CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/19-21/97

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SLIDES

11-19-97

Quinolones & Pediatrics

Historical Background

Brad Leissa, M.D.
Medical Team Leader
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)

19 November, 1997

The Timeline

1962 NEGGRAM (nalidixic acid) tablet approved for use in pediatric patients >3 months old.

1972 Arthropathy first described in animals (Bailey)

1973 NEGGRAM suspension approved

The Timeline (contd.)

1977	Animal studies identifying histopathological joint changes
1989	Anti-Infective Advisory Committee discusses fluoroquinolones in peds (Closed session)
1993	Anti-Infective Advisory Committee discusses fluoroquinolones in peds (Open session)

19 November, 1997

The Timeline (contd.)

1994	"Pediatric Rule" finalized in Federal Register
1995	FDA sends letter to the NEJM warning against fluoroquinolones and tendon rupture (esp. achilles)
Sept. 1997	CIPRO (ciprofloxacin) suspension approved

19 November, 1997

Current FQ Labeling

- **Pediatric Use :**

  Safety & effectiveness in children and adolescents less than 18 years of age have not been established. Quinolones cause arthropathy and osteochondrosis in juvenile animals.

19 November, 1997

1989 Advisory Committee

- **Q1 : Should clinical trials of quinolones in subjects under 18 years of age be allowed?**

- **A1 : "We feel it is reasonable to go ahead with clinical studies."**

19 November, 1997

1989 Advisory Committee
(Contd.)

- Q2 : If so, what age group?
- A2 : "6-year-old cut off"

19 November, 1997

1989 Advisory Committee
(Contd.)

- Q3 : What population and for what infections?
- A3 : Cancer, cystic fibrosis, sickle cell anemia with salmonella infections (i.e., salmonella osteomyelitis)

19 November, 1997

1989 Advisory Committee
(Contd.)

- **Q4 : Should each child's growth potential be evaluated before treatment as well as in the analysis of results?**

- **A4 :**
  - **Plain x-rays (no MRI) and good growth charting – monitor over a 2 year period.**
  - **"Have an expert examiner monitor these patients with joint examinations"**

19 November, 1997

1993 Advisory Committee

Guests :

- Urs Schaad, MD - Basel, Switzerland
- Jamshed Kanga, MD - Lexington, Kentucky
  → cystic fibrosis treatment center

Company presentations :

- Otsuka America (William Pitlick, PhD)
- Miles (Roger Echols, MD)

19 November, 1997

1993 Advisory Committee
(Schaad)

- Pediatric treatment indications for FQs:
  - cystic fibrosis
  - complicated urinary tract infections
  - chronic suppurative otitis media
  - pseudomonal osteomyelitis
  - invasive enteritis due to multiple-resistant pathogens
  - febrile neutropenia
  - elimination of nasopharyngeal meningococci

19 November, 1997

1993 Advisory Committee

- **Q1 : Should the investigation of quinolones in children and adolescents be limited only to certain special disease entities where the products potentially offer significant advantage over present therapies (for example, CF, GI disease due to multiply-resistant organisms)?**

- **A1 : Yes (unanimous)**

19 November, 1997

A Quote Regarding A1

(Russell Steele, M.D., New Orleans)

"We do not know about the toxicity. ... So, it still ends up being what was very nicely displayed as an analysis of risk-benefit. With cystic fibrosis, I think there is feeling among pulmonologists, as we heard today, that there is significant benefit to be offered, so we can assume those risks.

19 November, 1997

A Quote -- *contd.*

(Russell Steele, M.D., New Orleans)

"But if the question is whether there should be studies for otitis media encouraged, I think that they might be considered if indeed we reach that point in time where that might be the most logical class of antibiotics to use for a resistant pneumococcus, but we are not there yet. I think we are a long way from there.

19 November, 1997

A Quote -- *contd.*

(Russell Steele, M.D., New Orleans)

"We are really seeing relative resistance but not that much absolute resistance. So, I do not think there will be that much enthusiasm among pediatric investigators to pursue the more routine indications, particularly otitis media or streptococcal tonsillitis/pharyngitis, pneumonia, sinusitis, etc."

19 November, 1997

1993 Advisory Committee

(Contd.)

- Q2 : If the answer to Q1 is NO, are there restrictions the committee would suggest at this time on the investigative use of these products or does the Committee recommend them for general investigative use in children and adolescents?

- A2 : Not applicable

19 November, 1997

1993 Advisory Committee
(Contd.)

- **Q2 : Are there any further recommendations to Committee would like to make regarding the investigation of quinolones and adolescents?**
- **A2 : No**

19 November, 1997

Has Anything Changed from 1993?

- Is bacterial resistance a greater concern today than it was in 1993?
- Do we know more about the clinical relevance of arthropathy seen in juvenile animals? The mechanism?
- Have we (globally) accumulated additional pediatric safety experience since 1993?

19 November, 1997

Has Anything Changed from 1993? (contd.)

- Are pharmaceutical manufacturers interested in developing FQs for pediatric populations?
- Is there an increased clinical demand on the part of pediatricians and ID specialists for FQs in 1997 -- or the near future?

19 November, 1997

ADAC#62 11-19-97

Future Role for Quinolones in Pediatric Patients

Robert Hopkins M.D., M.P.H. & T.M.
Medical Officer

Division of Special Pathogens and
Immunologic Drug Products
CDER/FDA

Outline for Discussion

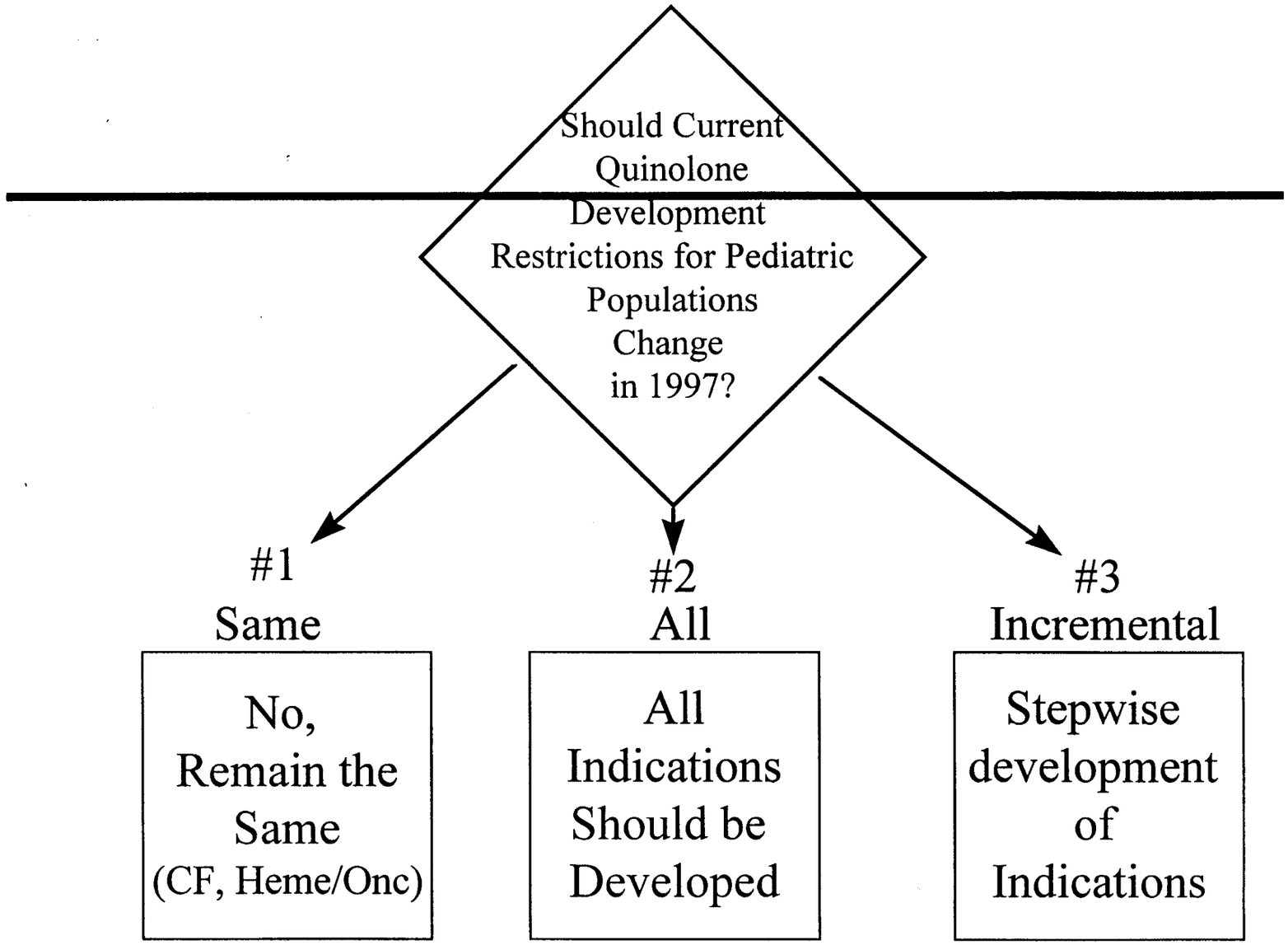
- Review factors to be considered when addressing quinolone development in pediatric populations
- Outline three possible approaches to quinolone development in pediatrics
- Discuss questions raised for each approach

