



ANTIBIOTIC USE IN CHILDREN

by:

Solmaz Hassani

**Pharm. D, Board Certified Clinical
Pharmacist**

Classifications of antibiotics

β -Lactam Antibiotics

Cephalosporins

First-generation

Cefadroxil (Duricef)
Cefazolin (Ancef)
Cephalexin (Keflex)

Second-generation

Cefaclor (Ceclor)
Cefamandole (Mandol)^a
Cefonicid (Monocid)
Ceforanide (Precef)
Cefotetan (Cefotan)
Cefoxitin (Mefoxin)
Cefprozil (Cefzil)
Cefuroxime (Zinacef)
Cefuroxime axetil (Ceftin)

Third-generation

Cefdinir (Omnicef)
Cefditoren (Spectracef)
Cefixime (Suprax)
Cefotaxime (Claforan)
Cefpodoxime proxetil (Vantin)
Ceftazidime (Fortaz)
Ceftibuten (Cedax)
Ceftizoxime (Cefizox)
Ceftriaxone (Rocephin)

Fourth-generation

Cefepime (Maxipime)

Fifth-generation

Ceftaroline (Teflaro)

Penicillinase-resistant penicillins

Isoxazolyl penicillins (dicloxacillin, oxacillin, cloxacillin)
Nafcillin (Unipen)

Combination with β -lactamase inhibitors

Augmentin (amoxicillin plus clavulanic acid)
Avycaz (ceftazidime plus avibactam)
Timentin (ticarcillin plus clavulanic acid)^a
Unasyn (ampicillin plus sulbactam)
Zerbaxa (ceftolozane plus tazobactam)
Zosyn (piperacillin plus tazobactam)

Aminoglycosides

Amikacin (Amikin)
Gentamicin (Garamycin)
Neomycin (Mycifradin)
Netilmicin (Netromycin)
Streptomycin
Tobramycin (Nebcin)

Protein synthesis inhibitors

Azithromycin (Zithromax)
Clarithromycin (Biaxin)
Clindamycin (Cleocin)
Chloramphenicol (Chloromycetin)
Dalbapristin/Quinupristin (Synercid)
Dirithromycin (Dynabac)
Erythromycin (Erythrocin)
Fidaxomicin (Difcid)
Linezolid (Zyvox)
Tedizolid (Sivestro)
Telithromycin (Ketek)
Tetracyclines (doxycycline, minocycline, tetracycline, tigecycline)

Classifications of antibiotics

β -Lactam Antibiotics

Carbacephems

Loracarbef (Lorabid)

Monobactams

Aztreonam (Azactam)

Penems

Doripenem (Doribax)

Ertapenem (Invanz)

Imipenem (Primaxin)

Meropenem (Merem)

Penicillins

Natural penicillins

Penicillin G

Penicillin V

Aminopenicillins

Ampicillin (Omnipen)

Amoxicillin (Amoxil)

Bacampicillin (Spectrobid)^a

Folate inhibitors

Sulfadiazine

Sulfadoxine (Fansidar)

Trimethoprim (Trimpex)

Trimethoprim-sulfamethoxazole (Bactrim, Septra)

Quinolones

Ciprofloxacin (Cipro)

Gemifloxacin (Factive)

Levofloxacin (Levoquin)

Moxifloxacin (Avelox)

Norfloxacin (Noroxin)

Ofloxacin (Floxin)

Dalbavancin (Dalvance)

Daptomycin (Cubicin)

Oritavancin (Orbactiv)

Telavancin (Vibativ)

Vancomycin (Vancocin)

Metronidazole (Flagyl)

Acute otitis media in children

- ✓ Acute otitis media (AOM) is defined by moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to acute otitis externa accompanied by acute signs of illness and signs or symptoms of middle ear inflammation.
- ✓ AOM is slightly more common in boys than girls.
- ✓ It occurs at all ages but is most prevalent between 6 and 24 months of age, after which it begins to decline.

RISK FACTORS

- ✓ **Age**

The age-specific attack rate for AOM peaks between 6 and 18 months of age [6,19]. After that, the incidence declines with age, although there is a small increase between 5-6 years (the time of school entry).

