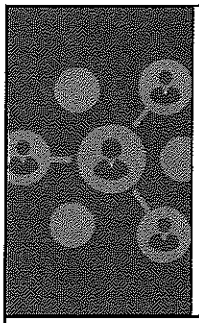

Reconnect & Rediscover:
A Convening Pediatric Experts and Advocates

Oct. 2-4, 2021

National Association of Pediatric Nurse Practitioners

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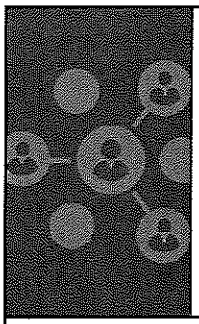

Pediatric Antibiotic Update: 2021

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National Association of Pediatric Nurse Practitioners

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Disclosure

- No financial disclosures

3

Learning Objectives

- Discuss current and emerging antibiotic resistance threats in the US
- Understand antibiotic resistance patterns locally and nationally impact prescribing decisions
- Discuss common pediatric infections and recommendations for treatment
- Examine implications of antibiotic prescribing stewardship for practice

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Antibiotic Resistance in the US

- CDC *Antibiotic Resistance Threats in the United States, 2019*
- Urgent threats
  - *Clostridioides difficile (C. difficile)*
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*
- Serious threats
  - Drug-resistant Candida
  - Methicillin-resistant *Staphylococcus aureus (MRSA)*
  - Drug-resistant *Streptococcus pneumoniae*
  - Drug-resistant Tuberculosis

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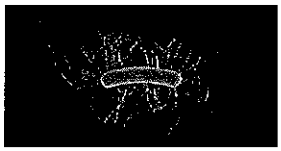
Clostridioides difficile (C. difficile)

- Healthcare-associated infections are decreasing
- Community-acquired *C. difficile* unchanged
- Guh et al, 2020



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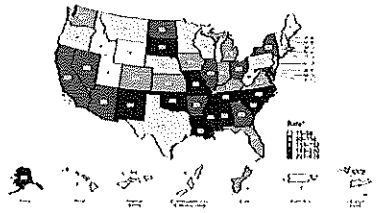
Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Gonorrhea — Rates of Reported Cases by State, United States and Territories, 2019



Per 100,000

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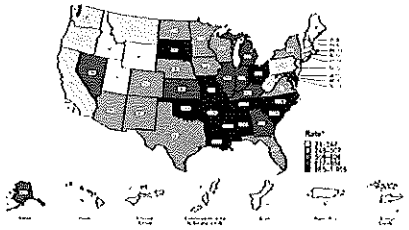
Gonorrhea — Rates of Reported Cases Among Females Aged 15–24 Years by State, United States and Territories, 2019



* Per 100,000

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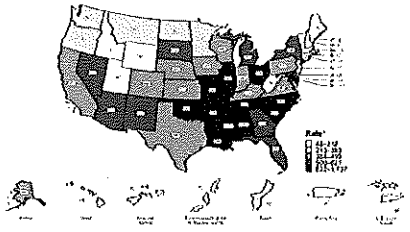
Gonorrhea — Rates of Reported Cases Among Males Aged 15–24 Years by State, United States and Territories, 2019



* Per 100,000

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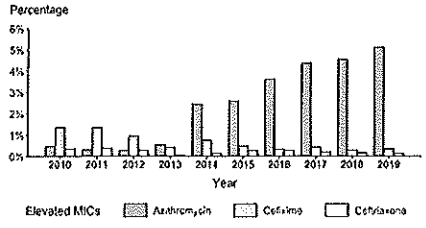
Neisseria gonorrhoeae — Percentage of Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin, Cefixime, and Ceftriaxone, Gonococcal Isolate Surveillance Project (GISP), 2010–2019



NOTE: Elevated MIC = Azithromycin: ≥ 2.0 µg/mL; Cefixime: ≥ 0.25 µg/mL; Ceftriaxone: ≥ 0.125 µg/mL

10

Neisseria gonorrhoeae — Prevalence of Tetracycline, Penicillin, or Ciprofloxacin Resistance* or Elevated Cefixime, Ceftriaxone, or Azithromycin Minimum Inhibitory Concentrations (MICs)†, by Year — Gonococcal Isolate Surveillance Project (GISP), 2000–2019

* Resistance: Ciprofloxacin = MIC ≥ 1.0 µg/mL; Penicillin = MIC ≥ 2.0 µg/mL or Beta-lactamase positive; Tetracycline = MIC ≥ 2.0 µg/mL.

