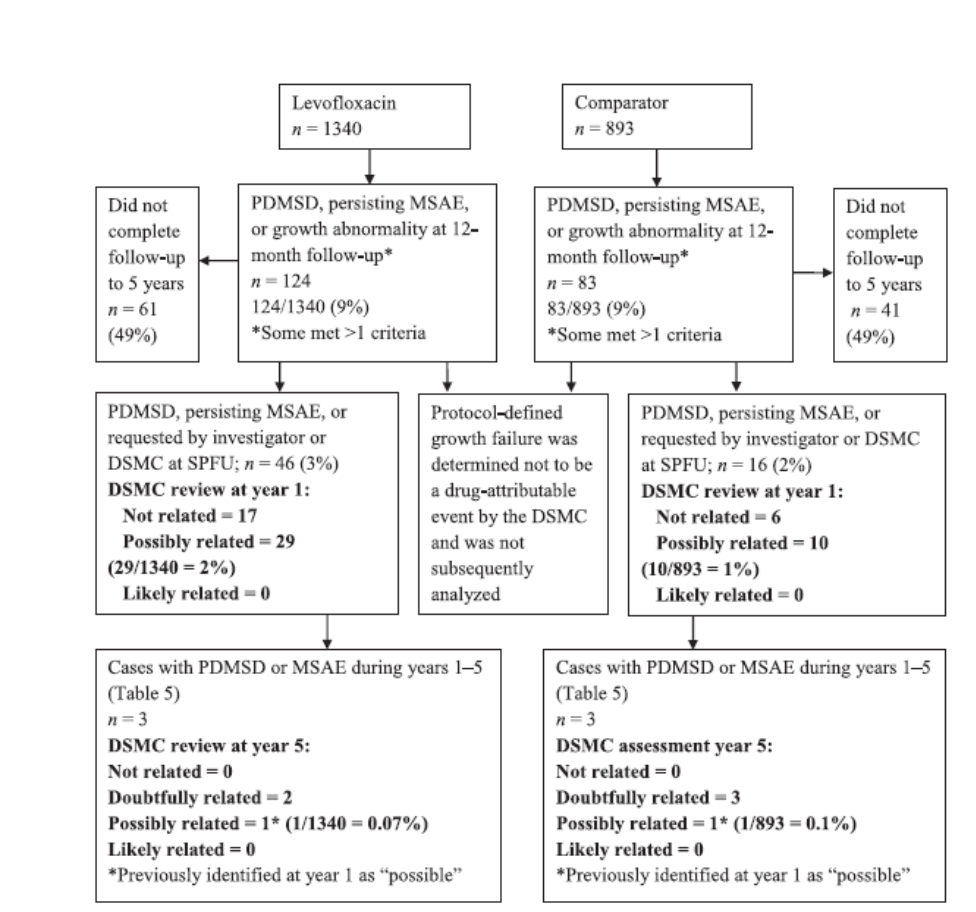
**Assessment of muscoloskeletal toxicity 5 years after therapy with levofloxacin**

*Bradley JS Pediatrics 2014;134:146-53.*

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Bambini che avevano già partecipato al precedente studio e che erano considerati a maggior rischio di tossicità ossea o articolare (es: **precedente evento avverso muscolo-scheletrico, ritardo di crescita**).

Valutati annualmente con raccolta di dati anamnestici , visita e misurazione dell'altezza.



International Journal of Antimicrobial Agents

Available online 7 February 2015

In Press, Corrected Proof — Note to users

Review

# Appropriate use of fluoroquinolones in children

Nicola Principi, Susanna Esposito

Recent short- and long-term evaluations appear to indicate that at least for levofloxacin this risk, if present at all, is marginal

Dipartimento di Scienze della Salute, Università di Firenze

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology
Chien S
Volume 45, Issue 2, pages 153–160, February 2005
ACCP

# Levofloxacin Pharmacokinetics in Children

| Age Group | $C_{max}$ (μg/mL) | $t_{1/2}$ (h) | AUC (μg•h/mL) | Vss (L/kg) | CL (L/h/kg) | $CL_R$ (L/h/kg) |
|---|---|---|---|---|---|---|
| **Pediatric subjects, Single IV dose, 7 mg/kg** | | | | | | |
| 0.5–2 y (n=6) | 5.19±1.26 | 4.1±1.3 | 21.5±6.12 | 1.56±0.30 | 0.35±0.13 | NA |
| 2–5 y (n=7) | 6.02±1.07 | 4.0±0.8 | 22.7±4.66 | 1.50±0.21 | 0.32±0.08 | NA |
| 5–10 y (n=9) | 6.11±0.88 | 4.8±0.8 | 29.2±6.40 | 1.57±0.44 | 0.25±0.05 | 0.18±0.07 |
| 10–12 y (n=7) | 6.12±1.19 | 5.4±0.8 | 39.8±11.3 | 1.44±0.35 | 0.19±0.05 | 0.15±0.06 |
| 12–16 y (n=11) | 6.15±1.55 | 6.0±2.1 | 40.5±7.56 | 1.56±0.53 | 0.18±0.03 | 0.11±0.04 |
| **Adults, Single IV dose, 500 mg*** | | | | | | |
| 18–45 y (n=23) | 6.18±1.04 | 6.0±1.0 | 48.3±5.40 | 1.27±0.12 | 0.15±0.02 | NA |

Children younger than 5 years cleared LVX nearly twice as fast as adults

provide compatible levofloxacin exposures associated with clinical effectiveness and safety in adults, children > or =5 years need a daily dose of 10 mg/kg, whereas children 6 months to <5 years should receive 10 mg/kg every 12 hours.

# Uso approvato di fluorochinolonici in pediatria

Dipartimento di Scienze della Salute, Università di Firenze

**ciprofloxacin** → inhalation anthrax, complicated urinary tract infections
l**evofloxacin** → inhalational anthrax.

**ciprofloxacin** → bronchopulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*, complicated urinary tract infections, and inhalation anthrax (both for postexposure prophylaxis and curative treatment)

**ciprofloxacin** → for the treatment of dysentery , but its use in children is only warranted if the benefits outweigh the risk of arthropathy.

**WHO Expert Committee For The Selection and Use of Essential Medicines**

effectiveness and safety of FQs in the treatment of **life-threatening bacterial infections, such as resistant tuberculosis, dysentery,** in children have been sufficiently established.

**WHO guideline for drug-resistant TB**

second-line antituberculosis regimens should include a later-generation FQ such as **moxifloxacin**

# Uso possibile di fluorochinolonici in pediatria secondo la *American Academy of Pediatrics*

Dipartimento di Scienze della Salute, Università di Firenze

**Committee on Infectious Diseases.**
**The use of systemic fluoroquinolones.** *Pediatrics 2006;118:1287–1292.*

- Exposure to aerosolized *Bacillus anthracis* to decrease the incidence or progression of the disease (FDA licensed)
- Urinary tract infections caused by *P. aeruginosa* or other multidrug-resistant, gram-negative bacteria (FDA licensed for complicated *Escherichia coli* urinary tract infections and pyelonephritis attributable to *E. coli* in patients 1-17 years old)
- **Exacerbation of pulmonary disease in patients with cystic fibrosis** who are colonized with *P. aeruginosa* and can be treated in an ambulatory care setting-
- **Gastrointestinal tract infections** caused by **multidrug-resistant** *Shigella* species, *Salmonella* species, *Vibrio cholerae*, or *Campylobacter jejuni*
- **Mycobacterial infections** caused by isolates known to be susceptible to FQs
- **Chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa***
- **Chronic or acute osteomyelitis or osteochondritis caused by *P. aeruginosa*** (but not for prophylaxis of nail puncture wounds to the foot)
- - **Serious infections attributable to FQ-susceptible pathogen(s) in children with a life-threatening allergy to alternative agents**
- **Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present**
- Documented bacterial **septicemia or meningitis attributable to organisms with in vitro resistance to approved agents**

**Committee on Infectious Diseases.**
**The Use of Systemic and Topical Fluoroquinolones.** *Pediatrics 2011;128;e1034;*

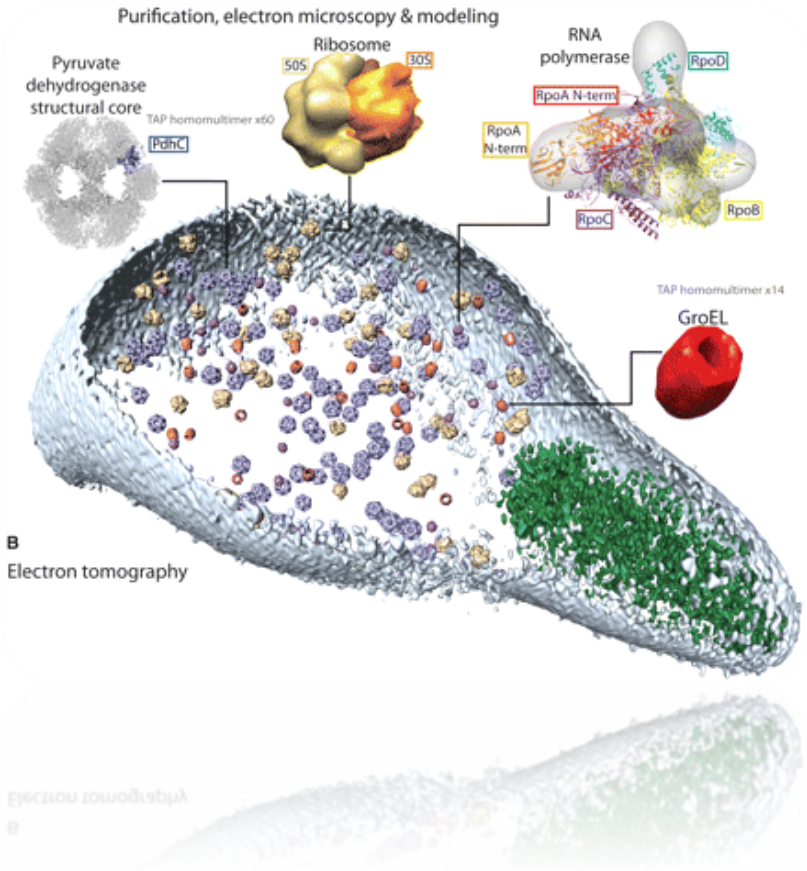
**Levofloxacin was recommended in certain situations as an alternative treatment option for *Streptococcus pneumoniae*, *Haemophilus influenzae* (typeable [A-F] or nontypeable), *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae*.**