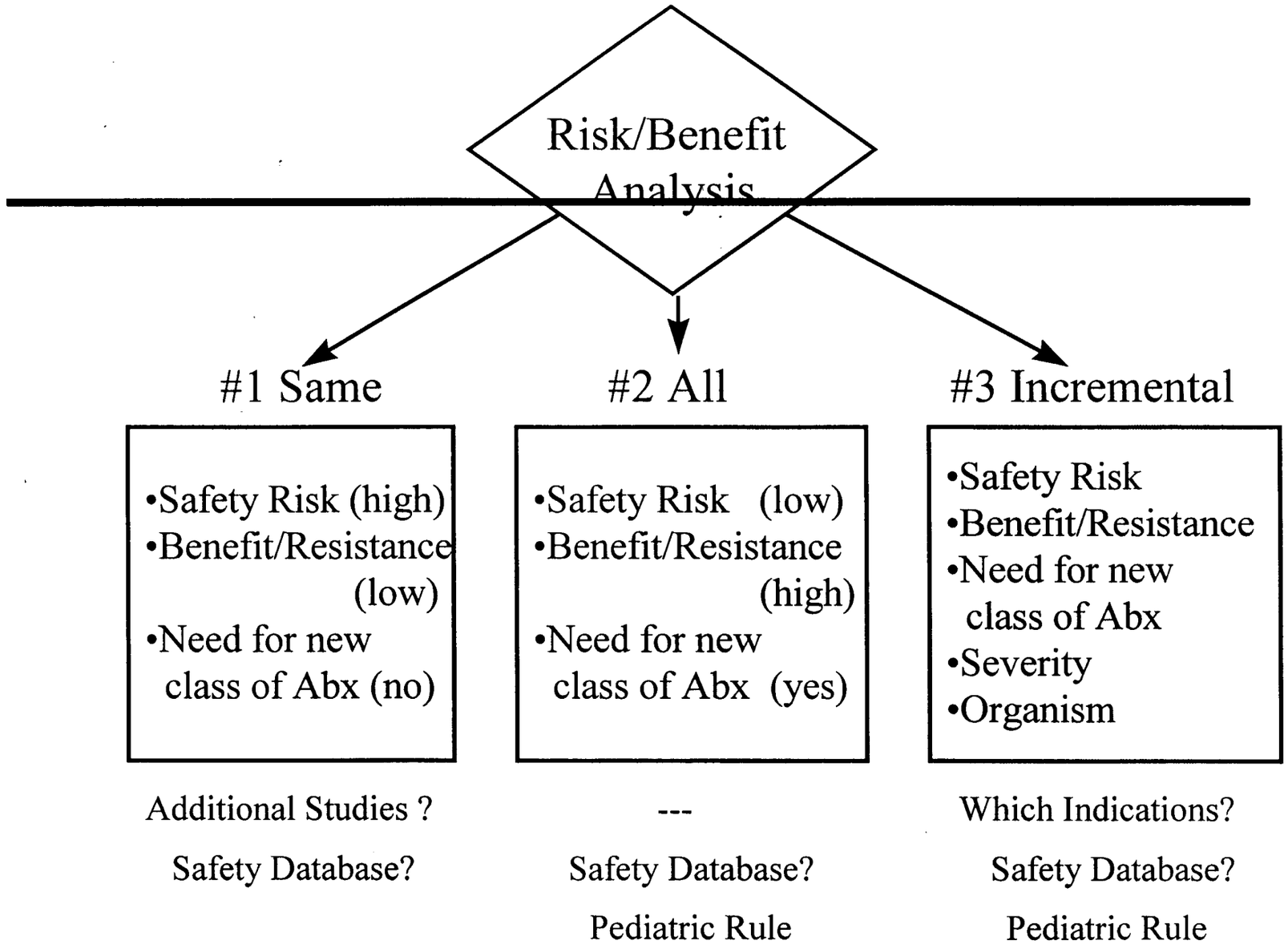
Factors To Consider: Efficacy

- Efficacy/Resistance (e.g. *S. pneumoniae*)
  - Current and future resistance rates
  - Virulence of resistant strains
- Need for a new class: Quinolones
  - Oral dosing
  - Daily dosing
  - Tissue penetration

Factors To Consider: Safety

- Preclinical toxicology data (e.g. arthropathy)
- Pediatric clinical safety database
  - Incidence
  - Severity
  - Duration


Should Current Quinolone Development Restrictions for Pediatric Populations Change in 1997?
#1
Same
No, Remain the Same (CF, Heme/Onc)
#2
All
All Indications Should be Developed
#3
Incremental
Stepwise development of Indications


Risk/Benefit Analysis
#1 Same
•Safety Risk (high)
•Benefit/Resistance (low)
•Need for new class of Abx (no)
Additional Studies ?
Safety Database?
#2 All
•Safety Risk (low)
•Benefit/Resistance (high)
•Need for new class of Abx (yes)

Safety Database?
Pediatric Rule
#3 Incremental
•Safety Risk
•Benefit/Resistance
•Need for new class of Abx
•Severity
•Organism
Which Indications?
Safety Database?
Pediatric Rule

Safety Questions

- What AEs should be monitored?
  - Permanent Lameness
  - Reversible Lameness
  - Effusions
  - Pain
  - Latent articular disease/damage
  - Others

Safety Questions

- How well should rare (but severe) AEs be estimated?
- For example:
  - 0/100: upper bound 95% CI = 3.0 %
  - 0/1000: upper bound 95% CI = 0.3 %
  - To be 95% confident in detecting a 1% AE risk, need a sample size of 300

Option #3: Severe Indications ?