† Elevated MICs: Azithromycin = MIC ≥ 1.0 µg/mL 29 (2000–2004); ≥ 2.0 µg/mL (2005–2019); Ceftriaxone = MIC ≥ 0.125 µg/mL; Cefixime = MIC ≥ 0.25 µg/mL.

NOTE: Cefixime susceptibility was not tested in 2007 and 2009.

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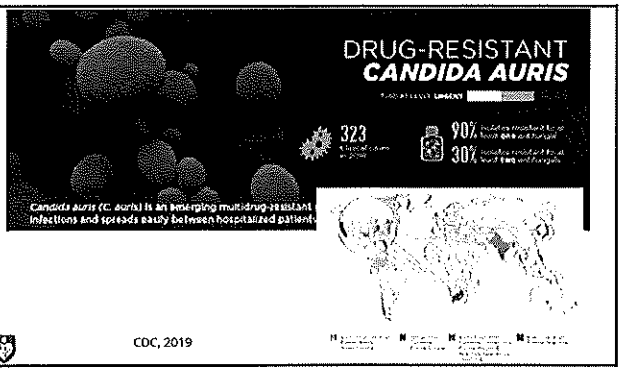

CDC, 2019

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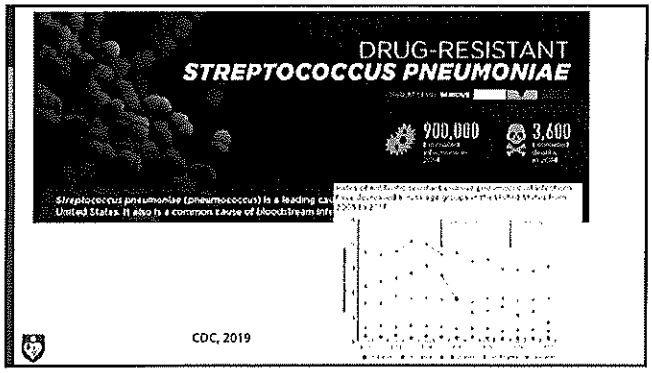
Drug-resistant *Candida auris* (*C. auris*)

Chen et al, 2020

13



CDC, 2019

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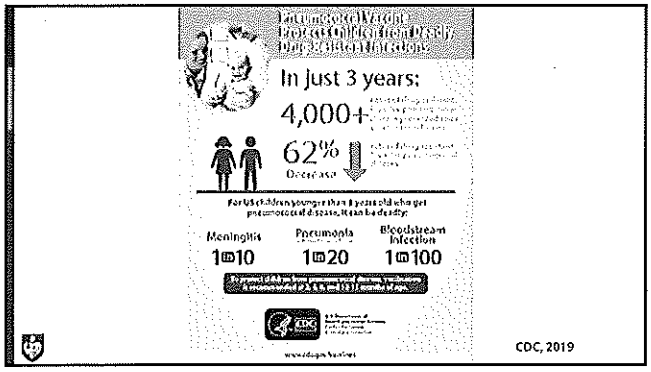


CDC, 2019

15

Threats (CDC, 2019)

