

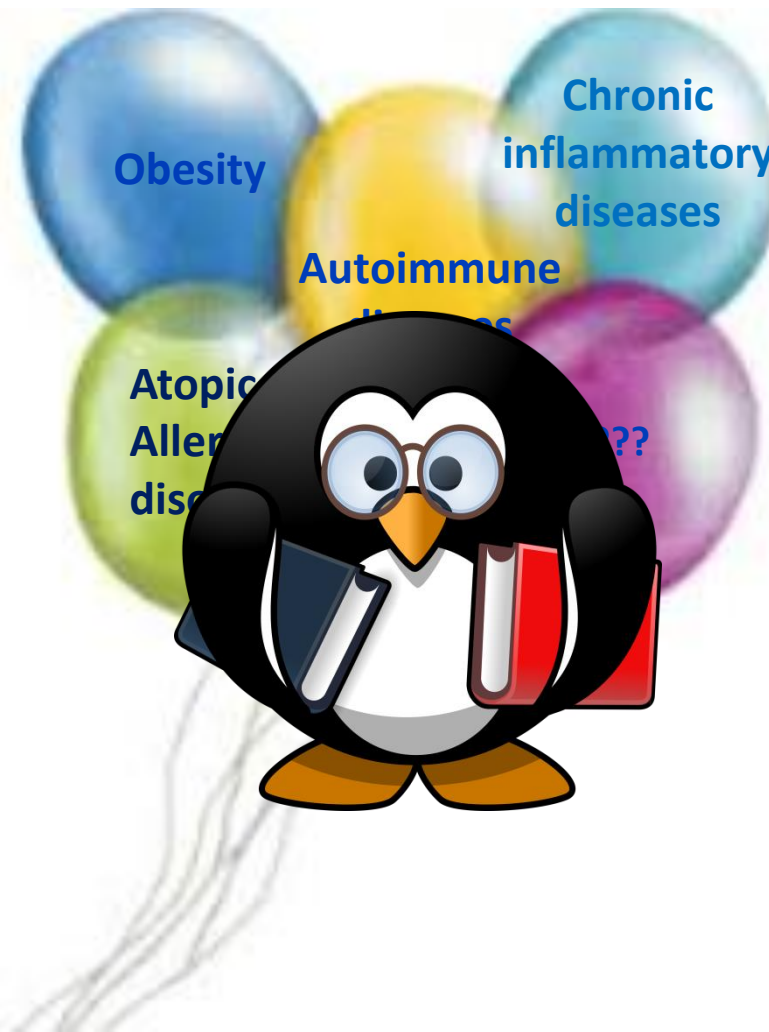
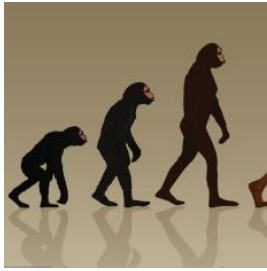
Bugs and Drugs: Optimal Use of Antibiotics in the Outpatient

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**Disclosure: Dr. Long is an associate editor of the Red Book 2018-2021
and *The Journal of Pediatrics***



- Microbial Jobs:**
- Manage competition/quorum sensing
 - Convert food calories into body mass
 - Ferment indigestible CHO to sc fatty acids
 - Biotransform conjugated bile salts
 - Synthesize vitamins
 - Degrade dietary oxalates
 - Hydrolyze urea
 - More and more and more

Mucosal Immune System 101

The Microbiome in Health and Disease
 Aberrations are potentially fundamental to development of disease
 Healthy microbiome is important for education of mucosal immunity



A double blind randomized placebo-controlled trials of treatment for acute otitis media in children <2 years of age shows

- A. Noninferiority of 5 days v 10 days of antibiotic therapy**
- B. Superiority of 10 days v 5 days of therapy**
- C. Neither of the above**



Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D.,
Diana H. Kearney, R.N., C.C.R.C., Sonika Bhatnagar, M.D., M.P.H.,

The Question

Could short-course Abx therapy AOM be successful and limit exposure/Abx resistance?