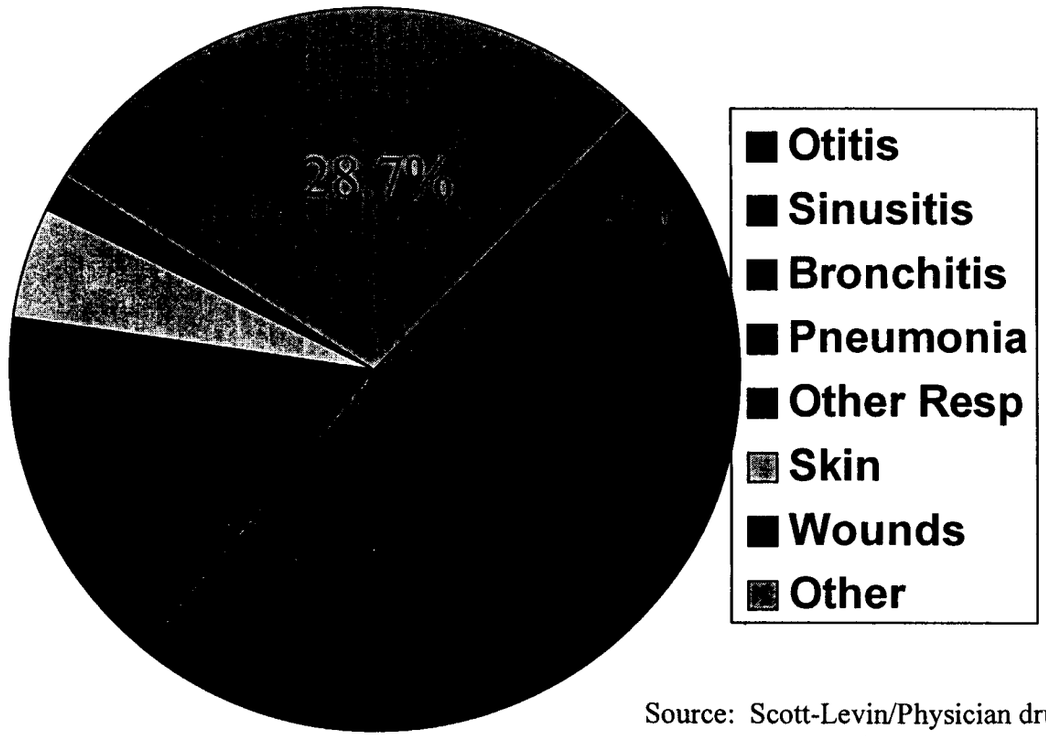
- Bacterial meningitis
- Nosocomial pneumonia
- Complicated UTI
- Endocarditis
- Complicated intra-abdominal infections
- Osteomyelitis (acute and chronic)
- Acute bacterial arthritis
- Empiric febrile neutropenia
- Complicated skin infections

Option #3: Less Severe Indications?

- Acute otitis media

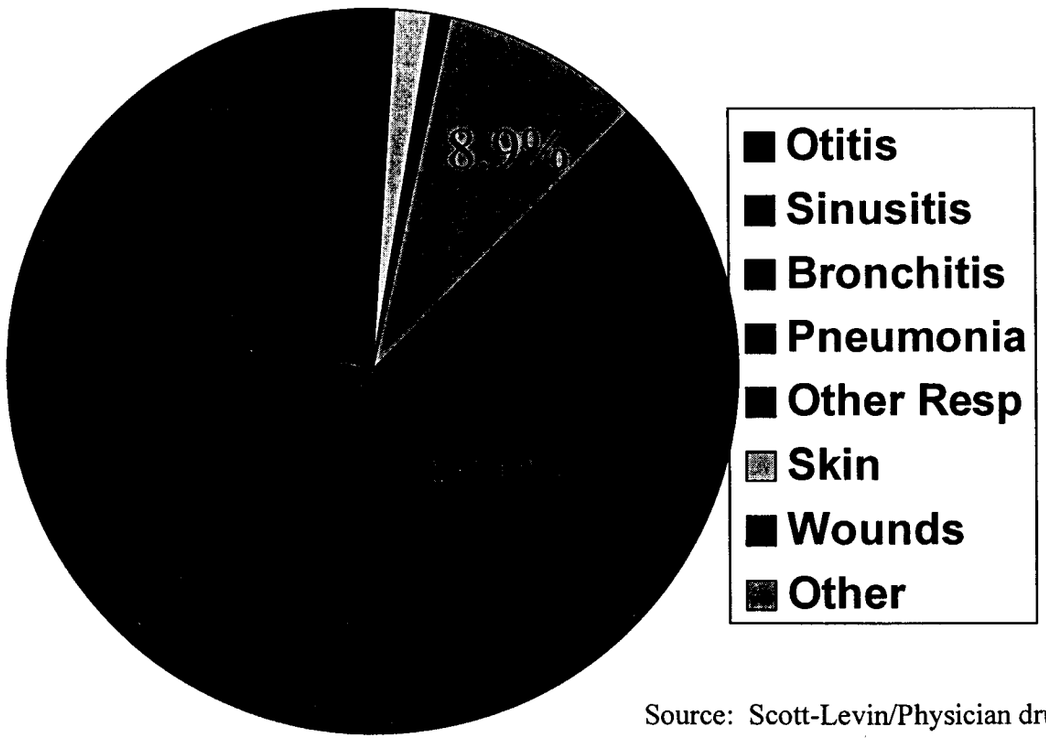
- Acute sinusitis
- Community acquired pneumonia
- Streptococcal pharyngitis
- Uncomplicated UTI
- Acute prostatitis
- Uncomplicated intra-abdominal infections
- Gonococcal and non-gonococcal infections
- Gynecologic Infections/PID/Bacterial vaginosis
- Uncomplicated skin infections

Market Share of Antimicrobials in 1995: Adults



Source: Scott-Levin/Physician drug and Diagnosis Audit

Market Share of Antimicrobials in 1995: Pediatrics



Source: Scott-Levin/Physician drug and Diagnosis Audit

Question # 1

- Of the following three options, which approach does the Advisory Committee recommend for the development of quinolones in pediatric populations?
  - 1. Continue restricted development only in patients with cystic fibrosis and hematologic/oncologic disorders
  - 2. No restrictions on the types of indications for which quinolones may be developed
  - 3. Incremental development of indications

Question # 2

- If option # 3 is recommended, which indications should be studied first?

Question # 3

- Keeping in mind the approach recommended in question # 1, does the Committee believe the safety profile of quinolones for adults and children differs significantly for arthropathy (or other potential safety problems)? If so, how does the Committee recommend that the FDA address this concern? (e.g., specific clinical testing, duration of exposure, size of the pediatric safety database)

HANDOUT AIDAC #6 2
11-19-97

FLUOROQUINOLONES FOR USE IN PEDIATRIC PATIENTS

John S. Bradley, MD
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Children's Hospital, San Diego
Associate Clinical Professor of Pediatrics
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Quinolone-class antibiotics have not been widely prescribed in children, due to concerns regarding potential toxicity to weight-bearing cartilage, as demonstrated in a number of animal models. With respect to antibiotic therapy for neonates, infants and children, considerations of safety have always taken precedence over considerations of convenience or cost.

Two situations currently exist in which oral quinolone therapy may be of significant benefit in pediatrics: treatment of infections caused by *Pseudomonas aeruginosa*; and treatment of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. Of increasing importance is the therapy of infections caused by cephalosporin-resistant and trimethoprim/sulfamethoxasole-resistant enteric Gram-negative organisms, such as *Enterobacter* sp.