Concerning Threats

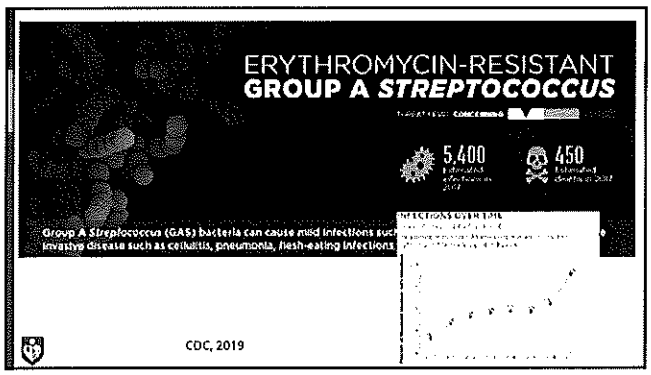
- **Erythromycin-resistant Group A *Streptococcus***
- Clindamycin-resistant Group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium* (*M. genitalium*)
- Drug-resistant *Bordetella pertussis* (*B. pertussis*)

CDC, 2019

16



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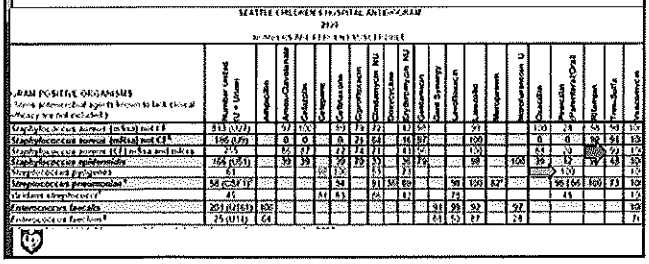
DO know your local resistance pattern.

Seattle Children's Antibiogram (2019)



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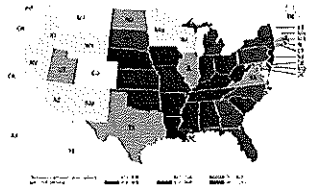
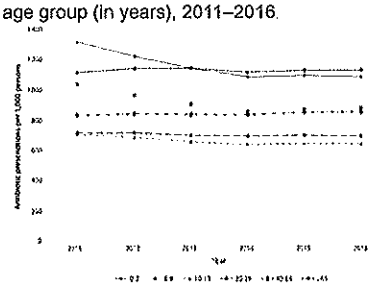
US outpatient oral antibiotic prescriptions per 1000 persons by state, 2016.



OXFORD

19

US outpatient oral antibiotic prescriptions per 1000 persons, by age group (in years), 2011–2016



King et al, 2019

OXFORD

20

Upper Respiratory Pathogens (AOM/Sinusitis)

- *S. pneumoniae (15-25%)*
- Non-typeable *H. influenzae (50-60%)*
- *M. catarrhalis (12-15%)*
- Sterile (15-20%)

Viruses

Wald & DeMuri, 2018

21

AOM/Sinusitis Guidelines

Acute Otitis Media (Lieberthal, AS et al.,2013)

- First line: High dose amoxicillin
- Second line:
  - High-dose amoxicillin-clavulanate
  - Cefdinir (14 mg/kg/day)
  - Cefuroxime (30 mg/kg/day)
  - Cefpodoxime (10 mg/kg/day)
  - Ceftriaxone (50 mg/kg IM)
- PCN Allergy:
  - First line: Cefdinir or Cefuroxime
  - Second line: cefpoximine or ceftriaxone

Bacterial Sinusitis (Wald et al, 2103)

- First line:
  - Amoxicillin 45 mg/kg/day
  - High risk of resistance use high dose amoxicillin
  - If > age 2 yrs, no daycare and no antibiotics for 4 weeks use high dose amoxicillin-clavulanate
- Second line:
  - High-dose amoxicillin-clavulanate
  - Cefdinir (14 mg/kg/day)
  - Cefuroxime (30 mg/kg/day)
  - Cefpodoxime (10 mg/kg/day)
  - Ceftriaxone (50 mg/kg IM)
- PCN allergic
  - Cefdinir, cefuroxime or cefpodoxime
  - Moderate to severe sinusitis in children < 2 yrs with Type I allergy: Clindamycin and cefixime

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AOM Pathogens

- Systematic Review of 48 studies, 15,871 cultures (Mather et al, 2019)
  - 67% of cultures grew bacteria
    - 30% *Streptococcus pneumonia*
    - 23% *H. flu*
    - 5% *Moraxella catarrhalis*
  - Antibiotic effectiveness
    - Amoxicillin 86%
    - Amoxicillin-clavulanate 93%
    - Erythromycin 64%
- Bacterial pathogens with spontaneous rupture of TM in children vaccinated with PCV13 (Levy et al, 2019)
  - 53.4% no otopathogen
  - Pathogens
    - Non-typable *H. flu 48.4%*
    - Gp A Strep 34.7%
    - *S. pneumonia 27.9%*
  - By age
    - Infants/toddlers NTHI 53.1%
    - Older children GAS

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Time to rethink the guidelines?