The Study

Prospective randomized double-blind placebo controlled non-inferiority trial

Children 6-24 mos AOM Pittsburgh/Bardstown 2012-2015

AOM + severity-of-symptoms (SoS) score: 7 items; scale 0-2 ea; max 14 (→ granularity data)

Subjects got 2 bottles, ea with 5 days meds: Amox-clav 14:1(2) vs Amox-clav(1) + placebo(1)

Follow up: Parent daily structured AOM-SoS score

Telephone day 4-6 and office visit day 12-14 + q 6 wks to end respiratory season
+ final visit @ start new respiratory season

Primary outcome: Clinical failure @ day 14 (↑symptoms, TM bulging or lack of complete/nearly complete resolution S/S)

Second outcomes: Symptom burden day 6-14

Recurrence of AOM

Outcomes of recurrent treatments

Nasopharyngeal colonization with Pen Non-S organisms

Other: Missed work, special arrangements, satisfaction with management

Results

Characteristics of the Study Population

Characteristic @ entry	10-day Group	5-day Group
Age 6-11 months	50%	51%
AOM SoS score	8.6	8.2
SoS score 9-14	54%	50%
Severe (pain and fever)	57%	53%
One ear affected	53%	49%
Mod/marked bulging	86%	82%
<i>S. pneumoniae</i> NP	49%	53%
<i>H. influenzae</i> NP	33%	24%

Total 1569 children screened, 890 eligible, 520 randomized.
 Demog + Follow up similar: End-of-treatment visit ~90%
 Reported receipt meds $\geq 90\%$ bottle 1 + 80% bottle 1 + 2
 Mean duration follow-up ~ 4 months

Primary and Secondary Outcomes by Treatment Arm

End of Rx Outcomes	10-day Group	5-day Group
Clinical failure	16%	34% NNT = 6
AOM-SoS score $\downarrow < 50\%$	9%	20% P = .003
OME	62%	65%
Follow-up Outcomes		
Recurrence(s)	Risk-related*	Risk-related*
		NS
NP Pen-S to Pen-NS	47%	44%

* Risk = OME, exposure ≥ 3 children 10 hr/wk, bilateral AOM

Hoberman Conclusions AOM 6-24 mo

Abx 5 days vs 10 days \rightarrow less favorable outcomes
 Adverse events/Abx R same after 5 or 10 days Rx



A Cost-Utility Analysis of 5 Strategies for the Management of Acute Otitis Media in Children

Nader Shaikh, MD, MPH^{1,2}, Emily E. Dando, BA², Mark L. Dunleavy, BS³, Dorothy L. Curran, BS⁴, Judith M. Martin, MD^{1,2}, Alejandro Hoberman, MD^{1,2}, and Kenneth J. Smith, MD, MS⁵

- Cost-utility analysis is more robust than cost-benefit analysis
- Can study costs of interventions with different levels benefit/harm, in light of added variables (drug cost, probability AOM, speed of cure, quant/qual side effects, family “costs” >drug)

The Study

Decision-analytic model to compare cost effectiveness (cost per QALD gained) of 5 options for mngt children with AOM to reduce time: to resolution, of overall symptom burden, of TM signs of infection

Strategies modelled
 Immediate amoxicillin
 Immediate amox-clav
 Immediate cefdinir
 Delayed prescription
 Watchful waiting

Probabilities Outcomes
 Persistent symptoms (Early failure v success)
 AOM recurrence
 Mastoiditis
 Diarrhea
 Diaper rash
 Body rash

Disutility Values
 Mastoiditis
 AOM
 Diarrhea
 Body rash
 URI
 Diaper dermatitis

Costs per Episode
 Antibiotic
 Barrier cream
 Antifungal cream
 Diapers
 Office visits (Prov, Non-med, work)
 Hosp for mastoiditis

Probability estimates are from med literature
 Utility estimates: 1QALD = 1 day of perfect health
 Disutilities (0-1) are subtracted from 1