Although infections with *Pseudomonas aeruginosa* may occasionally develop in immunocompetent children, they are most prevalent in children with cystic fibrosis (CF), and most serious in immune compromised children. Parenteral therapy has been and continues to be available for treatment of *Pseudomonas aeruginosa* infections in children. However, for all children, oral therapy has distinct advantages over parenteral therapy. Parenteral therapy, either in the hospital or in the home, carries a small, but definable morbidity. It is important to be able to assess the morbidity associated with quinolone therapy so that risks of the two treatment modalities may be compared.

Streptococcus pneumoniae is the most prominent bacterial pathogen to cause bloodstream infections and respiratory tract infections in children. Many strains of *Streptococcus pneumoniae* have become increasingly resistant to antibiotics over the past 5 to 10 years, both in the United States and worldwide. Approximately 78,000 cases of meningitis caused by *S. pneumoniae* occur annually in children under two years of age in the United States. Recent data from 8 Children's Hospitals in the United States (through August, 1996) suggest that organisms resistant to standard cephalosporin therapy represent up to 9% of all bloodstream and cerebrospinal fluid isolates.

Vancomycin is now used routinely in combination with a cephalosporin for empirical therapy of suspected pneumococcal meningitis. However, if resistance should develop to vancomycin, it is crucial that we have well studied, effective, safe antibiotic therapy available to treat these children.

Other serious, but not usually life-threatening infections caused by *S. pneumoniae* include pneumonia, otitis media, sinusitis, and bacteremia. At the present time, the great majority of these infections will respond to currently available antibiotics, administered intravenously or in high doses by the oral route. However, if resistance to beta-lactam antibiotics continues to increase, therapy with penicillins and cephalosporins may not be efficacious. Quinolone antibiotics active against *S. pneumoniae* may be required to treat these infections in the future. Data on the safety of quinolones in children are important to collect prospectively. Clinicians will prescribe quinolone antibiotics for children, based on efficacy data in adults, if needed to treat antibiotic-resistant organisms, even without adequate knowledge of the safety of this class of antibiotics in children. I believe it is important to collect prospective data on safety and efficacy of quinolones in children who have failed conventional antibiotic therapy.

I believe a reasonable, balanced approach to investigation of quinolones in children is needed, considering the unknown risks of cartilage toxicity, and the need for effective therapy. I fully support studies in serious community infections, most importantly meningitis, as well as in nosocomial infections caused by antibiotic-resistant organisms. At the same time, I believe it is important to collect data prospectively on the safety of oral quinolones in children without endorsing the uncontrolled use of quinolones or suggesting that this class of antibiotics be used as first-line therapy for respiratory tract infections in children. Only by means of careful, prospective evaluation will we understand the role of this class of antibiotics in children.

FREIE UNIVERSITÄT BERLIN **FU BERLIN**

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WHO - Collaborating Centre for Developmental Toxicology

Datum
17. November 1997

Antiinfectives Advisory Committee Meeting, Nov. 19, 1997

Dear Dr. McGoodwin,

your colleague Dr. Amy Ellis recently asked me to send some comments with regard to the upcoming Meeting of the „Antiinfectives Advisory Committee Meeting" on November 19, 1997.

My group has published a series of papers over the last years and I assume that you are aware of our data on this topic. To further underline my opinion on the use of quinolones in pediatrics I am sending the Introduction Section of a supplement issue of „Chemotherapic Journal" where we published the proceedings of a symposium entitled „Quinolones in Pediatrics - Indications and Restrictions". This meeting was held in October 1995 in Berlin.

Of course, I gladly will make further comments on this issue if necessary. For today, I hope that this general statement will be sufficient. Please let me know if you need any further information. I hope that your meeting will be a great success and remain

Yours sincerely

Prof. Dr. med. Ralf Stahlmann

Quinolones in pediatrics – indications and restrictions

Ralf Stahlmann, Berlin

The symposium "Quinolones in Pediatrics – Indications and Restrictions" was organized to discuss the pros and cons of *quinolone therapy in non-adult patients*.

The structures of the most often used drugs are very similar. All quinolones used today in human or veterinary medicine possess a fluorine atom at position 6 and it is justified to call this group of chemotherapeutic agents *fluoroquinolones*. Two essential parts of all quinolone formulas are the carboxyl group in position 3 and the carbonyl group in position 4. Alterations at this site are associated with loss of antibacterial activity. Very probably, the drugs bind to the bacterial enzyme gyrase via these parts of the structure. This also is the part of the molecule which causes chelation with divalent cations, such as magnesium or calcium and some authors have speculated that the drugs actually bind to a DNA gyrase complex via a magnesium ion.

Not all of the many thousand derivatives that were synthesized during the last decade will be available for antimicrobial chemotherapy, but we do have several new drugs of this class "ante portas". Because some of these drugs exhibit important new characteristics – such as *enhanced activity against gram-positive bacteria or anaerobes* – we will face a broadened panel of fluoroquinolones in our therapeutic armentarium in the near future.

Quinolones can cause cartilage damage in juvenile animals of multiple species. As a consequence of these toxicological findings, quinolones are contraindicated in children and adolescents as well as in pregnant and lactating women.

In principle, joint cartilage of *all animal species studied so far reacts similarly*, although there are some differences for example in the location of the effect. Joint cartilage of immature dogs reacts with typical blister formation in weight bearing joints. In principle, rats react very similar, although usually blisters are not detectable macroscopically. Besides these two species cartilage toxicity was also seen in non-human primates, guinea pigs, rabbits, mice and other mammalian species. There is no reason to assume that humans are the only species that is completely insensitive towards this toxic effect. However, human data still are a matter of controversy and some pediatricians argue that the susceptibility of man will not be proven until it is histologically confirmed.

Information from the therapeutic use of quinolones in children and adolescents collected so far indicated that obviously there is no major risk under therapeutic conditions. *The vast majority of the children treated – for example with ciprofloxacin – showed no clinical symptoms of arthropathy.*

So, if human data show that there is no major risk under therapeutic conditions, why organize a symposium? Is the whole issue brought up by toxicologists to bother pediatricians without any reason? The answers are probably "no", because several aspects have not been mentioned so far which make it worthwhile to discuss the problem on a broad basis with experts from different disciplines.

First, in a considerable number of case reports joint problems have been described in juvenile patients in association with quinolone therapy. The first case reports had been published many years before the chondrotoxicity of these drugs was demonstrated in dogs.

Of course, the interpretation of case reports is problematic and the causal relationship will always remain obscure. But do we have to assume, that all of these case reports are pure coincidental events with no causal relationship? Or do they perhaps indicate that only a small minority of subjects are extraordinarily sensitive for reasons that are unknown so far?

Furthermore, information with some quinolones – for example pefloxacin – seems to indicate that they induce more joint problems than others. From a clinic in France comparative data on pefloxacin and ofloxacin derive. Young patients with cystic fibrosis were treated for their severe pulmonary infections with these drugs. Although this was not a prospective, randomised comparative clinical trial data indicate that there might be important differences between the fluoroquinolones with respect to a risk of arthropathy for humans.

Differences between drugs can be explained either by pharmacodynamics or pharmacokinetics. It is difficult to evaluate the pharmacodynamics – or toxicodynamics – of quinolone-induced arthropathy as long as the mechanism of action is not known in all details. But pharmacokinetic differences between the individual fluoroquinolones are well known. Differences of more than tenfold do exist under therapeutic conditions between the drugs. Whereas the AUC-value for norfloxacin is 5 mg/l × h, this value is higher than 50 mg/l × h for pefloxacin or fleroxacin. This indicates that it is most probably not justified to generalize the experience made with one fluoroquinolone for the whole group of these drugs.