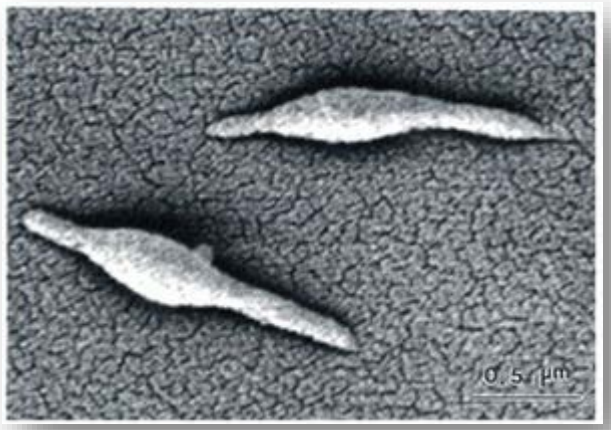
**Levofloxacin is preferred in oral therapy** (step-down therapy or mild infection) for CAP caused **by penicillin-resistant *S. pneumoniae*** in **skeletally mature adolescents**.

**FQ is recommended as an alternative oral agent for CAP caused by *M. pneumoniae* and *Chlamydia* species in skeletally mature adolescents**.

**Levofloxacin for the treatment of *Mycoplasma pneumoniae* -associated meningoencephalitis in childhood.**
***Esposito S. Int J Antimicrob Agents 2011;37:472-5***

**Macrolide-resistant Mycoplasma pneumoniae in paediatric pneumonia.**
***Cardinale F. Eur Respir J 2011;37:1522-4.***




Dipartimento di Scienze della Salute, Università di Firenze

Anaesthesia and Intensive Care

## Ciprofloxacin in critically ill children

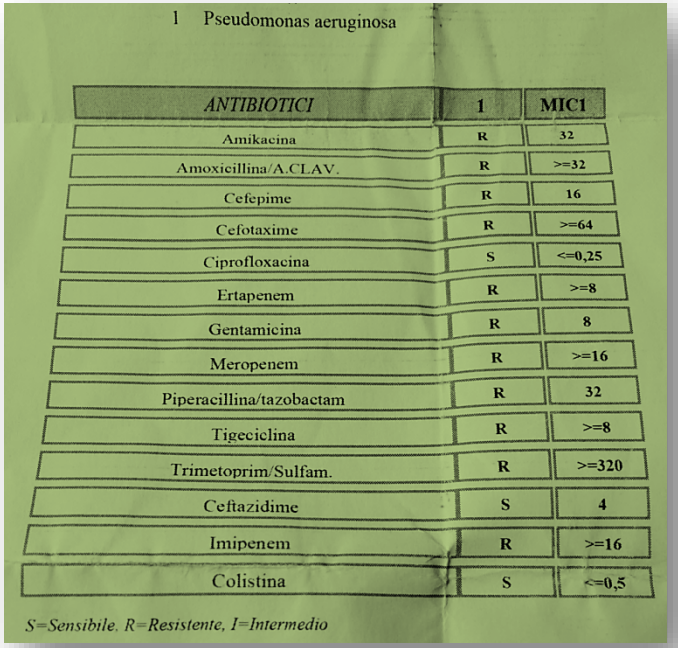
Sideri G. Anaesth Intensive Care 2011;39:635-9

Fourteen patients had bacteraemia (mainly caused from Gram-negative pathogens) one had *Stenotrophomonas maltophilia* pneumonia, while no pathogen was identified in three patients.

The latter patients received ciprofloxacin due to the severity of their clinical manifestations.

All patients with microbiologically documented infections recovered. Three deaths attributed to the underlying diseases were noted.

Within a 10-day follow-up, two cases of diarrhoea, one case of vomiting and one case of reversible supraventricular tachycardia were noted. No case of QT prolongation was noted.



1 Pseudomonas aeruginosa

| ANTIBIOTICI | 1 | MIC1 |
|---|---|---|
| Amikacina | R | 32 |
| Amoxicillina/A.CLAV. | R | >=32 |
| Cefepime | R | 16 |
| Cefotaxime | R | >=64 |
| Ciprofloxacina | S | <=0,25 |
| Ertapenem | R | >=8 |
| Gentamicina | R | 8 |
| Meropenem | R | >=16 |
| Piperacillina/tazobactam | R | 32 |
| Tigeciclina | R | >=8 |
| Trimetoprim/Sulfam. | R | >=320 |
| Ceftazidime | S | 4 |
| Imipenem | R | >=16 |
| Colistina | S | <=0,5 |

*S=Sensibile, R=Resistente, I=Intermedio*

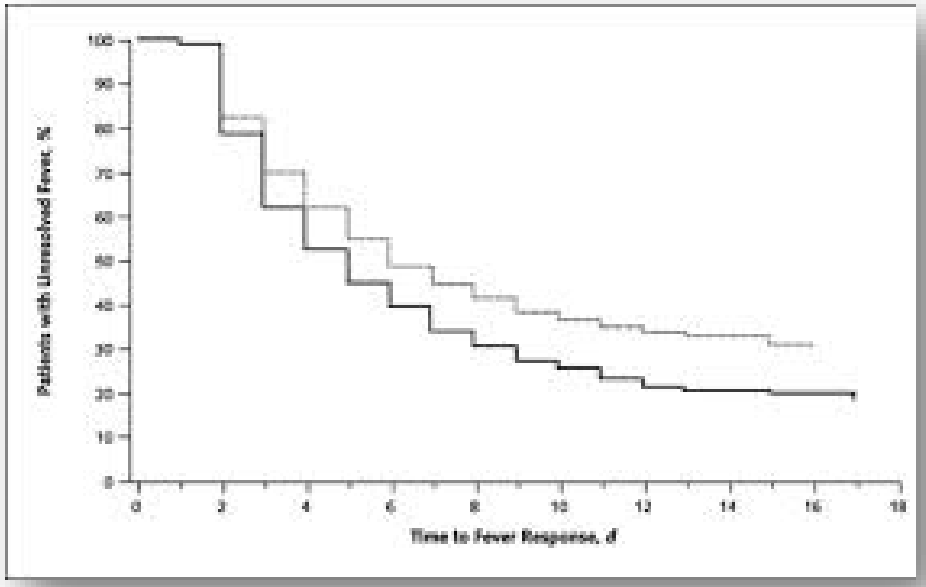
Dipartimento di Scienze della Salute, Università di Firenze

# *Empirical Treatment for Fever in Neutropenic Children With Cancer*

***Ciprofloxacin plus Piperacillin Compared with Tobramycin plus Piperacillin as Empirical Therapy in Febrile Neutropenic Patients: A Randomized, Double-Blind Trial.*** *Peacock JE. Ann Intern Med.* 2002;137:77-87

Febrile (temperature >/= 38 degrees C), neutropenic (neutrophil level < 1 x 10(9) cells/L) hospitalized patients who had leukemia, lymphoma, or solid tumors, or were undergoing bone marrow transplantation

Patients received piperacillin, 50 mg/kg of body weight intravenously every 4 hours, and ciprofloxacin, 400 mg intravenously every 8 hours, or tobramycin, 2 mg/kg intravenously every 8 hours