Relative Cost Utilities of 5 Management Strategies for AOM



Efficacy	Overall Cost
Immed Amox-clav	Rescue Amox script
Immed Amox	Immed Amoxicillin
Immed Cefdinir	Watchful waiting
Watchful waiting	Immed Amox-clav
Rescue Amox script	Immed Cefdinir

Rescue Amox script is baseline

* ICER Immed Amox vs Rescue Amox
\$101 per QALD gained
(1.7 days ↓ symptoms)

* ICER Immed Amox-clav vs Amox
\$2331 per QALD gained
(Limited extra QALD at ↑ cost)

* ICER – Incremental cost-effectiveness ratio. Considers cost of next expensive strategy relative to extra clinical benefit. Society willing to pay \$274/1 QALD gained (\$100,000/1 QALY gained)

Conclusions

- In children <2 years with AOM and no recent Abx exposure, immediate amoxicillin seems to be the most cost-effective initial management
- PCPs' improved diagnostic accuracy for AOM could → substantial ↓ costs for "AOM"



Shaikh et al



- The model comprises a series of "what ifs" re probabilities and alternative assumptions
- Results are as close to the truth as is likely with current state of AOM science and data
- The best care + antibiotic stewardship will result from *precise and accurate diagnosis*

Acute Otitis Media: A Brief Time



**Azithromycin?
TMP-SMX?**



**1998 CDC Consensus
Amoxicillin 90/kg 1st line**

From Pen, Erthro and Sulfisox.
To Amoxicillin and Cefaclor.
To Cephalosporin taste greats.
To Penicillin-R pneumococcus

Studies rediscover spontaneous
resolution.
RCT Abx Rx mild AOM → benefit

Shaikh Modelling shows immed.
Rx Amoxicillin for <2yrs w AOM
most cost effective mngt strategy



Tympanocentesis
Microbiology AOM
Spontaneous
resolution rate/org

PCVs ↓ AOM

Hoberman RCT shows benefit
Abx AOM 10 days vs 5 days



**2004 AAP/AAFP Guidelines
Includes watchful waiting
and rescue script**

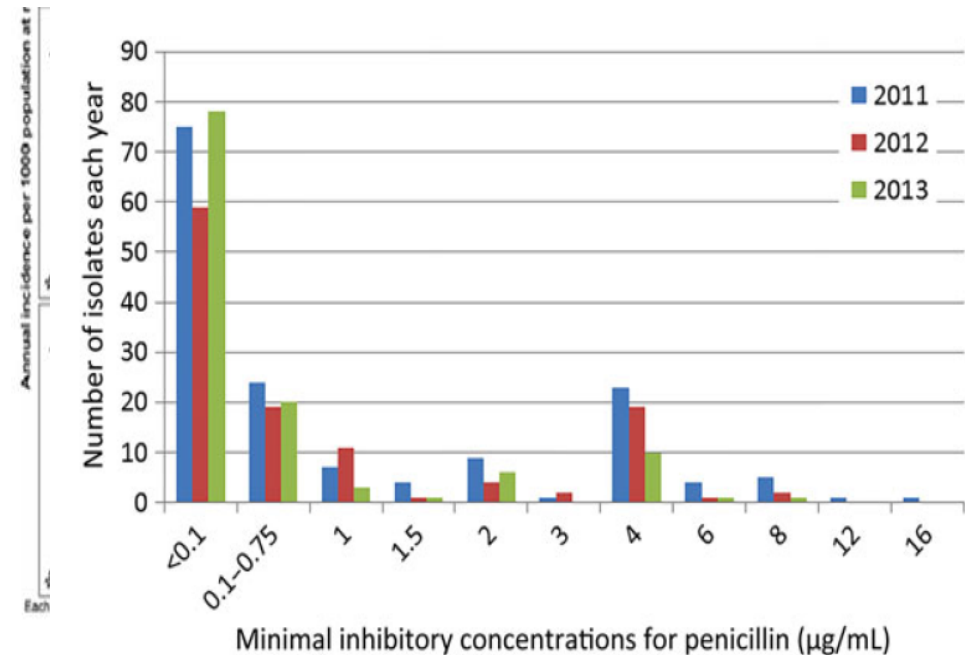


**2013 AAP/AAFP Guidelines
1st Amox 90/kg (or Cefdinir)
2nd Amox-Clav 14:1 90/kg**



With the implementation of pneumococcal conjugate vaccine (PCV13) in infancy, the incidence of non-pneumococcal acute otitis media in children has