- Prevalence of *S. pneumoniae* primary pathogen has decreased from 40-45% in 1999 to 15-25% in 2017 (Wald & DeMuri, 2018)
- High-dose amoxicillin was based on penicillin resistant *S. pneumoniae*
- *H. flu and M. catarrhalis* are resistant to amoxicillin
- Regular dose amoxicillin-clavulanate will treat resistant *H. flu and M. catarrhalis – no need for high dose amoxicillin clavulanate*
- Consider amoxicillin-clavulanate 45 mg/kg/d in 2 divided doses of 400 mg/57 mg

Wald, ER & DeMuri, GP (2018)

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Community Acquired Pneumonia

- *S. pneumoniae* is the most common cause of bacterial pneumonia in patients of all ages
- Infants 4 to 16 weeks:
  - Consider chlamydia
- Respiratory viruses most common in first 2 to 3 years of life (80% of CAP)
- Adolescence:
  - Consider mycoplasma
- CA-MRSA
- Virus
- ISDA Peds Guideline: Bradley et al (2011)
- New ISDA Pediatric CAP guidelines under development

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Pneumonia antibiotic choices in Children

(Bradley et al., 2011)

Infants and children < age 5 years

- Fully immunized with bacterial pneumonia (*S. pneumoniae*)
  - Amoxicillin 80-90 mg/kg/day
  - PCN allergy: Clindamycin or a macrolide
- Unimmunized for Hib or PCV
  - Ceftriaxone 50 mg/kg
- Infant with suspected chlamydial pneumonia
  - Azithromycin (American Academy of Pediatrics Red Book, 2018)

Children 5 yrs or older

- Guidelines say amoxicillin 90 mg/kg to max 4 gm per day
- Treat for 10 days
- Mycoplasma or other atypical most likely
  - Azithromycin
  - Erythromycin
  - Doxycyline if > 7 yrs

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Shorten therapy for Pediatric CAP

- Double blind RCT
- Children age 6 months to 10 years (median age 2.6 yrs)
- 5 days high-dose amoxicillin + 5 days placebo vs 5 days + 5 days of high-dose amoxicillin
- Clinical cure at 14 to 21 days was 85.7% in the intervention group vs 84.1% in the control group

Pernica et al, 2021

27

Strep Pharyngitis

- Pathogen: Streptococcus pyogenes
- Strep 20-30% of pharyngitis
- The incubation period for streptococcal pharyngitis is 2 to 5 days (AAP Red Book, 2021)
- Most rapid strep tests are 90 to 95% accurate
  - Rapid tests and throat cultures cannot differentiate between GAS pharyngitis and GAS carriers
- Likelihood of positive strep is higher with fewer viral symptoms (cough, rhinorrhea)
  - patients with any viral feature were ~30% less likely to have GAS, and patients with ≥2 features were >40% less likely to have GAS (Shapiro et al, 2017)

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Strep Pharyngitis

Treatment (Red Book, 2021; ISDA, 2012):

- Penicillin
  - PO 250 mg BID if < 27 kg or 500 mg BID if > 27 Kg
  - IM penicillin G benzathine single dose of 600 000 U (<27kg), > 27 kg and adults 1.2 million U
- Amoxicillin 50 mg/kg in a single daily dose (max 1gm)
  - No statistical difference in negative cultures after treatment between QD, BID or TID dosing (Nako et al, 2019)
- 1st generation cephalosporin
  - Cephalexin (Keflex) 40-50 mg/kg/day dosed BID (max 500 mg BID)
  - Cefadroxil (Duricef) 30 mg/kg/day (max 1 gm)
- Clindamycin 7 mg/kg/dose tid (max 500 mg tid)