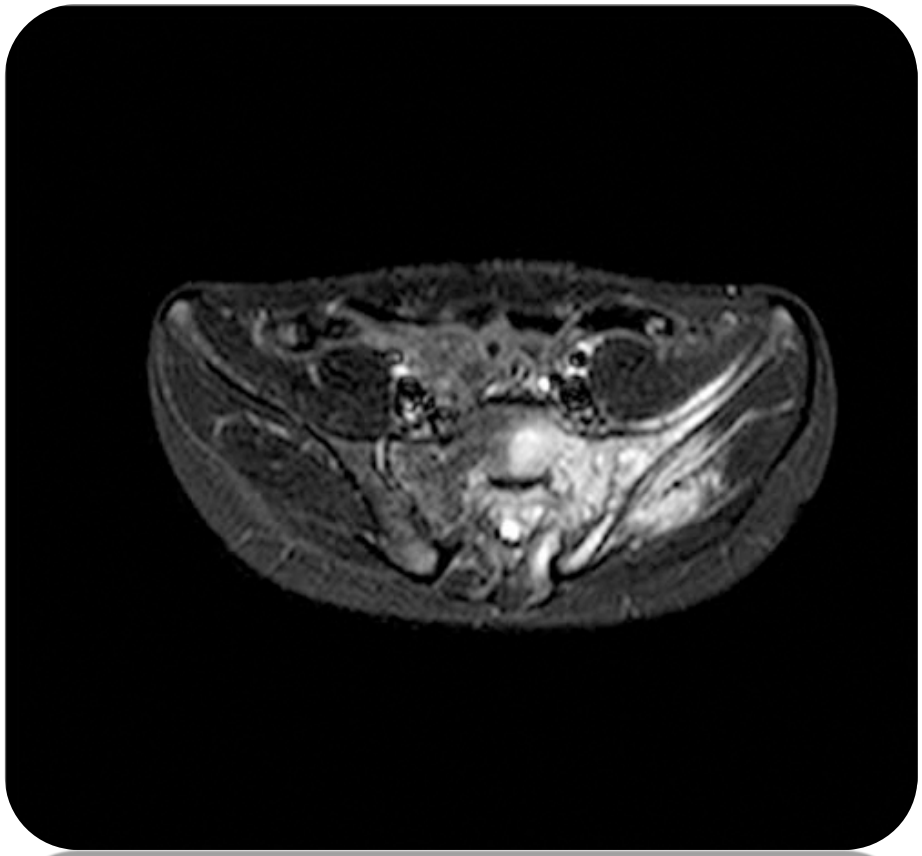

543 febrile episodes were evaluated, of which 471 were clinically evaluable (234 in the ciprofloxacin-piperacillin group and 237 in the tobramycin-piperacillin group). **Success rates** in the ciprofloxacin-piperacillin group (63 of 234 febrile episodes) and tobramycin-piperacillin group (52 of 237 episodes) **were similar (27% vs. 22%,** respectively; difference, 5.0 percentage points [95% CI, -2.3 to 12.8 percentage points]), **as was survival (96.2% of patients receiving ciprofloxacin-piperacillin versus 94.1% of patients receiving tobramycin-piperacillin**; difference, 2.1 percentage points [CI, -2.2 to 6.4 percentage points

# **Salmonella pelvic osteomyelitis in an immunocompetent child.**

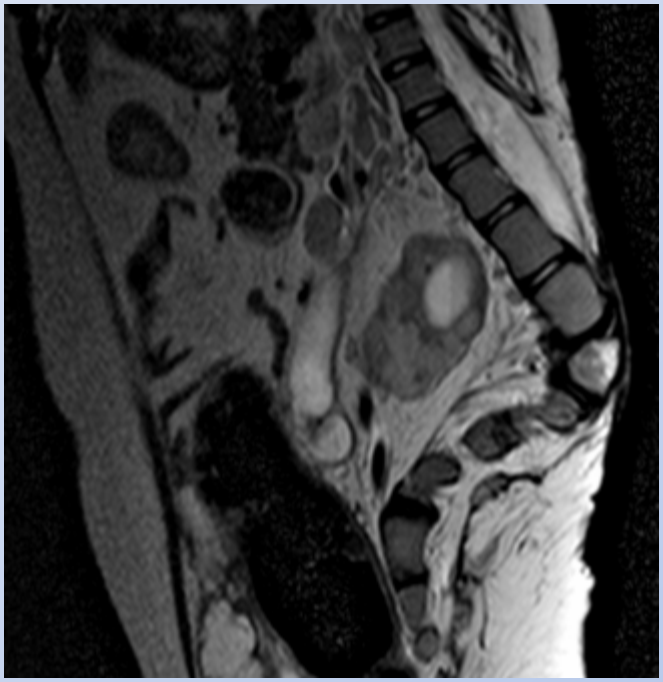
Canessa C. BMJ Case Rep 2011; May 11

A case of *Salmonella enteritidis* osteomyelitis isolated from the pelvis in a healthy adolescent is reported.

Salmonella, typically responsible for bone infection in sickle cell anaemia, is unusually involved in healthy children.



# PRE



# POST

# Moxifloxacin in Pediatric Subjects With Complicated Intra-abdominal Infection (MOXIPEDIA)

This study is ongoing, but not recruiting participants.

**Sponsor:**
Bayer

**Information provided by (Responsible Party):**
Bayer

**ClinicalTrials.gov Identifier:**
NCT01069900

First received: February 15, 2010
Last updated: July 29, 2014
Last verified: July 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

## Purpose

The primary focus of the study is the evaluation of the safety of treatment with moxifloxacin in a pediatric population 3 months to <18 years old. Approximately 450 pediatric subjects with a complicated intra-abdominal infection will be enrolled in the study and treated with either moxifloxacin intravenously and orally if switched to oral therapy or ertapenem (intravenously) and, if switched to oral therapy, amoxicillin/clavulanate.

| Condition | Intervention | Phase |
|---|---|---|
| Intraabdominal Infections | Drug: Moxifloxacin (Avelox, BAY12-8039)<br>Drug: Ertapenem, Amoxicillin/clavulanate | Phase 3 |

http://clinicaltrials.gov/ct2/show/study/NCT01069900.

The Pediatric Infectious Disease Journal

## An open-label, double tympanocentesis study of levofloxacin therapy in children with, or at high risk for, recurrent or persistent acute otitis media

*Arguedas A*
*Pediatr Infect Dis J* 2006;25: 1102-98

254 children with recurrent acute otitis media, treatment failure, or both (80%< 2 yrs)

Tympanocentesis was performed at study entry and at least at 3 to 5 days into therapy for children for whom treatment failed or who had persistent effusion, including 84% infected by pneumococci and 100% infected by *Haemophilus influenzae*. Levofloxacin treatment was well tolerated; vomiting in 4% of the patients was documented as the most common adverse effect.

The Pediatric Infectious Disease Journal

## A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media

*NoelGJ. Pediatr Infect Dis J 2008;27:488-89*

1305 evaluable children older than 6 months and compared levofloxacin to amoxicillin-clavulanate (1:1)
**equivalent clinical cure rates of 75% in each treatment arm**.
However, because tympanocentesis was not required, microbiological cure rates could not be determined

# Interventions for acute otitis externa. Cochrane Database Syst Rev. 2010;(1):CD004740

**a review of 19 randomized controlled trials, including 2 from a primary care setting, which yielded 3382 participants**.

Aminoglycoside-containing otic preparations were reported to cause ototoxicity if the tympanic membrane was not intact;

**fluoroquinolone-containing preparations represent a safer alternative for treating both otorrhea associated with tympanic membrane perforation and tympanostomy tube otorrhea**

THE COCHRANE LIBRARY
Independent high-quality evidence for health care decision making

The Pediatric Infectious Disease Journal

# Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia.

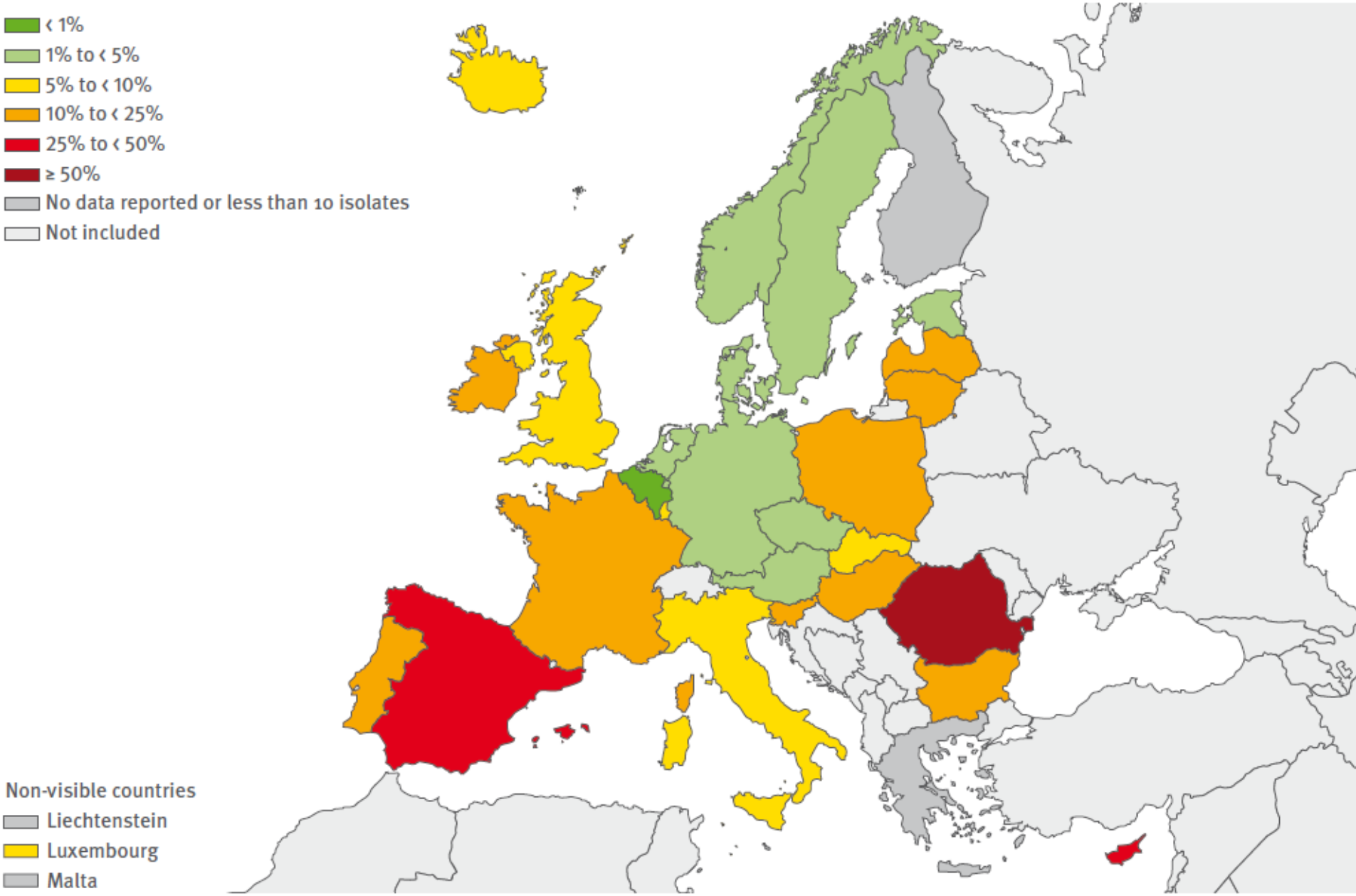
*Bradley JS. Pediatr Infect Dis J 2007;26:868–878*