- A. Increased
- B. Decreased
- C. Not changed





Clinical Features, Virus Identification, and Sinusitis as a Complication of Upper Respiratory Tract Illness in Children Ages 4-7 Years

Gregory P. DeMuri, MD¹, James E. Gern, MD¹, Stacey C. Moyer, RN, MSN¹, Mary J. Lindstrom, PhD², Susan V. Lynch, PhD³, and Ellen R. Wald, MD¹



The Study

Observational cohort 4-7 y olds 2 practices WI
Nasal samples during URI and wellness
Rate of sinusitis complicating URIs

The Results

1.3 URIs/child/year
Virus(es) detected during 81% URIs
Virus(es) detected during 33% wellness
Resolution URI <10 days in 72%
Sinusitis complicated 8.8% URIs

Diagnosis and Management of Acute Bacterial Sinusitis: 2013 AAP Guidelines



1. Presumptive dx of acute bacterial sinusitis

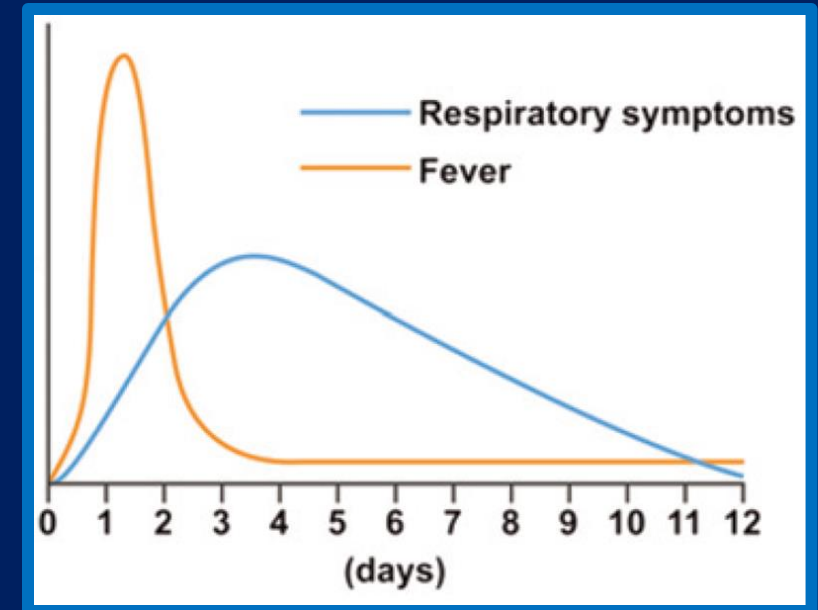
- Persistent illness
(≥ 10 d nasal discharge or daytime cough)

OR

- Worsening course
(or new onset nasal dc, cough or fever)

OR

- Severe onset
(concurrent temp >39 + pur nasal dc x 3d)



2. Do not obtain imaging to distinguish ABS from viral URI

(No plain film, contrast CT, MRI or U/S)



3. Obtain contrast CT (or MRI) of paranasal sinuses if complication suspected

(Orbital, bony or CNS)



= Rec



= Strong rec



= Option



4. Prescribe antibiotic if diagnosis because of worsening symptoms or severe onset

5. Prescribe antibiotic or observe course 3 days if diagnosis because of persistent symptoms



Effectiveness of Amoxicillin/Clavulanate Potassium in the Treatment of Acute Bacterial Sinusitis in Children