Obviously, there are many open questions with regard to quinolone-induced arthropathy. Without any doubt severely ill children have the right to be treated with the most appropriate drugs available – if we can exclude the possibility of short-term or long-term side effects on the skeletal system with the necessary scientific carefulness.

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Publications on Quinolone Use and Toxicity

1. Original papers

Stahlmann R, Merker H-J, Hinz N, Chahoud I, Webb J, Heger W, Neubert D (1990) Ofloxacin in juvenile non-human primates and rats. Arthropathia and drug plasma concentrations. Arch Toxicol 64: 193-204

Schröter-Kermani C, Hinz N, Risse P, Stahlmann R, Merker HJ (1992) Effects of Ofloxacin on Chondrogenesis in Murine Cartilage Organoid Culture. Toxicol in Vitro 6:465-474

Förster C, Baumann-Wilschke I, Stahlmann R (1993) Binding capacity of quinolones to cartilage components. Drugs (Suppl 3): 283-285

Stahlmann R, Förster C, Van Sickle D (1993) Quinolones in children: are concerns over arthropathy justified? Drug Safety 9:397-403

Shakibaei M, Förster C, Merker H J, Stahlmann R (1995) Effects of ofloxacin on integrin expression on epiphyseal mouse chondrocytes *in vitro*. Toxicol in vitro 9:107-116

Förster C, Shakibaei M, Schilcher H, Stahlmann R (1995) Expression of ß1-integrins on epiphyseal chondrocytes is reduced by ofloxacin. Drugs 49 (Suppl 2): 279-282

Shakibaei M, Förster C, Merker HJ, Stahlmann R (1995) Ofloxacin alters expression of integrins on chondrocytes from mouse fetuses *in vitro*. Drugs 49 (Suppl 2): 293-295

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Förster C, Kociok K, Shakibaei M, Merker H-J, Stahlmann R (1996) Quinolone-induced cartilage lesions are not reversible in rats. Arch Toxicol 70: 474-481

Shakibaei M, Merker HJ, Kociok K, Förster C, Vormann J, Günther T, Stahlmann R (1996) Comparative evaluation of ultrastructural changes in articular cartilage of juvenile rats after treatment with ofloxacin and in magnesium-deficient rats. Toxicol Pathol 24: 580-587

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Vormann J, Förster C, Zippel U, Lozo E, Günther T, Merker HJ, Stahlmann R (1997) Effects of magnesium-deficiency on magnesium and calcium content in bone and cartilage in developing rats in correlation to chondrotoxicity. Calc Tiss Intl 61: 230-238

Günther T, Rücker M, Förster C, Vormann J, Stahlmann R (1997) In vitro Evidence for a Donnan distribution of Mg^{2+} and Ca^{2+} by Chondroitin Sulfate in Cartilage. Arch Toxicol 71: 471-475

Burkhardt JE, Hill MA, Lozo E, Förster C, Stahlmann R (1997) Immunohistochemistry of joint cartilage from immature Beagles after treatment with difloxacin. Toxicol Pathol (in press)

Stahlmann R, Vormann J, Günther T, Förster C, Zippel U, Lozo E, Schwabe R, Kociok K, Shakibaei M, Merker HJ (1997) Effects of Quinolones, Magnesium Deficiency or Zinc Deficiency on Joint Cartilage in Rats. Magn Bull 19: 7-22

Stahlmann R, Zippel U, Förster C, Shakibaei M, Merker HJ, Borner K (1997) Chondrotoxicity and Toxicokinetics of Sparfloxacin in Juvenile Rats. Antimicrob Agents Chemother (submitted)

Förster C, Schwabe R, Lozo E, Zippel U, Vormann J, Günther T, Merker HJ, Stahlmann R (1997) Quinolone-induced arthropathy: Exposure of magnesium-deficient aged rats or immature rats, mineral concentrations in target tissues and pharmacokinetics. Arch Toxicol (in press)

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HANDOUT AIDAC #62
11-19-97

Pediatric Use of Fluroquinolones

Roger M. Echols, M.D.

Vice President

Infectious Disease

Pharmaceutical Research & Development

Bristol-Myers Squibb

Two Issues

- Risk benefit of clinical trials involving fluroquinolones in pediatric patients
- Incentives and obstacles that impact product labeling information for pediatric patients

Historical Perspective

- 1989 Advisory Committee meeting recommendations: Cystic Fibrosis and neutropenia; age $\geq$ 5 years
- Follow-up negotiations for filing supplemental NDA
- 1993
  - International Chemotherapy Society
  - Second FDA Advisory Committee meeting

Perception and Realities

- Off-label prescribing
  - Substantial experience
    (>1,000,000 prescriptions)

- Research in developing countries
  - Medical need
  - Publicity concern

Risk Benefit 1997

- Penicillin - resistant *Strep. pneumoniae*
  - Cross resistance with cephalosporins/ macrolides
- Potential benefits of newer quinolones
  - Bioavailability and infection site penetration
  - Spectrum includes all respiratory pathogens

Recommendations

- Permit clinical trials in appropriate indications
  - Not just meningitis
- Encourage appropriate commercial development through labeling
  - Need liquid formulation, appropriate dose size

Norfloxacin Pediatric Use in Japan 1993-1997

	Total No. of pediatric patients (no. of less than 4 years old)*	
April 1993 - March 1994	255,000	(24,000)
April 1994 - March 1995	274,000	(26,000)
April 1995 - March 1996	162,000	(15,000)
April 1996 - March 1997	263,000	(25,000)
April 1997 - September 1997	83,000	(8,000)
Total	1,037,000	(98,000)

*Based on number of 50mg tablets

Communications from Kyorin Pharm. Co., LTD

HANDOUT ATDAC #62 11-19-97.

ADVISORY COMMITTEE
(19 November, 1997)
Fluoroquinolone Development in Pediatric Populations
- abstract -

It has long been recognized that fluoroquinolones and their derivatives are associated with arthropathy in juvenile animals. Owing to these pre-clinical findings, in both 1989 and 1993 the Anti-Infective Drugs Advisory Committee discussed in open sessions whether drug development in pediatric populations should be allowed. At both meetings, the Advisory Committee recommended to the U.S. Food and Drug Administration that fluoroquinolone drug development be limited to pediatric populations with cystic fibrosis and/or hematologic-oncologic disorders where the benefits of fluoroquinolone use outweigh the risks.

Since 1993 concerns about drug resistance (e.g., penicillin-resistant *Streptococcus pneumoniae* or *Pseudomonas aeruginosa*) have increased and therefore a renewed interest for the development of fluoroquinolones in pediatric populations is underway. In addition, fluoroquinolone use in pediatric populations has gradually increased. Drug developers, clinicians, epidemiologists, and the FDA recognize that as concerns about resistance increase, safe and effective anti-infective therapeutic options for pediatric populations may become increasingly limited.

In revisiting this issue, the Anti-Infective Drugs Advisory Committee meeting will include presentations by foreign and domestic regulatory scientists, academicians, clinicians, drug developers, and representatives from the American Academy of Pediatrics (AAP) as well as the Centers for Disease Control and Prevention (CDC).

At the conclusion of presentations and discussion, the Agency will ask the Advisory Committee to recommend one of three options:

(1) Continue current restrictions for pediatric populations with fluoroquinolone drug development limited to cystic fibrosis and/or hematologic-oncologic disorders.

(2) Open clinical development to all treatment indications in pediatric populations.