- ✓ **Family history**

- ✓ **Day care**

RISK FACTORS

- ✓ **Lack of breastfeeding**

In pooled analysis of six studies (2548 children), the risk of AOM was decreased among children who were breastfed for at least three months

- ✓ **Tobacco smoke and air pollution**

- ✓ **Pacifier use**

- ✓ **Race and ethnicity**

Other risk factors

- ✓ Social and economic conditions (poverty and household crowding increase the risk)
- ✓ Season (increased incidence during the fall and winter months)
- ✓ Altered host defenses and underlying disease (eg, HIV, cleft palate, Down syndrome, allergic rhinitis)

Bacterial pathogens

- ✓ **Streptococcus pneumoniae**
 - ✓ **Haemophilus influenzae**
 - ✓ **Moraxella catarrhalis**
 - ✓ **Group A Streptococcus**
 - ✓ **Staphylococcus aureus**
-
- ✓ **Viral pathogens/Dual pathogen infection**

CLINICAL MANIFESTATIONS

- ✓ Children with AOM, particularly infants, may present with nonspecific symptoms and signs, including :
 - ✓ Fever
 - ✓ Irritability
 - ✓ Headache
 - ✓ Apathy
 - ✓ disturbed or restless sleep,
 - ✓ Poor feeding/anorexia
 - ✓ vomiting, and diarrhea

Acute otitis media in children:

Treatment

- ✓ **SYMPTOMATIC THERAPY:**
- ❖ oral ibuprofen or acetaminophen rather than other analgesics for pain control in children with AOM.
- ❖ Topical procaine or lidocaine preparations (if available) are an alternative to oral analgesics for children ≥ 2 years but should not be used in children with tympanic membrane perforation.
- ❖ Topical benzocaine is avoided in children < 2 years because of the risk of methemoglobinemia

Unproven therapies

- ✓ **Decongestants and antihistamines**
- ✓ **Distraction**
- ✓ **external application of heat or cold**
- ✓ **instillation of olive oil or herbal extracts into the external auditory canal to treat pain in children with AOM**

ANTIBIOTIC THERAPY VERSUS OBSERVATION

- ✓ In addition to pain control, there are two strategies for initial management of AOM:
 - immediate treatment with antibiotics
 - observation with initiation of antibiotic therapy if the symptoms and signs worsen or fail to improve after 48 to 72 hours.

ANTIBIOTIC THERAPY VERSUS OBSERVATION

- ✓ The choice of strategy depends upon the age of the child, the severity of illness, and parental preference:
- ✓ We recommend that children <6 months with AOM be treated immediately with an appropriate antibiotic.

ANTIBIOTIC THERAPY VERSUS OBSERVATION

- ✓ We suggest that children six months to two years with unilateral or bilateral AOM be treated immediately with an appropriate antibiotic.
- ✓ We suggest that children ≥ 2 years who appear toxic, have persistent otalgia for more than 48 hours, have temperature $\geq (39^{\circ}\text{C})$ in the past 48 hours, have bilateral AOM or otorrhea, or have uncertain access to follow-up be immediately treated with an appropriate antibiotic.

ANTIBIOTIC THERAPY VERSUS OBSERVATION

- ✓ For children ≥ 2 years who are normal hosts (eg, immune competent, without craniofacial abnormalities) with mild symptoms and signs and no otorrhea, initial observation may be appropriate if the caretakers understand the risks and benefits of such an approach.

INITIAL ANTIMICROBIAL THERAPY

- ✓ When the decision is made to treat AOM with antimicrobial agents, the selection among available drugs is based upon:
 - Clinical and microbiologic efficacy
 - Acceptability (taste, texture) of the oral preparation
 - Absence of side effects and toxicity
 - Convenience of the dosing schedule
 - Cost

First-line therapy

- ✓ **No recent beta-lactam therapy**
- ✓ **no concomitant purulent conjunctivitis**
- ✓ **no history of recurrent AOM**

- ✓ We suggest **amoxicillin** as the 1st line therapy for children with AOM who are treated with antibiotics and at low-risk for amoxicillin resistance:
 - have not received a beta-lactam antibiotic in the previous 30 days
 - do not have concomitant purulent conjunctivitis
 - no history of recurrent AOM unresponsive to amoxicillin)

First-line therapy

- ✓ The dose is 90 mg/kg per day of amoxicillin divided in two doses (we suggest a maximum of 3 g/day).