Ellen R. Wald, David Nash, Jens Eickhoff

Pediatrics 2009;124:9

Background

- Prior random placebo-controlled trials
Wald 1986 → Treatment benefit
Garbutt 2001 → No treatment benefit
- Equipoise – Justifies RPCT

The Study

- Pittsburgh trial Amox-clav (90mg/k) vs placebo
Ages 1-10 yrs Outcomes = clinical scores
Screened 2,135 children → 135 (6.5%) ABS
(Max dose amox-clav 14:1 is 4 g/day div bid)

The Results

<u>Outcome</u>	<u>Amox-Clav</u>	<u>Placebo</u>
Cured	50%	14%
Improved	14%	18%
Failed Rx	14%	68%

Initial Antibiotic Choice



6. Prescribe amoxicillin with or without clavulanate x 7 days after “free of signs and symptoms” (min 10 days)

Amox 90/k/day in 2 div doses, max 4g/day div bid

Math = 70% culture +

Change over decades = S pneumo : H flu : M cat

30 : 20 : 20 → 30 : 30 : 10

S. pneumoniae 10 - 40% Amox non-susceptible

H. influenzae 10 - 40% Amox resistant

M. catarrhalis 100% Amox resistant

Likelihood isolate is Amox^{resist} = $.7 \times (.12 + .10) = 15\%$

OR

Amox-clav 14:1 90/k/day in 2 div doses, max 2g/dose

Math = Amox^{resist} ↑ in daycare

< 2 yrs

Antibiotic in < 30 days

Reassessment and Change in Therapy



7. Reassess if caretaker says worse/not improved at 72h



8. Change antibiotic if initially prescribed

Amoxicillin → Amox-clav
Amox-clav → Clindamycin + cefixime
or
Linezolid + cefixime
or
Levofloxacin



9. Prescribe antibiotic if initially observed without



No recommendation re adjunctive therapies
(Lack of appropriately designed studies)



A 4 year old girl has the acute onset of high fever, complains of headache and has a rash beginning on her wrists and ankles which is progressing up her arms. It's summer.

On examination on day 2 of fever she is ill but not toxic appearing, and has mild conjunctival erythema. The rash is non-blanching and there is edema of her distal arms/hands.

**You are considering outpatient management.
The most appropriate therapy is:**

- A. Antipyretic but no antibiotic**
- B. Doxycycline**
- C. Erythromycin**
- D. Clindamycin**
- E. Ceftriaxone IM**



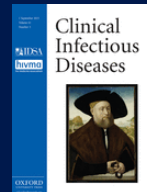
Know your map for RMSP



Self-Reported Treatment Practices by Healthcare Providers Could Lead to Death from Rocky Mountain Spotted Fever

J Pediatr 2014;164:416
Jillian Zientek, DVM¹, F. Scott Dahlgren, MSPH², Jennifer H. McQuiston, DVM², and Joanna Regan, MD¹

- ✓ Survey of U.S. doctors showed that 80% identified doxycycline as Rx for RMSF in patients ≥ 8 yrs, but only 35% correctly chose doxycycline in patients < 8 yrs

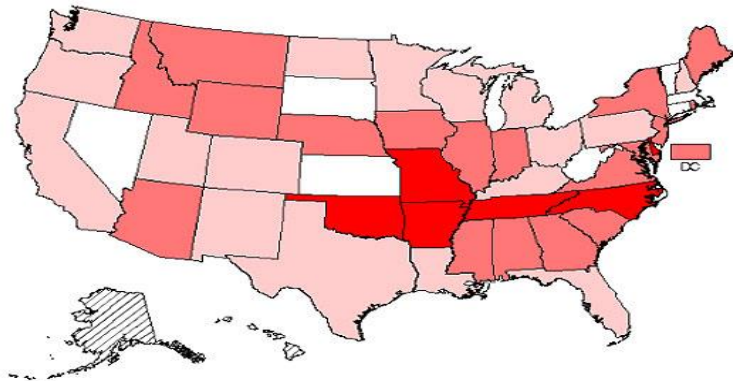


Risk Factors for Fatal Outcome From Rocky Mountain Spotted Fever in a Highly Endemic Area—Arizona, 2002–2011