(3) An incremental development approach : Open up clinical trials to pediatric populations in pursuit of serious infections (e.g., bacterial meningitis) due to resistant pathogens (e.g., penicillin-resistant *Streptococcus pneumoniae*). Depending on the results generated by these studies, clinical trials for less serious treatment indications could be addressed in the future.

HANDOUT ATDAC#62 11-19-97
BAYER

Pediatric Indications for Quinolones: The Ciprofloxacin Experience

FDA Advisory Committee Meeting
Deborah A. Church, M.D.
Deputy Director, Medical Research

Bayer

Overview

- Historical perspective
- Toxicology
- Selection of appropriate pediatric indications for development
- Ciprofloxacin clinical experience in pediatrics
- Summary and conclusions

Historical Perspective - Ciprofloxacin

- **1989:** sixteen and seventeen year old women excluded from enrollment in a single dose gonorrhea study
- Bayer approached by medical community, e.g. CF, cancer to look at the use of ciprofloxacin in pediatrics
- Compassionate use pediatric database
- Bayer sponsored prospective studies based on medical need in CF and cancer

Bayer

Quinolone-Induced Articular Cartilage Lesions

- Differences among juvenile animal species (dog > rat)
- Evolves within days
- Dose/treatment duration dependent
- Joint effusion, pain, lameness
- Variability in arthropathic potential among quinolones (nalidixic acid > ciprofloxacin)

Bayer

Quinolone-Induced Articular Cartilage Lesions

- No final explanation for the age related difference in susceptibility to quinolone chondrotoxicity
- Nalidixic acid human experience not associated with the type of articular lesion seen in juvenile animals
- Humans appear to be less sensitive to developing quinolone-induced arthropathy than experimental animals

Compassionate Use - Ciprofloxacin

- **Total number of patients:** 1,795 (2,030 courses)
- **Ages (years):** (71%), (26%), <5 (3%)

	IV	PO
Median Dose (mg/kg/day)	8	25
Median Duration (days)	7	14

- **Arthralgias:** 1.5%

Note: Arthralgias occur in up to 8% in CF patients

Bayer

Selection of Pediatric Indications

- Clinical safety well demonstrated in adult populations
- Initiate pediatric studies in patients with greatest medical need
- Specific indications considered for ciprofloxacin development
  - Cystic fibrosis
  - Diarrheal disease (e.g., drug resistant shigellosis)
  - Febrile neutropenia
  - Gram negative osteomyelitis
  - Complicated urinary tract infection

Bayer

Cystic Fibrosis

- **Rationale:** IV ⇨ PO antibiotic with antipseudomonal activity for acute pulmonary exacerbations
- **Bayer Experience:** Two comparative clinical trials from 1991-1995 (U.S./Europe, South Africa and Israel) in CF patients ages ≥5 to <18 years

Cystic Fibrosis (United States)

- **Study Design:** Double-blind, comparative, multicenter
- **Drug Regimen:** Ciprofloxacin IV 10mg/kg q 8hr ⇨ PO 20mg/kg q 12hr vs. ceftazidime/tobramycin IV q 8hr
- **Treatment Duration:** 10-21 days

Bayer

Cystic Fibrosis (United States)

- **Patients Enrolled:** 130 (67 ciprofloxacin)
- **Safety Procedures:**
  - Clinical joint assessments by treatment-blinded examiner
  - Independent blinded safety committee
- **Results:**
  - Overall safety and tolerability of ciprofloxacin were comparable to ceftazidime/tobramycin
  - Musculoskeletal events similar (21% ciprofloxacin vs. 22% ceftazidime/tobramycin)

Bayer

Cystic Fibrosis (Europe, South Africa, Israel)

- **Study Design:** Open, comparative, multicenter
- **Drug Regimen:** Ciprofloxacin PO 15mg/kg q 12hr
  vs. ceftazidime/tobramycin IV q 8hr
- **Treatment Duration:** 14 days

Bayer

Cystic Fibrosis (Europe, South Africa, Israel)

- **Patients Enrolled:** 108 (55 ciprofloxacin)
- **Safety Procedures:**
  - Clinical joint assessments by treatment-blinded examiner
  - Knee/hip ultrasounds
  - MRI imaging (29 patients)
- **Results:**
  - Overall safety and tolerability of ciprofloxacin were comparable to ceftazidime/tobramycin
  - Musculoskeletal events were similar (7% ciprofloxacin vs. 11% ceftazidime/tobramycin)
  - Ultrasound and MRI did not show any pathology

Clinical Trials

- Incidence of arthropathy in ciprofloxacin treated pediatric patients from randomized clinical trials was similar to patients who received control drugs

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Clinical Experience

Completed Pediatric Studies

Indication	Cipro Treated Patients
CF	250
Neutropenia	25
Diarrheal diseases	263
Meningococcal carriage	469
Total (prospective studies)	*1007*
Compassionate use	1795
Total patients	***2802***

Bayer

Summary and Conclusions

- Extensive clinical experience with ciprofloxacin has defined its safety profile in adults and children

– clinical studies (836)	⇨	158,731 adult patients, 1,174 pediatric patients
– compassionate use	⇨	1,795 pediatric patients
– marketing experience	⇨	156.5 million adult treatment courses, 4.3 million pediatric treatment courses

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Summary and Conclusions

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- Ciprofloxacin can be used safely in children with infectious diseases where there is a clinical need

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Summary and Conclusions

- Quinolones are a heterogeneous class
- Animal articular lesions do not correlate well with clinical experience e.g. nalidixic acid
- Experience with ciprofloxacin should not be extrapolated to other quinolones

HANDOUT AIDAC#62 11-19-97

Fluoroquinolone Use in Pediatrics
Epidemiology Review of
FDA AERS & Drug Use Data

Carolyn McCloskey, MD, MPH
Division of Pharmacovigilance & Epidemiology
November 19, 1997

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commercial

information

Limitations of Voluntary Reporting Databases

- Inconsistent Quality
- Duplicate Reports
- Under-Reporting of Event
- Multiple COSTARTs for each Report
- No Incidence Rate
- No Direct Estimate of Risk
- No Comparisons Between Drugs

Factors Affecting Drug Comparisons

- Length of Time Drug on Market
- Type of Drug Use
- Population Using Drug
- Drug Advertising

Foreign WHO FQ 0-18 yo ADRs

Age, years:	0-1	2-5	6-12	13-16	17-18
Arthropathies		5	8	8	5
CNS involve		4	3	10	10
Hypersensitivity	1	1	7	14	10
Rash/Allergy	10	9	20	31	55
Psychiatric	2	3	11	7	11
Photosensitivity	1	3	7	18	3

HANDOUT AIDAC #62
11-19-97

Quinolone-Induced Arthropathy in Juvenile Animals

Amy L. Ellis, Ph.D.
FDA/CDER
Division of Anti-Infective Drug Products

Quinolone-Induced Arthropathy

- Blisters observed on the articular cartilage of juvenile animals
- Species known to be sensitive include dog, rat, rabbit, marmoset, guinea pig
- Dog is the most sensitive species
- Lesions do not appear to be reversible

Scope of Quinolone Use

- Approved Quinolones: **9**
- Quinolones in Development : **8**
- Total: **24** (includes those not approved in the US and some that were withdrawn)

Quinolone #1

Species	**Age** (weeks)	**LOEL** (mg/kg/day)	**Multiple of Human Dose***	**NOEL** (mg/kg/day)
Dog	12	25 30 d, p.o.	0.2	<25 lower doses not tested
Rabbit	8	400 28 d, p.o.	1.8	200
Rat	4	250 7 d, p.o.	0.8	<250 lower doses not tested