29

Group A Strep pharyngitis: PCN allergic

- 1st generation cephalosporin (cephalexin)
- If immediate Type 1 hypersensitivity:
  - Clindamycin 20 mg/kg/day divided TID (max 1.8 gm/day)
  - Or macrolide
    - Azithromycin (12 mg/kg/day [maximum, 500 mg]) for 5 days
    - Macrolides have resistance **(up to 23%)**

(AAP Red Book, 2021)

30

GAS Carriers

- 20-25% of children may be asymptomatic carriers during the winter months (AAP Red Book, 2021)
  - May be colonized by GAS pharyngitis for ≥6 months
- Children who are carriers are more likely to present with URI sx and atypical symptoms (Rick, Zaheer & Martin, 2020)
- Eradication therapy (Red Book, 2021; ISDA, 2012)
  - Clindamycin 30 mg/kg/day in 3 doses (max 300 mg/dose) x 10 days
  - Augmentin 40 mg amoxicillin/kg/d in 3 doses daily (max = 2000mg amoxicillin/d) x 10 days
  - Penicillin V: 50 mg/kg/d in 4 doses × 10 d (max = 2000 mg/d) PLUS rifampin: 20 mg/kg/d in 1 dose × last 4 d of treatment (max = 600 mg/d)

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Nongroup A Streptococcal Pharyngitis in Children

- Large (N=116,578) retrospective study of children age 0 to 18 yrs
  - Non-group A beta-hemolytic strep (NGAS) 3.1% vs 22.8% Group A strep (GAS)
  - NGAS lower rates of fever, throat erythema, and lymphadenopathy and higher rates of cough and rhinorrhea compared with those with GAS
- Strep C or G
- Not detected with rapid strep
- Treatment:
  - Not known to trigger acute rheumatic fever
  - May treat if symptomatic (fever, tonsillar exudates, tender cervical lymphadenopathy)
  - Tx same as GAS: PCN, amoxicillin

(Frost et al., 2019)

32

Group A strep Vaccine

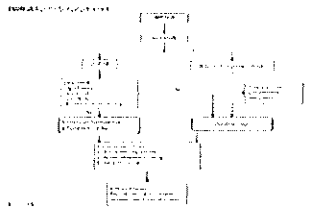
- GAS pharyngitis, sinusitis and AOM account for 26.9% of pediatric outpatient visits
- Vaccines for GAS are in development
- A GAS vaccine could prevent 5.4% of antibiotic prescriptions among 3 to 9 yr olds
- Routine tx of pharyngitis with antibiotics would be unnecessary

Lewnard et al, 2020

33

Impetigo

- New (Feb 2021) internationally developed algorithm for treatment of impetigo (Schachner et al, 2021)
- Localized
  - < 10 vesicles
  - Size < 36 cm^2
  - Age > 2 months
  - Immunocompetent



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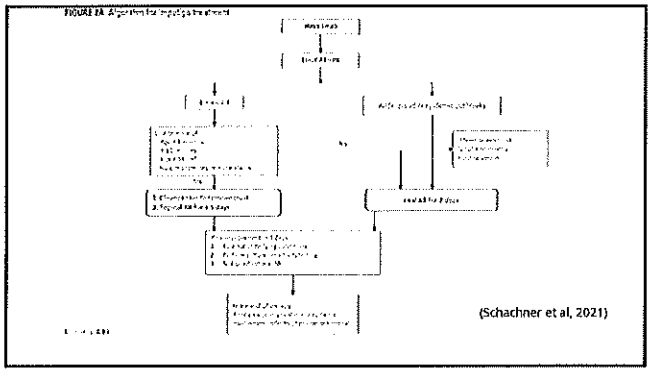

(Schachner et al, 2021)