Clin ID 2015;60:1659

Joanna J. Regan,¹ Marc S. Traeger,² Dwight Humpherys,² Dianna L. Mahoney,² Michelle Martinez,² Ginny L. Emerson,³

- ✓ Patients sought care at median day 2 of illness.
Doxycycline was begun at median day 7 in fatal cases
Doxycycline was begun at median day 3 in nonfatal cases
- ✓ Single factor in likelihood survival = timing of doxy dose 1



cases per million

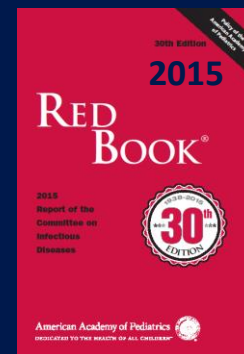
hatched	NN	white	0
light pink	0.2-1.5	medium pink	1.5-19
dark red	19-63		

Know exceptions to antibiotic rules



Disease	Treatment
Rocky Mountain spotted fever	Doxycycline
Rickettsialpox	Doxycycline
Murine (endemic) typhus	Doxycycline
Epidemic typhus	Doxycycline
Scrub typhus	Doxycycline
Human monocytic ehrlichiosis	Doxycycline
Anaplasmosis	Doxycycline
Q-fever	Doxycycline
Mediterranean tick fever	Doxycycline
African tick fever	Doxycycline

Previous and current recommendation



Disease	Treatment
Lyme disease	Doxycycline only ≥ 8 yrs
Staphylococcal SSTI	Doxycycline only ≥ 8 yrs
Mycoplasma	Doxycycline only ≥ 8 yrs
Alternative certain infections	Doxycycline only ≥ 8 yrs

Previous recommendation

Table I. Studies examining dental staining because of treatment of children with tetracyclines

Reference	Antibiotic (duration)	Study population	Proportion (%) exposed with stained teeth
Shwachman et al ¹	Chlortetracycline and oxytetracycline (long-term)	Patients with cystic fibrosis	40/50 (80%)
Wallman and Hilton ²	Tetracycline (short-term)	Neonates	46/50 (92%)
Swallow et al ⁴	Chlortetracycline, tetracycline, and oxytetracycline (long-term)	Patients with cystic fibrosis	24/63 (38%)
Conchie et al ⁵	Mixed tetracyclines (unknown duration)	Children who had received tetracycline prior to age of 6 and who are now 8-11 y	55/238 (23%)
Rebich et al ⁶	Mixed tetracyclines (unknown duration)	American Indian children 4-19 y	55/137 (40%)
Volovitz et al ⁷	Doxycycline (short-term)	Patients with asthma	0/31 (0%)



No Visible Dental Staining in Children Treated with Doxycycline for Suspected Rocky Mountain Spotted Fever

J Pediatr 2015;166:1246

Suzanne R. Todd, DVM¹, F. Scott Dahlgren, MSPH¹, Marc S. Traeger, MD², Eugenio D. Beltrán-Aguilar, DMD, DrPH³, Donald W. Marianos, DDS¹, Charlene Hamilton, MPH⁴, Jennifer H. McQuiston, DVM¹, and Joanna J. Regan, MD¹

Methods

Med and Pharm records on American Indian reservation with high incidence RMSF
 Dentists measured shade (spectrophotometry), enamel hypoplasia and staining per
 58 children who had received average of 1.8 courses doxycycline < 8 years of age
 Average age at exposure 4.5 years. Average age at examination 9.8 years
 213 children who had never received doxycycline. Average age at examination 11.8

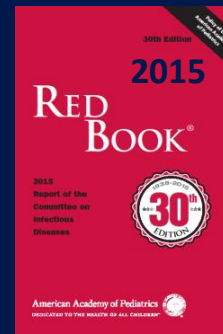


Findings

0/58 doxycycline exposed had tetracycline-like visible staining
No difference in shade or enamel hypoplasia between doxy-exposed and –unexposed groups