This is for the LOEL, based upon body surface area

LOEL: Lowest Observed Effect Level

NOEL: No Observed Effect Level

Quinolone #2

Species	**Age** (weeks)	**LOEL** (mg/kg/day)	**Multiple of Human Dose***	**NOEL** (mg/kg/day)
Dog	14	30 28 d, p.o.	0.6	<30 lower doses not tested
Rat	4	500 10 d, p.o.	4.1	250

* This is for the LOEL, based upon body surface area

Quinolone #3

Species	Age (weeks)	LOEL (mg/kg/day)	Multiple of Human Dose*	NOEL (mg/kg/day)
Dog	16	10 7 d, p.o.	0.4	5
Rat	5	90 90 d, p.o.	1.4	30

* This is for the LOEL, based upon body surface area

Quinolone #4

Species	**Age** (weeks)	**LOEL** (mg/kg/day)	**Multiple of Human Dose***	**NOEL** (mg/kg/day)
Dog	15	4.5 7-8 d, p.o.	0.4	<4.5 lower doses not tested
Rat	5	100 84 d, p.o.	3.1	30

* This is for the LOEL, based upon body surface area

Quinolones #5 and #6

- Quinolone #5

Dog (16-24 w):

LOEL- **50** mg/kg/day

(28 days, p.o.)

5.4 X Human Dose

NOEL- **15** mg/kg/day

- Quinolone #6

Dog (12 w):

LOEL- **80** mg/kg/day

(28 days, p.o.)

4.3 X Human Dose

NOEL- **60** mg/kg/day

Summary of Juvenile Dog Data
(Age: 12-24 weeks)

Quinolone	LOEL mg/kg/day	Multiple of Human Dose*	NOEL mg/kg/day
1	25 30 d, p.o.	0.2	Unknown
2	30 28 d, p.o.	0.6	Unknown
3	10 7 d, p.o.	0.4	5
4	4.5 7-8 d, p.o.	0.4	Unknown
5	50 28 d, p.o.	5.4	15
6	80 28 d, p.o.	4.3	60

This is for the LOEL, based upon body surface area

Cartilage Lesions May Also Occur After Single Doses

- Quinolone #2:

13 week old dogs:

100 mg/kg, p.o.

2.1 X Human Dose

- Quinolone #3

4 week old rats:

1000 mg/kg, p.o.

15.4 X Human Dose

Why are juvenile animals more susceptible to quinolone-induced arthropathies than adult animals?

SPONSOR HANDOUT ADAC #62 11-20-97

Rocephin® (ceftriaxone)

Acute Otitis Media

Hoffmann-La Roche Inc.

Rocephin®
sNDA 50-585

A Single IM Injection for the Treatment of Acute Otitis Media in Children

Clinical Development Program
Rationale

- Medical need for an addition to the armamentarium for the treatment of acute otitis media
- Optimal bacteriologic activity
- Optimal pharmacokinetics
- Efficacy associated with a well tolerated safety profile
- Assure compliance

Clinical Development Program

To study a single IM injection of ceftriaxone (50 mg/kg) for the safe and effective treatment of acute otitis media

- 1 pharmacokinetic study (Iceland)
- 2 bacteriology studies (US)
- 4 clinical studies (US)
- 1 clinical study (France)

Single Dose IM Rocephin for Treatment of Acute Otitis Media Offers:

- Favorable pharmacokinetics, pharmacodynamics and pharmaceutics
- Bactericidal activity in vitro against the three major pathogens
- Less potential for emergence of resistance due to PK properties and sustained duration of bactericidal activity in the middle ear fluid

Single Dose IM Rocephin for Treatment of Acute Otitis Media Offers:

- Efficacy comparable to standard treatment
- Well established safety profile

Single Dose IM Rocephin for Treatment of Acute Otitis Media Offers:

- Advantages of single dose parenteral therapy
- Guaranteed 100% full course treatment and compliance
- Parental preference for single IM dose

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Single Dose IM Rocephin for Treatment of Acute Otitis Media Offers:

A significant addition to the armamentarium for the treatment of acute otitis media

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Presentation Agenda

1. **Jerome Klein, MD**
   Vice Chairman for Academic Affairs
   Department of Pediatrics, Boston Medical Center
   Professor of Pediatrics
   Boston University School of Medicine, Boston, MA
   Overview of Otitis Media and Its Treatment

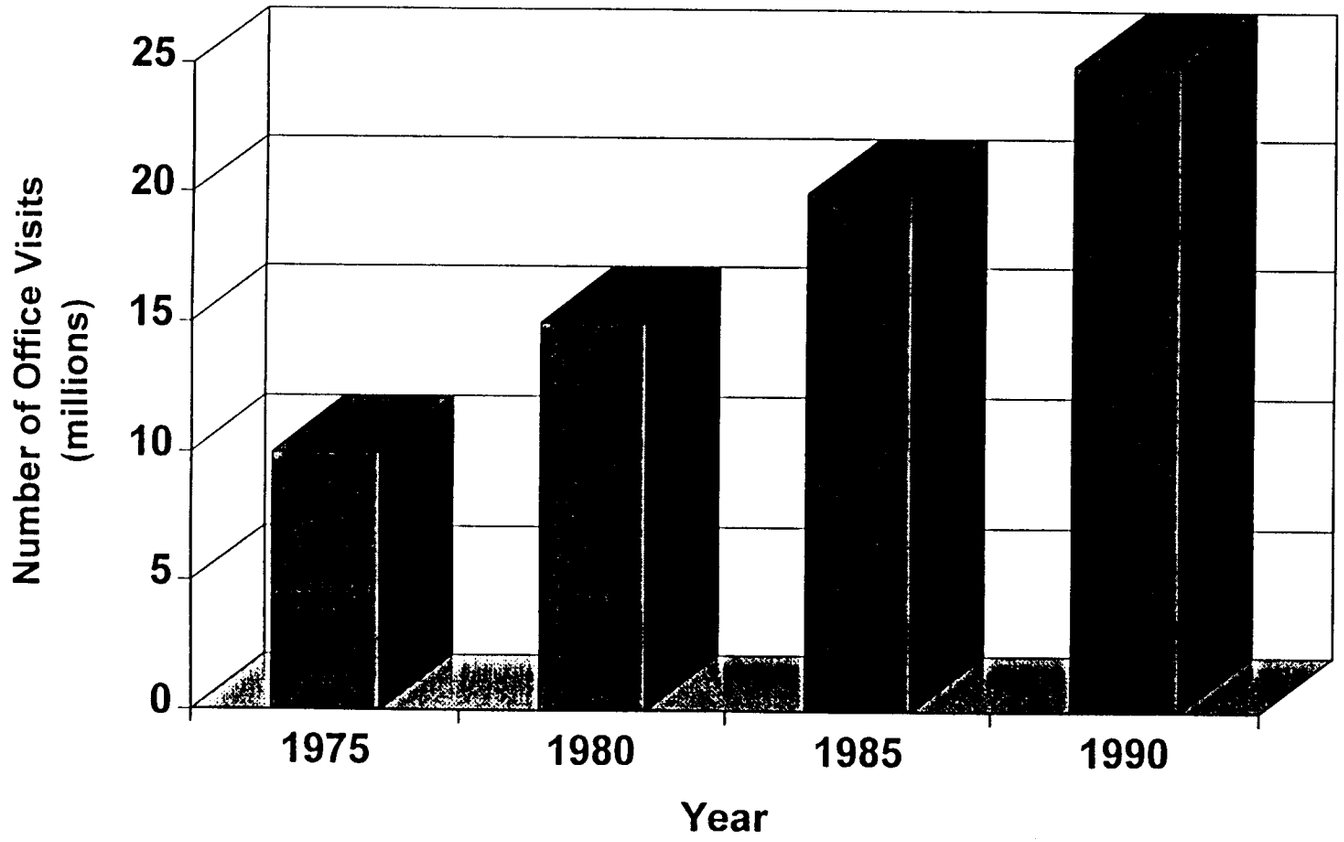
2. **Jeffrey Blumer, PhD, MD**
   Professor of Pediatrics and Pharmacology
   Case Western Reserve University
   Chief, Division of Pediatric Pharmacology and Critical Care
   Rainbow Babies and Childrens Hospital, Cleveland, OH
   Ceftriaxone Pharmacokinetics and Pharmacodynamics in Acute Otitis Media