For children aged **6 months to 5 years, levofloxacin** (oral or intravenous) was compared with **amoxicillin/clavulanate** (oral) or **ceftriaxone** (intravenous).
For children **5 years of age and older**, **levofloxacin (**oral) was compared with **clarithromycin** (oral), and **levofloxacin** (intravenous) was compared with **ceftriaxone** (intravenous) in combination with either **erythromycin** (intravenous) or **clarithromycin** (oral).

Clinical cure rates were **94.3% in the levofloxacin-treated group and 94.0% in the comparator group**, and there were similar rates of cure in both the younger and older age groups

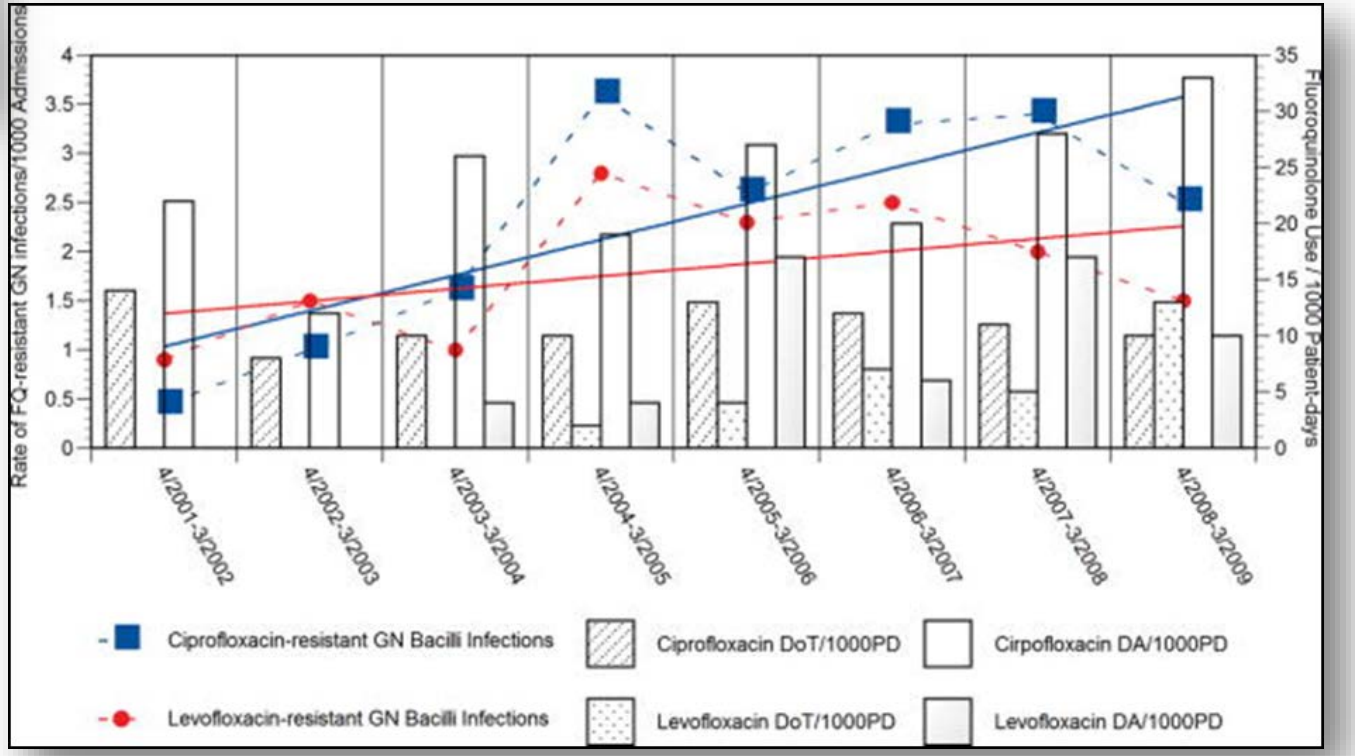
***other better-studied and safer antimicrobial agents are available to treat the majority of the currently isolated pathogens***

**Figure 4.31:** ***Streptococcus pneumoniae*: percentage (%) of invasive isolates non-susceptible to penicillin (PNSP), by country, EU/EEA countries 2011**



# The quest for the best metric of antibiotic use and its correlation with the emergence of fluoroquinolone resistance in children.

*Rose L Pediatr Infect Dis 2014;33:e158-61*




We evaluated the correlation between fluoroquinolone use, measured by doses administered and days of therapy, with the emergence of ciprofloxacin and levofloxacin resistance among Gram-negative bacilli infections in children hospitalized at one pediatric center between April 2001 and March 2009.

**Treatment regimens that include fluoroquinolones for 1 to 2 years for multidrug-resistant and extensively drug-resistant tuberculosis have not been prospectively studied in children.**

However, **the benefit of treatment of tuberculosis with an active compound when other active alternatives are not available is greater than the potential for arthropathy.**

**No joint toxicity has yet been reported in children who have received long-term therapy for tuberculosis**, but data on safety have not been collected systematically.

*World Health Organization. The selection and use of essential medicines. Report of the WHO expert committee, 2011.*

## Fluoroquinolones in pediatrics: review of hospital prescription use over 2 years.

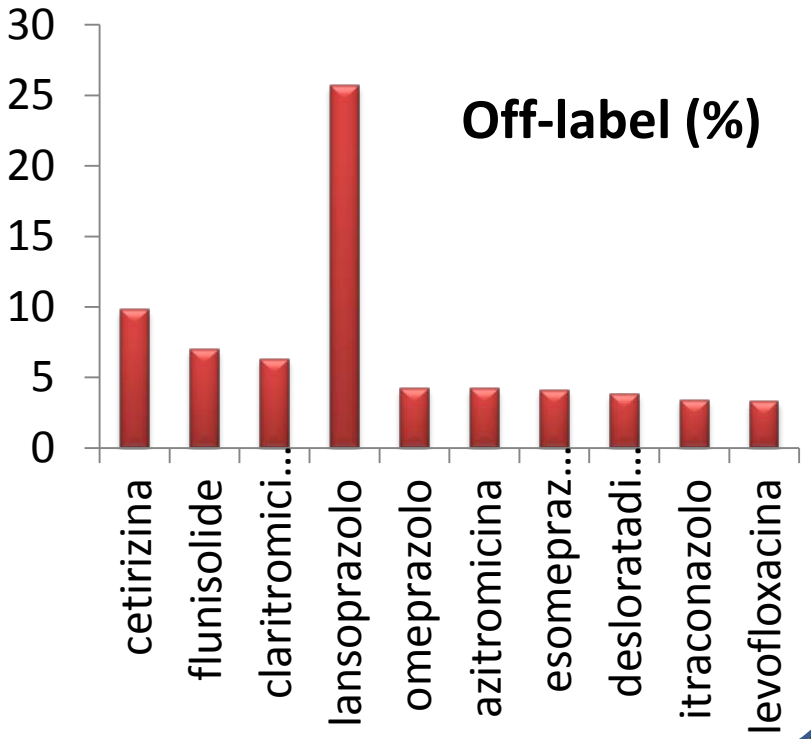
*Genuini M. Int J Clin Pharmacol Ther 2014 Aug 27. [Epub ahead of print]*

Singolo centro ospedaliero francese-
Gennaio 2009- Dicembre 2010. 397 bambini (3 giorni – 18 anni ).
Ciprofloxacin (96%)

## Paediatric drug use with focus on off-label prescriptions in Lombardy and implications for therapeutic approaches. *Carnovale C. Eur J Pediatr 2013;172:1679-85*

We analysed all dispensed outpatient prescriptions to children aged 0–18 years and the proportion of off-label drug use in 2011, using data from the regional administrative prescriptions database.