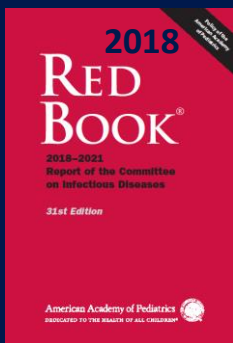
Disease	Treatment
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Human monocytic ehrlichiosis	Doxycycline
Anaplasmosis	Doxycycline
Q-fever	Doxycycline
Mediterranean tick fever	Doxycycline
African tick fever	Doxycycline

Previous and current recommendation



Revised to Liberalize

Disease	Treatment
Lyme disease	Doxycycline only ≥ 8 yrs
Staphylococcal SSTI	Doxycycline only ≥ 8 yrs
Mycoplasma	Doxycycline only ≥ 8 yrs
Alternative certain infections	Doxycycline only ≥ 8 yrs



- ✓ Throughout the 2018–2021 Red Book
Removed all age-related doxycycline recommendations
- ✓ Doxycycline can be administered for short durations (≤ 21 days) without regard to the patient's age
- ✓ Doxycycline is recommended equivalent to amoxicillin for Lyme localized disease, and is preferred for facial palsy, and as PO therapy for meningitis
- ✓ Advise care to avoid sun exposure due to assoc photosensitivity dermatitis



Azithromycin in Early Infancy and Pyloric Stenosis

Matthew D. Eberly, Matilda B. Eide, Jennifer L. Thompson and Cade M. Nylund

Pediatrics 2015;135:483

Erythromycin <2 wks of age in 200 infants assoc w IHPS in 1999

Macrolide is a motilin-receptor agonist

– stimulates migratory motor complexes in stomach

Risk of IHPS azithromycin vs. erythromycin?

Methods

Findings

Military health system records infants <90 days, 2001 – 2012

Births 1.1 million 1900 courses erythromycin 5000 courses azithromycin

IPHS ~2500 cases (2.29 per 100)

Adjusted Odds IHPS	Erythromycin	Azithromycin
DOL 1-14	13.3 (7-26)	8.3 (2.6-26)
DOL 15-42	4.1 (1.7-10)	2.9 (1.2-7)
DOL 43-90	No	No