35

Topical Antibiotics for impetigo

Order	Name of Drug	Indication	Antimicrobial activity	Dosing
1	Ozenoxacin (Xepi)	2 mo of age or older	Gram + bacteria, including MRSA, effective against mupirocin-resistant MRSA	BID x 5 days
2	Mupirocin 2% ointment, 1% ointment for 2mo to 16 yrs	2 mo of age or older	Effective against gram + bacterial, including MRSA	TID fro 7 to 10 days
3	Retapamulin 1% ointment	Impetigo in pts age 9 mo or older	Active again *S. aureus* & *S. Pyogenes*, not MRSA	TID x 7 to 10 days
4	Fusidic acid	No age limit	Active against *S.aureus, Streptococcus, Cornebacterium minutissimum*	TID x 7 to 10 days

(Schachner et al, 2021)

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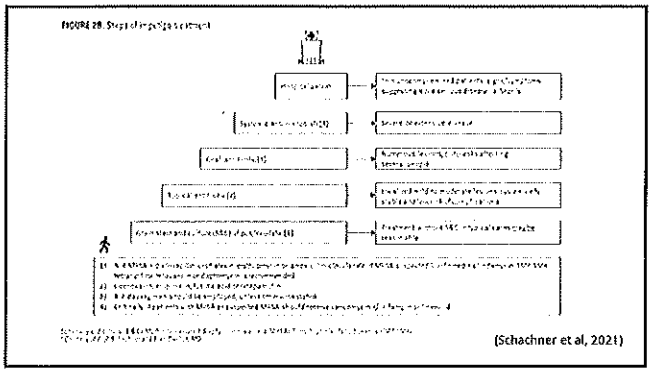
Comparison of topical antibiotics for impetigo

- Ozenoxacin (Xepi) - $320 for 30 gm tube
- Mupirocin 2% (Bactroban) - $55 for 22 gm tube
- Retapamulin (Altabax) 1% ointment - $350 for 15 gm tube
- fusidic acid (UK med)

Eudaley, 2020

37



(Schachner et al, 2021)

38

Oral antibiotics for impetigo

Not MRSA Infection	MRSA Infection
Dicloxacillin	Vancomycin IV
Cephalexin	Clindamycin PO
Erythromycin (based on sensitivity)	TMP/Sulfa PO
Amoxicillin/clavulanate	Doxycycline
Cefadroxil	Telavacin, Linezolid, Daptomycin all 3rd line

Oral antibiotics x 7 days

(Schachner et al, 2021)

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UTI in infants > 1 month and young children

- Use local resistance patterns to guide antibiotic choice
- Oral therapy
  - Afebrile and nontoxic – 1st gen cephalosporin (cephalexin 50 mg/kg/day divided BID)
  - Febrile – 3rd gen cephalosporin
    - Cefuroxime 30 mg/kg per day by mouth in two divided doses
    - -Cefixime 8 mg/kg once daily
    - -Cefdinir 14 mg/kg by mouth once daily
    - -Ceftibuten 9 mg/kg by mouth once daily
- Outpatient parenteral therapy
  - Ceftriaxone 50 mg/kg once daily (max 2000 mg)
  - Switch to oral antibx when afebrile for 24 hours

Shaikh & Hoberman, 2021

40

40

Prevalence of Inappropriate Antibiotic Prescribing

- Targets based on lowest prescribing regions for sinusitis, otitis media, streptococcal pharyngitis, and no antibiotics for asthma, allergy, bronchitis, bronchiolitis, influenza, URI
- For **0-19 yr olds: 29%** of antibiotic prescriptions are inappropriate
  - 100% of URI/asthma/bronchitis
- For all ages: **50% of antibiotics are inappropriately prescribed**

Fleming-Dutra et al., 2016

41

Guideline adherence

- Academic vs community practice adherence to guidelines (Abuali et al, 2019)
  - The correct prescribing rate: academic practice 67% vs 21% community practices
- Following pneumonia guidelines (Poole, Shapiro, Kronman & Hersh, 2019)
  - Amoxicillin 23%; azithromycin 47%; cephalosporins 26%
  - Azithromycin more likely in ED than private practice
- Guideline adherence for pharyngitis, AOM, sinusitis and pneumonia primary care vs urgent care vs peds ED (Islam et al, 2020)
  - Pharyngitis: UCC and ED, 26.3% prescribed antibiotics with no supporting diagnostic test
  - AOM: 91% of children > age 5 yrs had antibx for > 7 days
  - Sinusitis: first line antibiotics given 64% of the time, azithromycin most common non first line (14%)