3. **Jonathan Solsky, MD**
   Director, Clinical Medicine
   Medical Affairs, Hoffmann-La Roche
   Efficacy and Safety of Single Dose Ceftriaxone in the Treatment of Acute Otitis Media in Children

Jerome Klein, MD

Overview of Acute Otitis Media and Its Treatment

Office Visits with A Principal Diagnosis of Otitis Media in the US



Office Visits with a Principal Diagnosis of Otitis Media: United States, 1975-1990

"Dr. Klein's own slide"

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The Middle Ear System

"Dr. Klein's own slide"

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IDSA - FDA Guidelines for Diagnosis of Acute Otitis Media

- Identification of middle ear effusion
  - Pneumatic otoscopy
    - Decrease mobility
    - Air fluid level/bubbles
  - Tympanometry
  - Acoustic reflectometry

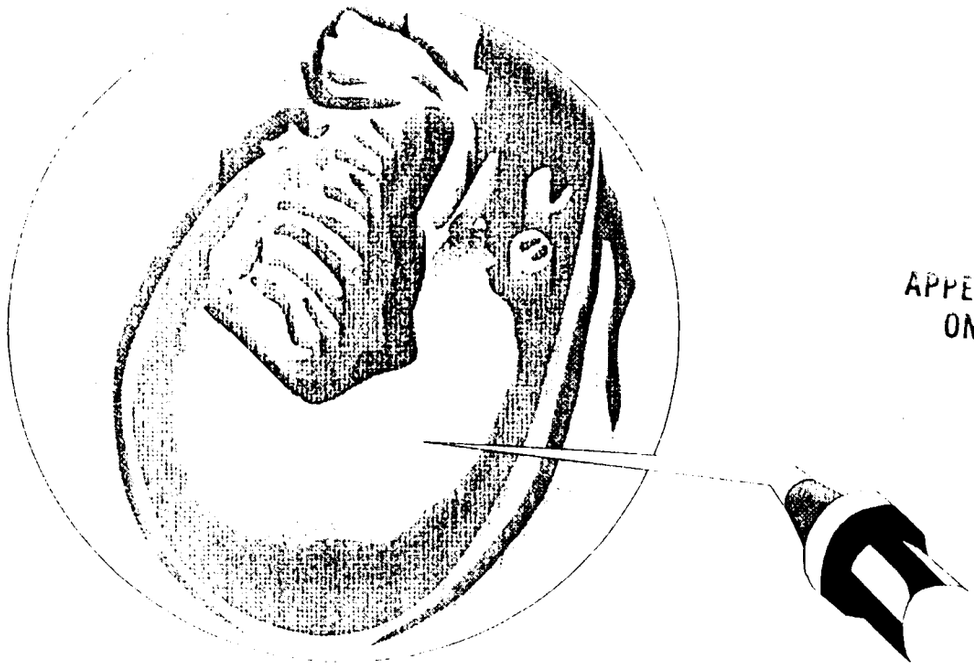
Chow, CID. 1992, 15:S69.

IDSA - FDA Guidelines for Clinical Diagnosis of Acute Otitis Media

- **Specific signs**
  - Otalgia
  - Otorrhea
  - Hearing loss
  - Vertigo
- **Nonspecific signs**
  - Fever*
  - Irritability*
  - Lethargy
  - Anorexia*
  - Vomiting*
  - Diarrhea
- **Efficacy Assessment: Week 2**

Chow, CID. 1992, 15:S69.

Method of Specific Bacteriological Diagnosis



Bluestone Charles D, Klein Jerome O; *Otitis Media in Infants and Children*, 2nd ed; W.D. Saunder Co 1995; p 127.

Bacteriologic Pathogens Isolated from Middle Ear Aspirates in Infants and Children with Acute Otitis Media

	1985 - 1992	
Bacterial Pathogen	Mean	Range
Streptococcus pneumoniae	38	
Haemophilus influenzae	27	
Moraxella catarrhalis	10	
Streptococcus Group A	5	
Staphylococcus aureus	2	
Miscellaneous bacteria	8	
None or nonpathogens	28	

Klein JO, Bluestone CD. Otits Media in Infants and Children. WB Saunders, Phila. 3rd Edition, p. 56.

Acute Otitis Media in the Pre-Antibiotic Era

"slide given by Klein"

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Acute Mastoidis in Tubigen, Germany 1975-1992

"Slide given by Klein"

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Persistence of Bacterial Pathogens in Middle Ear Fluid After Therapy for Acute Otitis Media

Drug	No. of Patients from Whom Organism was Recovered During Therapy / No. of Patients with Organism Isolated Before Therapy*	
	S. pneumoniae	*H. influenzae*
Placebo	46 / 57	13 / 25
Amoxicillin	8 / 136	3 / 23[1] 7 / 11[2]
Cefaclor	16 / 88	27 / 82
Cefixime	16 / 61	4 / 66
Clarithromycin	0 / 12	12 / 15
TMP-SMZ	6/51	15/61
Ceftriaxone	0 / 24	0 / 30

[1] β-lactamase negative
[2] β-lactamase positive
* Klein, J.O. Pediatr Infect Dis J, 1993, 12:973-975

Persistence of Bacterial Pathogens in Middle Ear Fluids After Therapy for Acute Otitis Media

Drug	No. of patients from Whom Organism was Recovering During Therapy / No. of Patients with Organism Isolated Before Therapy*				
	S. pneumoniae				*H. influenzae*
	Pen-Sens	Pen-Res	Az-Sens	Az-Res	
Amoxicillin	0/10	4/14	--	--	9/33
Cefaclor	3/16	11/17	--	--	14/28
Azithromycin**	--	--	0/12	6/6	24/34

* Pen Sens = <0.1; Pen-Res ≥ 0.1; Az-Sens and Res not defined further
** Given 3 days,

Dagan R. 1997.

Limitations of Oral Antimicrobial Agents for Treatment of Acute Otitis Media

Antimicrobial Spectrum:

- Beta-lactamase susceptible ..... Amoxicillin
- Ineffective for *S. pyogenes* ..... TMP-SMZ
- Decreased efficacy for *S. pneumoniae* ..... Cefixime, Ceftibuten
- Decreased efficacy for *H. influenzae* ..... Macrolides

Adverse Events:

- Diarrhea ..... Amox/Clav
- Stevens-Johnson syndrome ..... TMP-SMZ
- Serum sickness reaction ..... Cefaclor

Administrative Problems:

- >2 doses/day ..... Erythromycin/Sulfisoxazole, Amoxicillin, Cefaclor
- Bitter taste ..... Cefpodoxime, Cefuroxime axetil, Clarithromycin