A total of 4,027,119 prescriptions were dispensed, of which 133,619 (3.3 %) were off-label



Eur J Clin Pharmacol (2010) 66:919–927
DOI 10.1007/s00228-010-0842-1

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Off-label antibiotic use in children in three European countries

Alessandro Porta · Susanna Esposito · Esse Menson · Nikos Spyridis · Maria Tsolia · Mike Sharland · Nicola Principi

nei reparti di terapia intensiva neonatale, di pediatria e di chirurgia pediatrica  di Londra, Milano e Atene,

**616 bambini per un totale di 1244 prescrizioni di antibiotici.**

Solo in pazienti con gravi condizioni cliniche sono stati utilizzati antibiotici non licenziati per l'età,
ed **in particolare**

- **il meropenem nei neonati**
- **i chinolonici ed il linezolid nei bambini**

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Guidance for the Clinician in Rendering Pediatric Care

**Committee on Infectious Diseases.**
**The use of systemic fluoroquinolones.** *Pediatrics 2006;118:1287–1292.*
**The Use of Systemic and Topical Fluoroquinolones.** *Pediatrics 2011;128;e1034*

Although fluoroquinolones are **reasonably safe in children**, clinicians should be aware of the specific adverse reactions.
**Use of fluoroquinolones in children should continue to be limited to treatment of infections for which no safe and effective alternative exists (2011)**

# Mechanism of Action of Fluoroquinolones

Fluoroquinolone

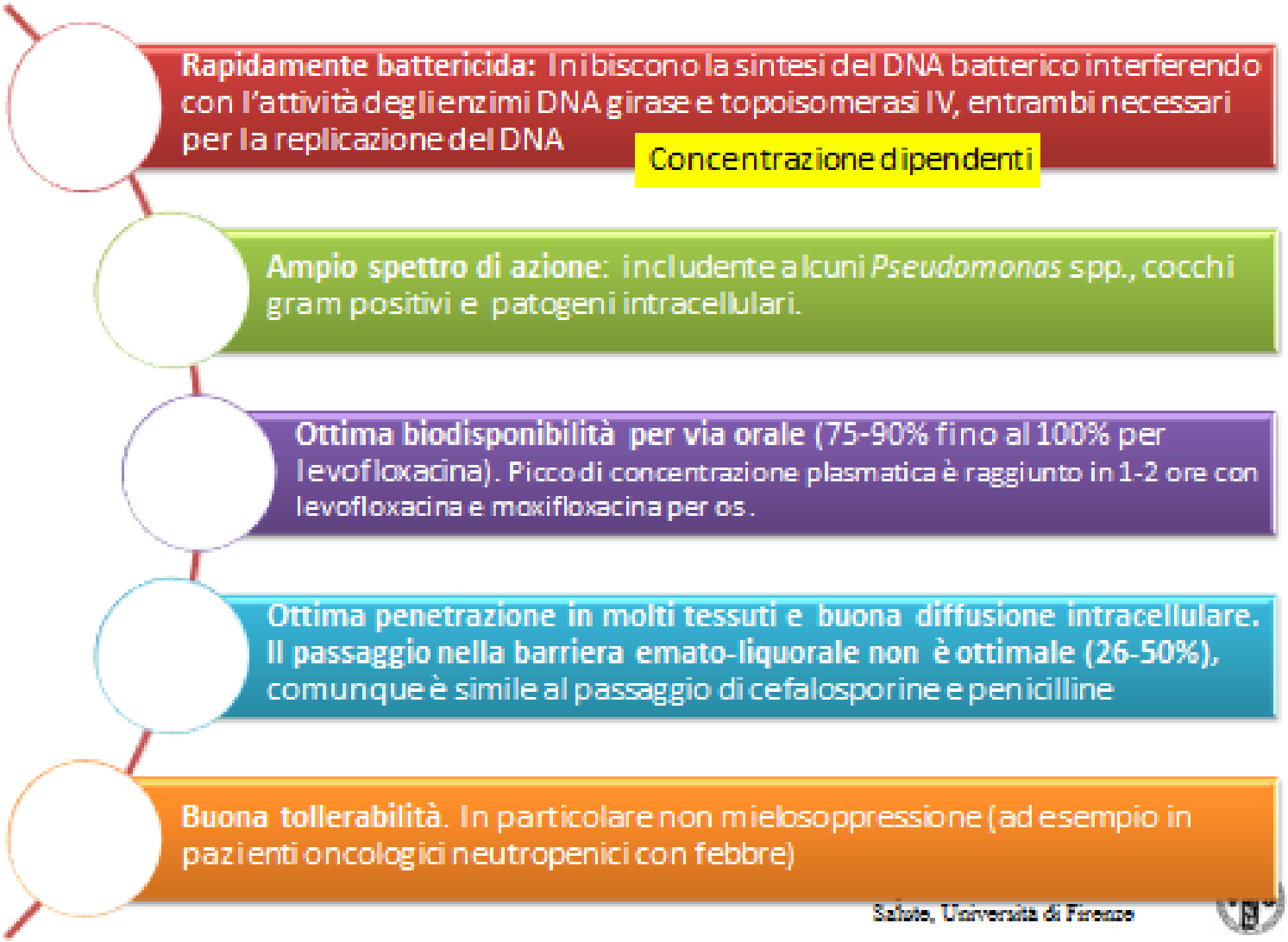
Topoisomerase IV

Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication

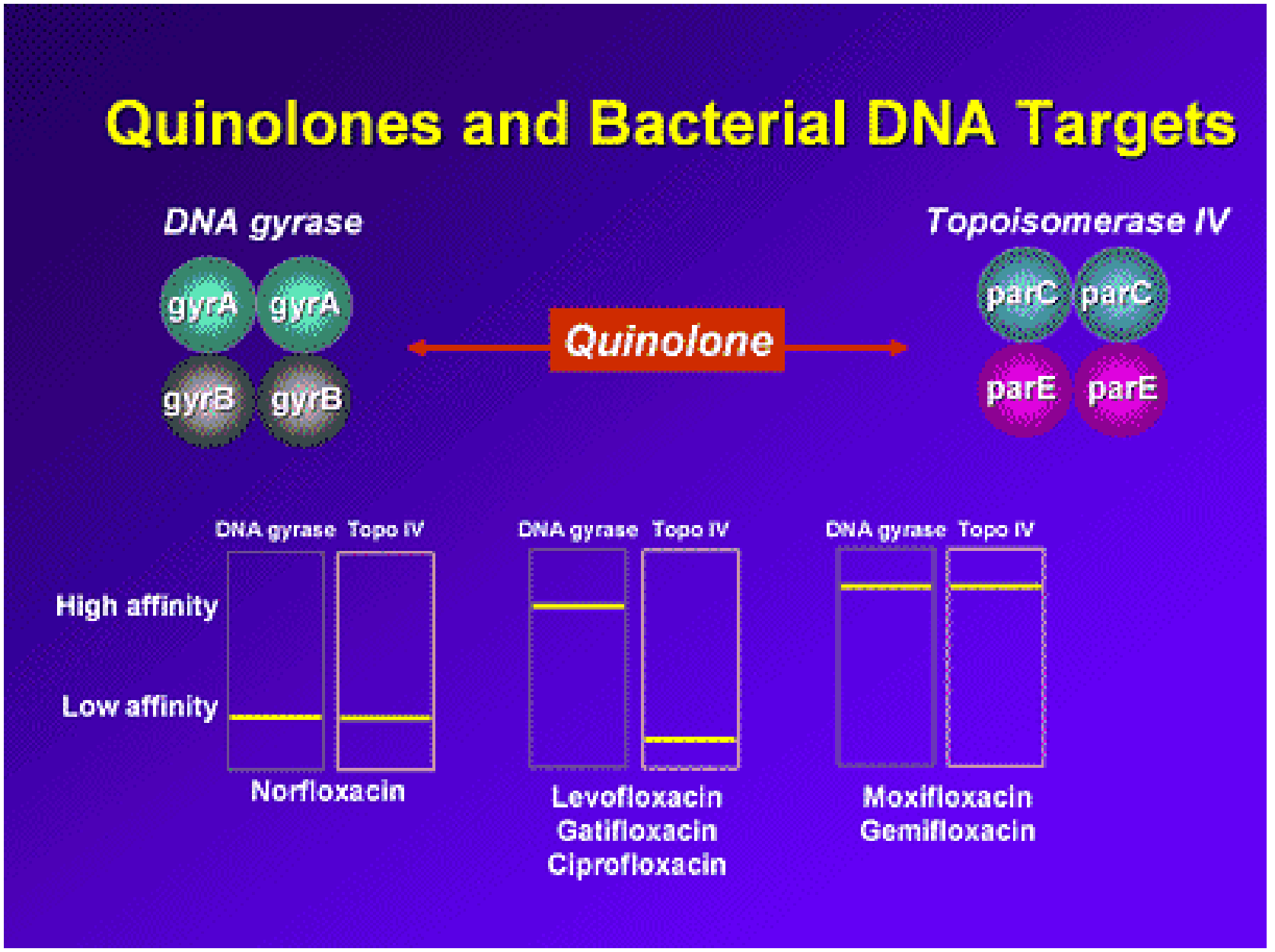
DNA gyrase

Zhanel G. Can J Infect Dis 1999;10:207

# Antibiotico ideale?



# Quinolones and Bacterial DNA Targets



# *S pneumoniae*: Fluoroquinolone MICs

| Drug | $MIC_{90}$ (ug/mL) |
|---|---|
| Ciprofloxacin | 2 |
| Levofloxacin | 1-2 |
| Sparfloxacin | 0.5 |
| Grepafloxacin | 0.5 |
| Trovafloxacin | 0.25 |
| Gatifloxacin | 0.25 |
| Moxifloxacin (Bay 12-8039) | 0.25 |
| Sitafloxacin (DU 6859a) | 0.12 |
| Gemifloxacin (SB 265805) | 0.03-0.06 |

Kelly et al. ICAAC 1998 abstr. F-87; Alexander Project 1998; Sentry 1998.