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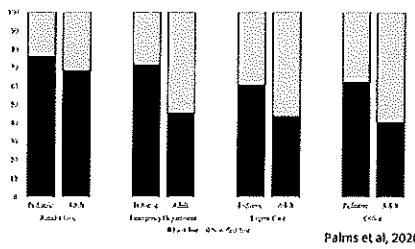
First-line antibiotic selection for pharyngitis, sinusitis, and pediatric AOM, according to age, across settings



Palms et al, 2020

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Antibiotic Prescribing During Pediatric Direct-to-Consumer Telemedicine Visits

- Acute respiratory infections
- 4604 telemedicine, 38,408 urgent care, and 485,201 PCP visits
- 52% of telemedicine visits versus 42% urgent care and 31% PCP visits received antibiotics ($P < .001$ for both comparisons)
- Guideline-concordant antibiotic management
  - 59% of DTC telemedicine visits versus 67% urgent care and 78% PCP visits ($P < .001$ for both comparisons)

Ray et al, 2019

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Antibiotic Prescribing in Children's Hospitals

(Tribble et al, 2020)

- 32 US children's hospitals, 34,927 children, 11,784 receiving antibiotics for infections
- Antibiotic Stewardship Program (ASP) review found 21.0% of antibiotics were considered suboptimal
  - 27.5% were drug-bug mismatch
  - 17.6% surgical prophylaxis > 24 hrs
  - 11.2% overly broad
  - 11.0% unnecessary treatment
- ASP recommendations
  - 44.7% stop antibiotic
  - 19.7% narrow the spectrum

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CDC Resources (www.cdc.gov/antibiotic-use)

- Extensive resources
- Pediatric Inpatient and Outpatient guidelines
- Patient Information
  - Handouts
  - Prescription pads
  - Posters
  - Infographics
  - Multiple languages (Spanish, Chinese, Korean, Vietnamese, French, Portuguese)

BE ANTIBIOTICS AWARE
SMART USE. BEST CARE.

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Penicillin Allergy

10% of the population reports a penicillin allergy but <1% of the whole population is truly allergic.

https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html

- Starts with accurate Hx & PE
- Characteristics of an IgE-mediated (Type 1) reaction:
  - Reactions that occur immediately or usually within one hour
  - Hives: Multiple pink/red raised areas of skin that are intensely itchy
  - Angioedema: Localized edema without hives affecting the abdomen, face, extremities, genitalia, oropharynx, or larynx
  - Wheezing and shortness of breath
  - Anaphylaxis
- Amoxicillin rash
  - occurs in 5% to 10% of children receiving amoxicillin
  - Appears 3 to 14 days from starting amoxicillin
  - Generalized dull, red, maculopapular rash
  - Begins on the trunk and spreads over most of the body. It may be most intense at pressure areas, elbows, and knees.
- Patients with EBV who receive amoxicillin may develop a non-allergic, non-pruritic rash

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CDC Recommendations for Penicillin Allergy Testing

- "Penicillin skin testing and challenge doses are reliable and useful methods for evaluating for IgE-mediated penicillin allergy"
- Skin testing
  - Predictive value of 95%
  - 100% if followed by oral challenge
- Patients with severe hypersensitivity syndromes should not have skin testing
- Cephalosporins can be used in patients with penicillin allergy
  - Pts with anaphylaxis may require allergy testing

https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html

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What YOU Can Do

- Know what pathogen you are treating and prescribe appropriately
- Know your local resistance pattern
- Do not prescribe antibiotics for viral infection
  - Avoid "Vitamin Z"
- Appropriately identify penicillin allergy
  - Not all rashes are due to hypersensitivity
- Consider an antibiotic stewardship program for your facility

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Thank you!

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