Bottom Line: Prescribe azithromycin appropriately

Rx Chlamydia and Rx/Pro Pertussis w azithromycin

Be alert for IHPS

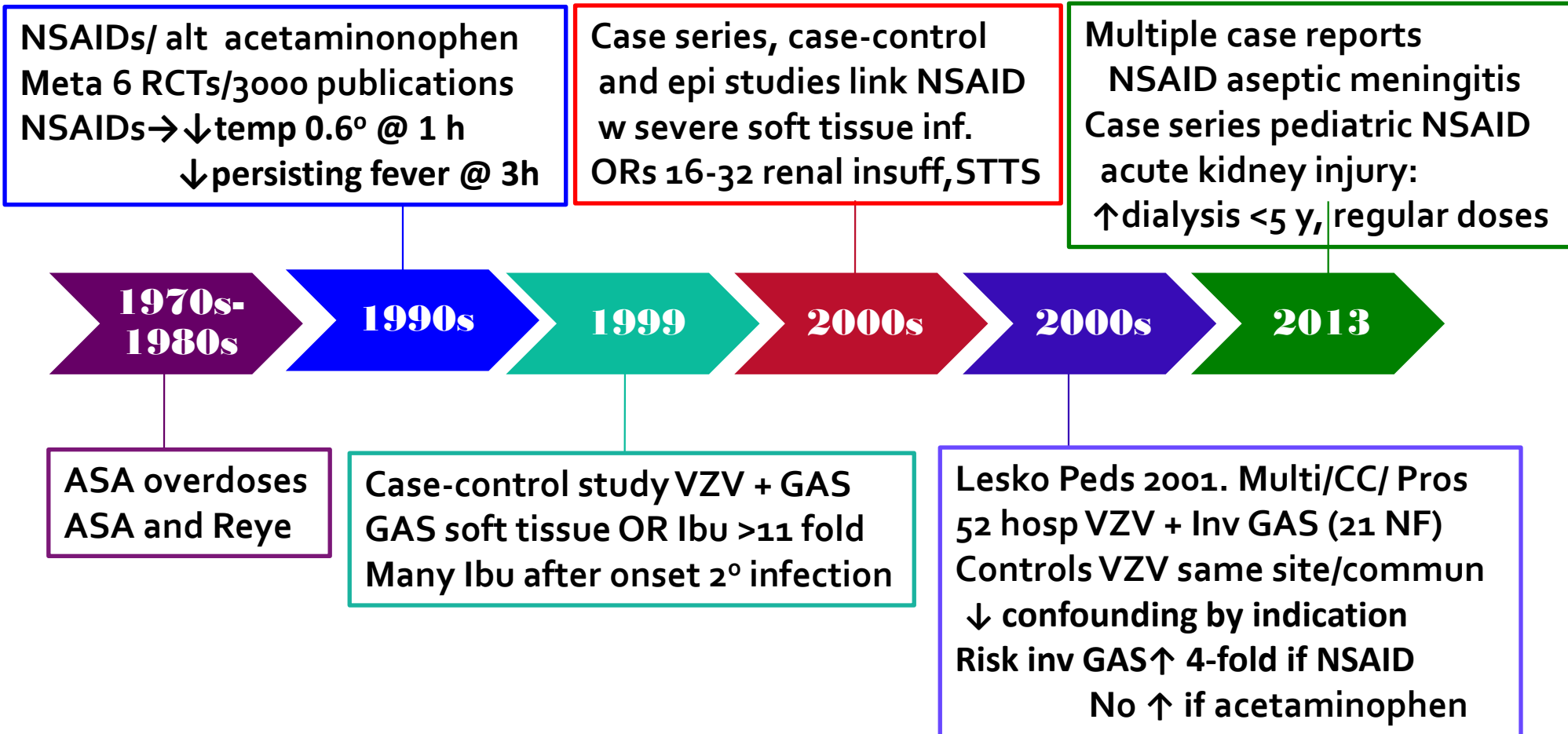


An 8-year-old previously healthy, fully immunized girl has the acute onset of fever, headache, nasal congestion, rhinorrhea and sore throat. She doesn't want to eat or drink. Temperature is 102.8°, HR 108, RR 20, BP 116/62. She has a reassuring physical examination and auscultation of the chest is normal. You endorse mother alternating acetaminophen and ibuprofen doses to reduce fever and discomfort.

The patient now will have increased risk of all of the following EXCEPT:

- A. drug-associated aseptic meningitis**
- B. drug-associated acute kidney injury**
- C. pulmonary empyema**
- D. Hypothermia**

NSAIDs: A Brief Timeline





Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children:

A Matched Case-Control Study

J Pediatr 2016; 175: 47

Muriel Le Bourgeois, MD¹, Agnès Ferroni, MD², Marianne Leruez-Ville, MD², Emmanuelle Varon, MD^{3,4}

What We Knew

Transcontinental incidence empyema in children ↑ in 2000s

The Question

To test hypothesis NSAIDs during virus ↑ empyema

The Study

Case-control study within 15 centers in France

Children 3-15 yrs of age with acute respiratory illness + virus detected

Cases = 83 with proven bacterial empyema w preceding resp virus confirmed

>3 days before dx of empyema + ≥1 day afebrile post virus pre dx

Controls = 83 age-matched children w virus detected same time/same practice

Evaluated drugs used in first 3 days for ≥1 day: antibiotic, acetaminophen, NSAID

The Findings

Cases and controls had similar viruses detected

NSAID received → ↑ empyema 2.8 fold (95% CI 1.4–56)

Acetaminophen → No ↑ empyema

Antibiotic + NSAID → No ↑ empyema

Mechanism of Action of NSAIDs

Nuts and Bolts