Bradley JS. Pediatrics 2011;128;e1034

**TABLE 4** Most Common Infections for Which Fluoroquinolones Are Effective Therapy (See Text)

| Infection | Primary Pathogen(s)[a] | Fluoroquinolone |
|---|---|---|
| Systemic antibiotic requirement[b] | | |
| UTI | *Escherichia coli* | Ciprofloxacin[c] |
| | *Pseudomonas aeruginosa* | |
| | *Enterobacter* species | |
| | *Citrobacter* species | |
| | *Serratia* species | |
| Acute otitis media; sinusitis | *Streptococcus pneumoniae* | Levofloxacin[d] |
| | *Haemophilus influenzae* | |
| Pneumonia | *Streptococcus pneumoniae* | Levofloxacin |
| | *Mycoplasma pneumoniae* (macrolides preferred for *Mycoplasma* infections) | |
| Gastrointestinal infections | *Salmonella* species | Ciprofloxacin[c] |
| | *Shigella* species | |
| Topical antibiotic requirement[e,f] | | |
| Conjunctivitis | *Streptococcus pneumoniae* | Besifloxacin |
| | *Haemophilus influenzae* | Levofloxacin |
| | | Gatifloxacin |
| | | Ciprofloxacin |
| | | Moxifloxacin |
| | | Ofloxacin |
| Acute otitis externa; tympanostomy tube–associated otorrhea | *Pseudomonas aeruginosa* | Ciprofloxacin[g] |
| | *Staphylococcus aureus* | Ofloxacin |
| | Mixed Gram-positive/Gram-negative organisms | |

| | |
|---|---|
| Ciprofloxacin | Acute uncomplicated cystitis in females (oral use only) |
| | Urinary tract infections |
| | Chronic bacterial prostatitis |
| | Uncomplicated cervical and urethral gonorrhea |
| | Skin and skin-structure infections |
| | Bone and joint infections |
| | Infectious diarrhea (oral use only) |
| | Typhoid fever (oral use only) |
| | Complicated intra-abdominal infections, in combination with metronidazole |
| | Acute sinusitis |
| | Lower respiratory tract infections |
| | Nosocomial pneumonia (iv use only) |
| | Empirical therapy for patients with febrile neutropenia, in combination with piperacillin sodium (iv use only) |
| | Inhalational anthrax (after exposure) |
| | Complicated urinary tract infections and pyelonephritis in pediatric patients (1–17 years old) |
| Levofloxacin | Uncomplicated urinary tract infections (mild to moderate) |
| | Complicated urinary tract infections (mild to moderate) |
| | Acute pyelonephritis (mild to moderate) |
| | Chronic bacterial prostatitis |
| | Uncomplicated skin and skin-structure infections (mild to moderate) |
| | Complicated skin and skin-structure infections |
| | Acute maxillary sinusitis |
| | Acute bacterial exacerbation of chronic bronchitis |
| | Community-acquired pneumonia[a] |
| | Nosocomial pneumonia |

*Andreole VT.*
*Clin Infect Dis 2005;41:S113–9*

# Ciprofloxacin

- Acute uncomplicated cystitis in females (oral use only)
- Urinary tract infections
- Chronic bacterial prostatitis
- Uncomplicated cervical and urethral gonorrhea
- Skin and skin-structure infections
- Bone and joint infections
- Infectious diarrhea (oral use only)
- Typhoid fever (oral use only)
- Complicated intra-abdominal infections, in combination with metronidazole
- Acute sinusitis
- Lower respiratory tract infections
- Nosocomial pneumonia (iv use only)
- Empirical therapy for patients with febrile neutropenia, in combination with piperacillin
- sodium (iv use only)
- Inhalational anthrax (after exposure)
- Complicated urinary tract infections and pyelonephritis in pediatric patients (1–17 years old)

# Levofloxacin

- Uncomplicated urinary tract infections (mild to moderate)
- Complicated urinary tract infections (mild to moderate)
- Acute pyelonephritis (mild to moderate)
- Chronic bacterial prostatitis
- Uncomplicated skin and skin-structure infections (mild to moderate)
- Complicated skin and skin-structure infections
- Acute maxillary sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Community-acquired pneumoniaa
- Nosocomial pneumonia

Heidelbaugh JJ. *Fam Pract* 2013;62:191-7

**Fluoroquinolones: Adverse effects to guard against*[2]**

| | |
|---|---|
| **Cardiovascular**<br>• Hypotension<br>• Torsades de pointes | **Immunologic**<br>• Anaphylactoid reaction<br>• Hypersensitivity reaction |
| **Dermatologic**<br>• Eruption (angioedema, pruritus, rash, urticaria) | **Musculoskeletal**<br>• Arthralgias<br>• Myalgias<br>• Polyarthritis<br>• Tendinopathies |
| **Drug-drug interactions**<br>• Antacids (calcium carbonate, histamine-2 receptor antagonists)<br>• Antiarrhythmics<br>• Digoxin<br>• Ferrous sulfate<br>• Phenytoin<br>• Sucralfate<br>• Theophylline<br>• Warfarin† | **Neurologic**<br>• Confusion<br>• Dizziness<br>• Drowsiness<br>• Hallucinations<br>• Headaches<br>• Seizures |
| **Endocrine/Metabolic**<br>• Glycosuria<br>• Hyper- and hypoglycemia | **Ocular**<br>• Diplopia<br>• Halos/hazy vision<br>• Photophobia<br>• Visual hallucinations |
| **Gastrointestinal**<br>• Diarrhea<br>• Hepatotoxicity<br>• Nausea/Vomiting | **Psychiatric**<br>• Psychoses<br>• Suicidal ideation |
| **Hematologic**<br>• Anemia<br>• Leukopenia<br>• Thrombocytopenia | **Respiratory**<br>• Dyspnea |

Pediatr Infect Dis J. 2015 Apr;34(4):355-60. doi: 10.1097/INF.0000000000000595.

# Acute otorrhea in children with tympanostomy tubes: prevalence of bacteria and viruses in the post-pneumococcal conjugate vaccine era.

van Dongen TM[1], Venekamp RP, Wensing AM, Bogaert D, Sanders EA, Schilder AG.

Author information

## Abstract

**BACKGROUND:** Acute tympanostomy-tube otorrhea is a common sequela in children with tympanostomy tubes. Acute tympanostomy-tube otorrhea is generally a symptom of an acute middle ear infection, whereby middle ear fluid drains through the tube. The widespread use of pneumococcal conjugate vaccination (PCV) has changed the bacterial prevalence in the upper respiratory tract of children, but its impact on bacterial and viral pathogens causing acute tympanostomy-tube otorrhea is yet unknown.

**METHODS:** This study was performed in the post-PCV7 era parallel to a randomized clinical trial of the clinical and cost-effectiveness of ototopical and systemic antibiotics and initial observation in 230 children aged 1 to 10 years with untreated, uncomplicated acute tympanostomy-tube otorrhea. Otorrhea and nasopharyngeal samples were collected at baseline (before treatment) and at 2 weeks (after treatment). Conventional bacterial culture was performed followed by antimicrobial-resistance assessment. Viruses were identified by polymerase chain reaction.

**RESULTS:** At baseline, Haemophilus influenzae (41%), Staphylococcus aureus (40%) and Pseudomonas aeruginosa (18%) were the most prevalent bacteria in otorrhea, followed by Streptococcus pneumoniae (7%) and Moraxella catarrhalis (4%). Most pneumococci were non-PCV7 serotypes. Viruses were detected in 45 otorrhea samples at baseline (21%). Most infections were polymicrobial and overall antimicrobial resistance was low.

**CONCLUSIONS:** H. influenzae, S. aureus and P. aeruginosa are the most common microorganisms in children with untreated uncomplicated acute tympanostomy-tube otorrhea. Prevalence of S. pneumoniae has decreased since the introduction of PCV and most pneumococci are nonvaccine serotypes.