First-line therapy

- ✓ **Recent beta-lactam therapy**
 - ✓ **concomitant purulent conjunctivitis**
 - ✓ **history of recurrent AOM unresponsive to amoxicillin**
-
- ✓ We suggest **amoxicillin-clavulanate** as the first-line therapy for children with AOM who are treated with antibiotics and at increased risk of beta-lactam resistance.
 - ✓ The dose is **90 mg/kg per day of amoxicillin** and **6.4 mg/kg per day of clavulanate** divided in two doses (we suggest a maximum daily dose of the amoxicillin component of 3 g).

Penicillin allergy

✓ Mild delayed reaction

Mild delayed hypersensitivity reactions to penicillin appear **after more than one dose**, typically **after days of treatment**. They lack features of immunoglobulin E (IgE)-mediated reaction (eg, **anaphylaxis, angioedema, bronchospasm, urticaria**) and serious/life-threatening delayed drug reactions (eg, **Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic anemia**, etc).

Penicillin allergy



Penicillin allergy

- ✓ The World Allergy Organization has recommended categorizing immunologic drug reactions based upon the timing of the appearance of symptoms.
- ✓ This system defines two broad categories of reactions: **immediate and delayed.**

Immediate reactions

- ✓ classically begin within **one hour** of the last administered dose and may begin within minutes.
- ✓ some immediate reactions appear after one hour, particularly if the drug was administered orally or taken with food.
- ✓ For these reasons, some guidelines include reactions beginning **up to six hours** after the last administered dose in the immediate category

Delayed reactions

- ✓ appear after multiple doses of treatment, typically **after days or weeks** of administration.
- ✓ Most delayed reactions begin after six hours and typically after days of treatment.
- ✓ As an example, delayed reactions to **amoxicillin** classically start on day **7 to 10** of treatment and may even begin one to three days after cessation of treatment.
- ✓ Delayed reactions are more common than immediate reactions.

Penicillin-induced urticaria



Penicillin-induced morbilliform rash



Penicillin-induced urticaria



TAKING A USEFUL DRUG

ALLERGY HISTORY

- ✓ Penicillins include the following:
 - ❖ The natural penicillins – Penicillin V (oral), penicillin G (parenteral), benzathine penicillin (intramuscular), and procaine penicillin (intramuscular)
 - ❖ The antistaphylococcal penicillins – Dicloxacillin, nafcillin, oxacillin, and cloxacillin
 - ❖ The aminopenicillins – Amoxicillin and ampicillin
 - ❖ The extended spectrum penicillins – Carbenicillin, ticarcillin, and piperacillin

COMMON CUTANEOUS REACTIONS

- ✓ The most common allergic reactions to penicillins are delayed cutaneous reactions. They are believed to be mediated by T cells in the skin.
- ✓ Common cutaneous reactions should not involve significant fever.
- ✓ In contrast, fever that begins after the acute infection has begun to subside and corresponds with the onset of **new severe drug reactions**.
- ✓ In this case, the penicillin **should be stopped immediately**, and the patient should be evaluated for other signs **of** severe reactions.

Management of symptoms

- ✓ Delayed cutaneous reactions resolve once the culprit drug is discontinued, usually **within one to two weeks**.
- ✓ symptoms may worsen for a few days even after the drug is stopped .
- ✓ **Oral antihistamines** may be administered at age-appropriate doses if there is a pruritic component.
- ✓ **Oral glucocorticoids** may be considered in patients with **severe eruptions** who do not respond to or are unable to tolerate antihistamines.

Referral for allergy evaluation

- ✓ If the patient/caregiver cannot provide a detailed description of the previous reaction, caution is warranted, and referral is indicated.
- ✓ In addition, if the patient's past reaction may have involved urticaria or angioedema, he/she should be referred to an allergy specialist for an evaluation for an IgE-mediated reaction before future use of penicillins and related drugs is considered.