- **2006, American Academy of Pediatrics Guidelines**
  - UTI with resistant organisms
    - *E.coli, Pseudomonas, Enterobacter, Citrobacter, Serratia*
  - Oral option for *Pseudomonas* infections
    - Cystic fibrosis, chronic suppurative otitis
  - Mycobacterial isolates (if susceptibility known)
  - GI infections
    - Resistant *Shigella, Salmonella, Campylobacter, Vibrio cholera*
  - Gram-negative bacterial infections in immunocompromised hosts
    - When oral therapy indicated or no other alternative
  - Sepsis or meningitis from resistant organism
  - Serious infections a patient with allergies

*AAP, Pediatrics 2006;118:1287*

# FQs in Children: Clinical Uses

- More recent IDSA / PIDS guidelines
  - **Pediatric community acquired pneumonia (2011)**
    - Use of levofloxacin in children as young as 6 months depending on allergies and pathogen
    - First-line agent for highly resistant *S.pneumo*

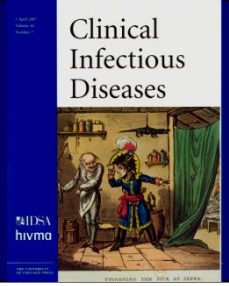
*Bradley et al, Clin Inf Dis Aug 2011*

  - **Pediatric bacterial sinusitis (2013)**
    - Use of levofloxacin in patients who are failing treatment with augmentin

*Wald et al, Pediatrics 2013;132;e262*

  - **Pediatric otitis media (2013)**
    - Use of levofloxacin as an "unconventional drug" (in consultation with specialist) for certain highly resistant strains of *S.pneumo*

*Lieberthal et al. Pediatrics 2013;131;e964*




# The molecular epidemiology of Streptococcus pneumoniae with quinolone resistance mutations.

Richter SS. Clin Infect Dis 2005;40:225-35 p

# Ciprofloxacin is currently not considered appropriate therapy for community-acquired pneumonia in adults.

Fluoroquinolones with enhanced activity against S pneumoniae compared with ciprofloxacin (**levofloxacin, moxifloxacin, gemifloxacin**) have been used in adults for single-drug treatment of community-acquired pneumonia.

These "**respiratory tract" fluoroquinolones** have demonstrated in vitro activity against the most commonly isolated pathogens: S *pneumoniae, Haemophilus influenzae (nontypeable), and Moraxella catarrhalis,* as well as *M pneumoniae, C pneumoniae*, and *Legionella pneumophila*.

recommended **for adults with underlying comorbidities** and **for those who have been exposed to antibiotic agents within the previous 3 months**

The **increase in drug exposure** at the higher dose is designed **to overcome the most common mechanism for the development of fluoroquinolone resistance**

Dipartimento di Scienze della Salute, Università di Firenze

PEDIATRICS®

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN

**Pediatric bacterial sinusitis (2013)**

- Use of levofloxacin in patients who are failing treatment with augmentin

*Wald et al, Pediatrics 2013;132;e262*

In young children (<2 years) with a serious type 1 hypersensitivity to penicillin and moderate or more severe sinusitis, it may be prudent to use a combination of **clindamycin (or linezolid) and cefixime** to achieve the most comprehensive coverage against both resistant *S pneumoniae* and *H influenzae.*

**Linezolid** has excellent activity against all *S pneumoniae*, including penicillin-resistant strains, but lacks activity against *H influenzae* and *M catarrhalis*.

**Alternatively, a quinolone, such as levofloxacin, which has a high level of activity against both *S pneumoniae* and *H influenzae*, may be prescribed.**

**Although the use of quinolones is usually restricted because of concerns for toxicity, cost, and emerging resistance, their use in this circumstance can be justified**

## From the American Academy of Pediatrics

# Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years

**TABLE 4**

Management of Worsening or Lack of Improvement at 72 Hours

| Initial Management | Worse in 72 Hours | Lack of Improvement in 72 Hours |
|---|---|---|
| Observation | Initiate amoxicillin with or without clavulanate | Additional observation or initiate antibiotic based on shared decision-making |
| Amoxicillin | High-dose amoxicillin-clavulanate | Additional observation or high-dose amoxicillin-clavulanate based on shared decision-making |
| High-dose amoxicillin-clavulanate | Clindamycin[a] and cefixime OR linezolid and cefixime OR levofloxacin | Continued high-dose amoxicillin-clavulanate OR clindamycin[a] and cefixime OR linezolid and cefixime OR levofloxacin |

[a] Clindamycin is recommended to cover penicillin–resistant *S pneumoniae*. Some communities have high levels of clindamycin–resistant *S pneumoniae*. In these communities, linezolid is preferred.

| | Ciprofloxacin | Levofloxacin | Moxifloxacin |
|---|---|---|---|
| Infections | Urinary tract infections | Acute otitis media and sinusitis | Multidrug-resistant tuberculosis |
| | *Escherichia coli* | *Streptococcus pneumoniae* | *Mycobacterium tuberculosis* |
| | *Pseudomonas aeruginosa* | *Haemophilus influenzae* | |
| | *Enterobacter* species | Pneumonia | |
| | *Citrobacter* species | *Streptococcus pneumoniae* | |
| | *Serratia* species | *Mycoplasma pneumoniae* | |
| | Gastrointestinal infections | Multidrug-resistant tuberculosis | |
| | *Salmonella* species | *Mycobacterium tuberculosis* | |
| | *Shigella* species | | |
| Dose | | | |
| Oral | 20–40 mg/kg/day, every 12 hours | 6 months to 5 years old: 16–20 mg/kg/day, every 12 hours | Adolescents: 400 mg once daily |
| | (maximum 750 mg/dose) | 5 years of age and older: 10 mg/kg/day, once daily | |
| | | (maximum 750 mg/dose) | |
| Intravenous | 20–30 mg/kg/day, every 8 to 12 hours | Same as oral dose | Adolescents: same as oral dose |
| | (maximum 400 mg/dose) | | |

*Choi SH. Korean J Pediatr 2013;56:196-201*

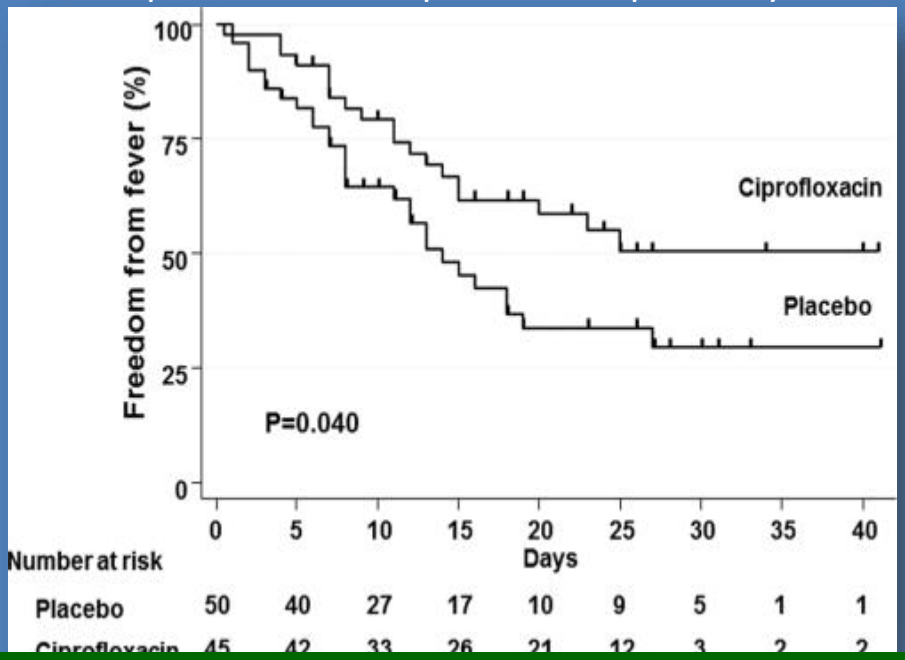
The Pediatric Infectious Disease Journal

# Ciprofloxacin reduces occurrence of fever in children with acute leukemia who develop neutropenia during chemotherapy.

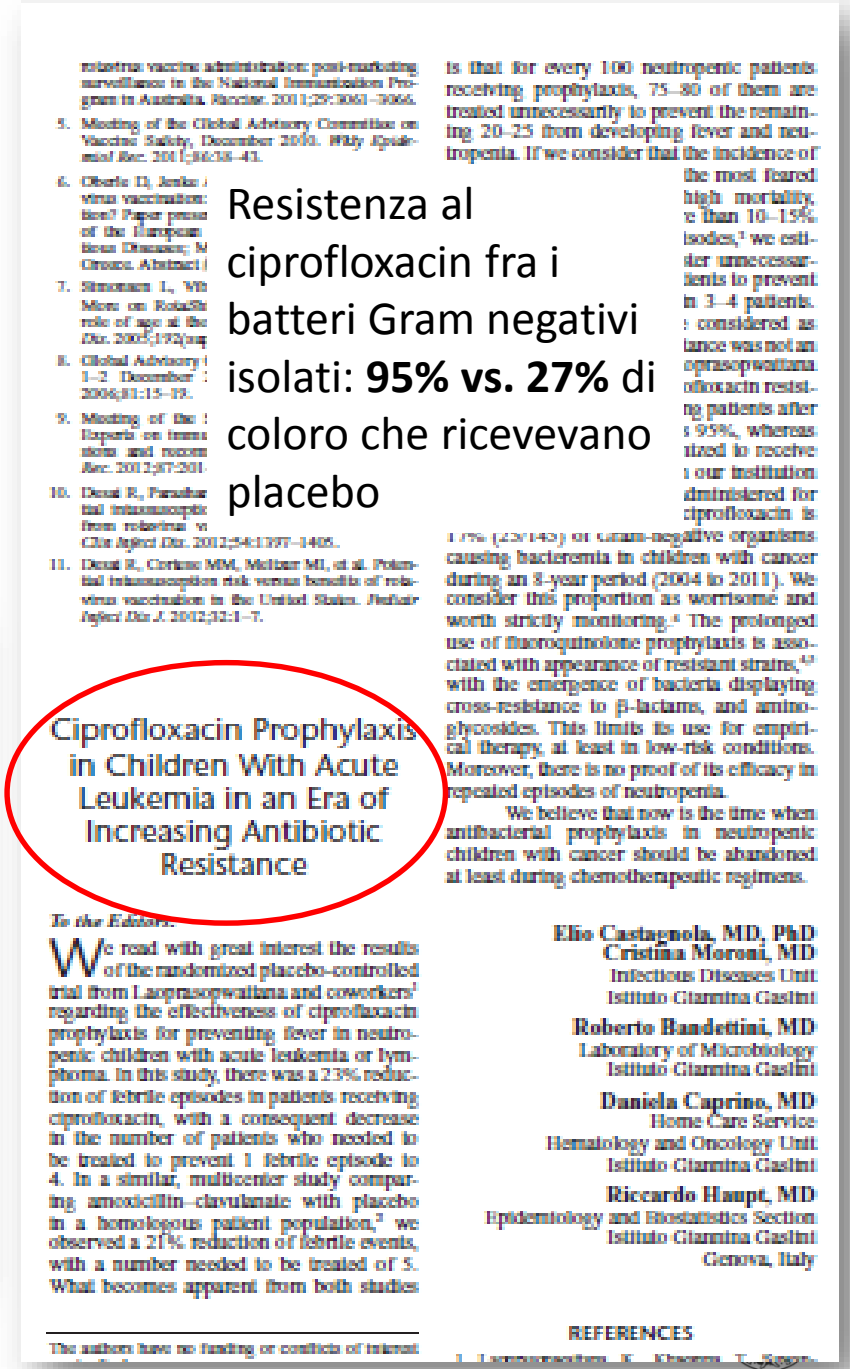
*K. Laoprasopwattana.*

*Pediatr Infect Dis J* 2013;32: e94–e98

95 patients, 45 and 50 patients received ciprofloxacin and placebo, respectively.




Resistenza al ciprofloxacin fra i batteri Gram negativi isolati: **95% vs. 27%** di coloro che ricevevano placebo



Ciprofloxacin Prophylaxis in Children With Acute Leukemia in an Era of Increasing Antibiotic Resistance

*To the Editors:*

We read with great interest the results of the randomized placebo-controlled trial from Laoprasopwattana and coworkers[1] regarding the effectiveness of ciprofloxacin prophylaxis for preventing fever in neutropenic children with acute leukemia or lymphoma. In this study, there was a 23% reduction of febrile episodes in patients receiving ciprofloxacin, with a consequent decrease in the number of patients who needed to be treated to prevent 1 febrile episode to 4. In a similar, multicenter study comparing amoxicillin–clavulanate with placebo in a homologous patient population,[2] we observed a 21% reduction of febrile events, with a number needed to be treated of 5. What becomes apparent from both studies is that for every 100 neutropenic patients receiving prophylaxis, 75–80 of them are treated unnecessarily to prevent the remaining 20–25 from developing fever and neutropenia. If we consider that the incidence of the most feared high mortality, ...e than 10–15% isodes,[3] we consi- der unnecessar- ilenis to prevent in 3–4 patients. ... considered as ...ance was not an ...oprasopwattana ...ofloxacin resist- ...g patients after ... 95%, whereas ...ized to receive ... our institution ...dministered for ...iprofloxacin is ...17% (26/143) of Gram-negative organisms causing bacteremia in children with cancer during an 8-year period (2004 to 2011). We consider this proportion as worrisome and worth strictly monitoring.[4] The prolonged use of fluoroquinolone prophylaxis is associated with appearance of resistant strains,[4,5] with the emergence of bacteria displaying cross-resistance to β-lactams, and aminoglycosides. This limits its use for empirical therapy, at least in low-risk conditions. Moreover, there is no proof of its efficacy in repeated episodes of neutropenia.

We believe that now is the time when antibacterial prophylaxis in neutropenic children with cancer should be abandoned at least during chemotherapeutic regimens.

**Elio Castagnola, MD, PhD**
**Cristina Moroni, MD**
Infectious Diseases Unit
Istituto Giannina Gaslini

**Roberto Bandettini, MD**
Laboratory of Microbiology
Istituto Giannina Gaslini

**Daniela Caprino, MD**
Home Care Service
Hematology and Oncology Unit
Istituto Giannina Gaslini

**Riccardo Haupt, MD**
Epidemiology and Biostatistics Section
Istituto Giannina Gaslini
Genova, Italy

The authors have no funding or conflicts of interest ...

REFERENCES

1. Laoprasopwattana K, Khuanyo T, Sripra...

The Pediatric Infectious Disease Journal

**Clinical and microbiologic outcomes of quinolone prophylaxis in children with acute myeloid leukemia..**

35 children

The use of CPx did not change

- the incidence of febrile or infectious episodes
- number of days of fever or antibiotic
- treatment o mortality.

CPx was associated with a significant decrease in infections caused by Gram-negative rods (13.4% vs 4.7%) but a concomitant significant increase in bacteremia caused by viridans streptococci (12% vs 28%), resulting in **no significant overall difference in the incidence of bacteremia between the 2 groups (35.9% vs 31.5%).**

Felsenstein S.
Pediatr Infect Dis J. 2015 ;34:e78-84

Cancer

**Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia.**

**Inhaba H.**
Cancer 20141;120:1985-92.

Creative approaches to shorten the duration of prophylaxis and thereby minimize resistance should be explored.

# *Infezioni enteriche*

**Treatment of *Salmonella typhi* Infection**

**randomized, open-label** trial, oral cefixime for 7 days was compared with oral ofloxacin for 5 days in 82 Vietnamese children with culture-proven typhoid fever.
*Cao XT. Pediatr Infect Dis J.1999;18 :245– 248.*

**Treatment of *Shigella dysenteriae* Infection**

The Zimbabwe, Bangladesh, South Africa (Zimbasa) Dysentery Study Group conducted **a multicenter, randomized, double-blind controlled clinical trial** in which 253 children between 1 and 12 years of age were randomly assigned to receive either **a 3- or 5-day course of oral ciprofloxacin 66% of the children in the short-course** group were cured clinically on day 5, compared **with 69% in the standard-course group.** *Zimbasa. Pediatr Infect Dis J.2002;21 :1136– 1141*

**Empirical Treatment of Bacterial Enteritis**

201 Israeli children 6 months to 11 years of age with clinically defined invasive diarrhea were randomly assigned **to receive either intramuscular ceftriaxone or oral ciprofloxacin in a double-blind controlled study**. **clinical cure or improvement was observed in 100% vs 99%**
***the empirical use of antibacterial agents to treat children with clinically defined invasive diarrhea is not indicated in most economically developed countries***. The authors also did not address the ***potential for antibacterial treatment to increase the likelihood of hemolytic uremic syndrome*** in patients with invasive diarrhea caused by shiga toxin-producing *E coli*. *Leibovitz E. Pediatr Infect Dis J.2000;19 :1060-7*
*Safdar M. JAMA.2002;288 :996– 1001*

## Treatment of *Francisella tularensis*

The outcomes of 12 Swedish children with ulceroglandular tularemia treated with oral ciprofloxacin were reported in a **retrospective study**; all of them recovered without complication. All isolates were susceptible to other antibacterial agents, and no comparison group was studied. *Johansson A. Pediatr Infect Dis J.2000;19 :449– 453*

## Meningitis

*Saez-Llorens X, McCoig C, Feris JM, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatr Infect Dis J.2002;21 :14– 22*

## Infezioni delle vie urinarie

The fluoroquinolones remain a potential first-line agent only in the setting of pyelonephritis or complicated UTI when typically recommended agents are not appropriate on the basis of susceptibility data, allergy, or adverse-event history.

**use ciprofloxacin as oral therapy for UTI and pyelonephritis caused by *P aeruginosa* or other multidrug-resistant Gram-negative bacteria in children aged 1 through 17 years**

A *large, prospective safety study conducted by Bayer compared (1)* ***intravenous ceftazidime with intravenous ciprofloxacin,*** *permitting oral step-down therapy, and (2)* ***oral ciprofloxacin with oral cefixime or trimethoprim-sulfamethoxazole for the treatment of complicated urinary tract infections in children aged 1-17 years****.*
*One of the primary objectives of the study was to evaluate musculoskeletal safety with ciprofloxacin therapy.*
***Bradley JS. Pediatrics 2011;128:e1034–e1045***

**Committee on Infectious Diseases.**
**The use of systemic fluoroquinolones.** *Pediatrics 2006;118:1287–1292.*
**The Use of Systemic and Topical Fluoroquinolones.** *Pediatrics 2011;128;e1034*

**In 2004, ciprofloxacin became the first fluoroquinolone agent approved for use in children 1 through 17 years of age.**

*In 2002 approximately 520,000 FQ prescriptions were written for patients younger than 18 years in the United States.*

An estimated 13,800 of those prescriptions were for children 2-6 years of age, and 2,750 were written for those 2 years and younger

**Committee on Infectious Diseases.**
**The Use of Systemic and Topical Fluoroquinolones.** *Pediatrics 2011;128;e1034;*

In addition, **levofloxacin is now recommended in children as a treatment option for acute bacterial rhinosinusitis** according to the IDSA clinical practice guideline (2012) for acute bacterial rhinosinusitis in children and adults:

**with a *history of type I hypersensitivity to penicillin*,**

**as a second-line agent for children with**

- **risk for antibiotic resistance,**
- **failed initial therapy, or**
- **severe infection requiring hospitalization.**