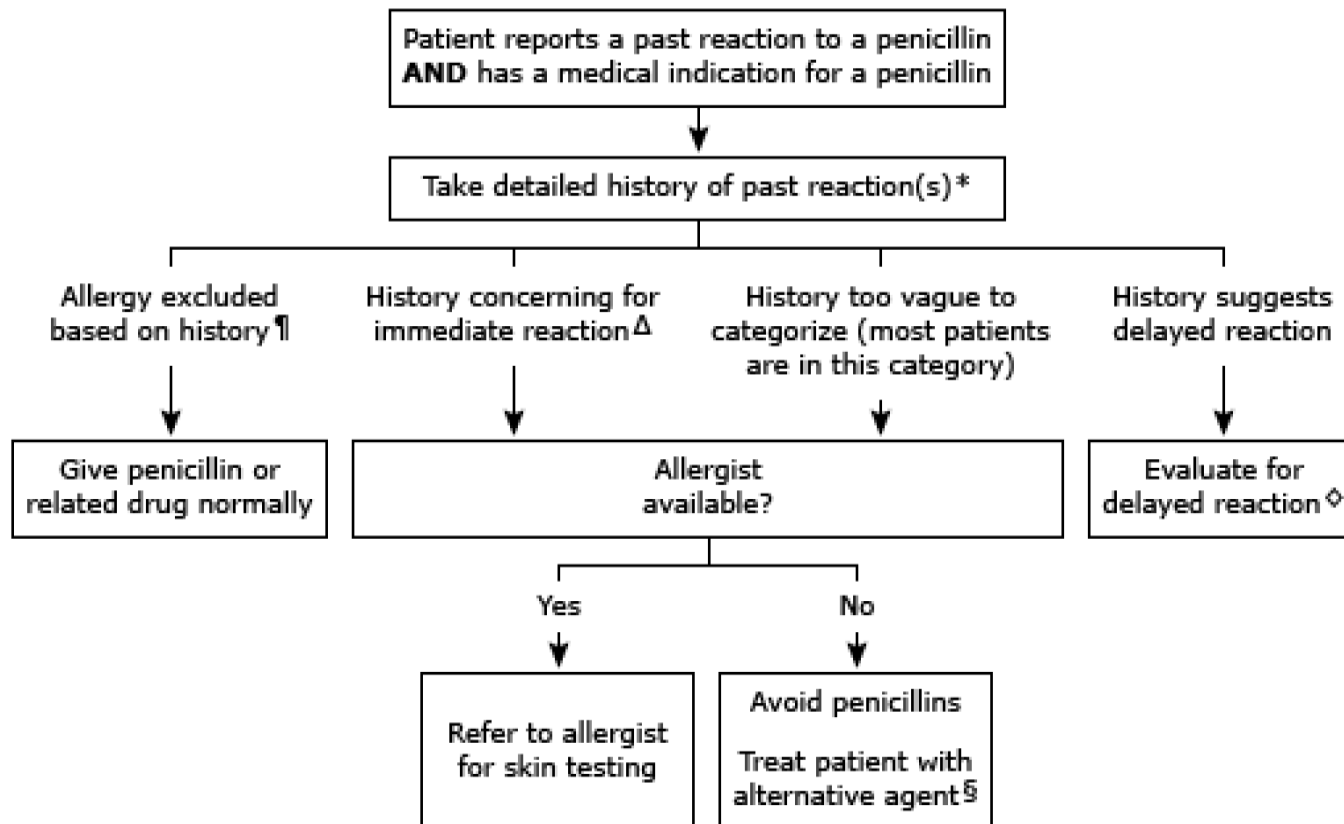
Future use of penicillins in patients with low-risk reactions

- ✓ If the clinician believes that the patient's past reaction was a delayed-onset eruption that:
 - ❖ had no features of immediate allergy
 - ❖ not accompanied by any systemic symptoms
 - ❖ did not involve blistering or exfoliation of the skin or mucous membranes

it is reasonable to consider treatment with the same or other penicillins in the future.

We advocate that readministration be supervised by an allergy specialist when possible and occur in a medically supervised setting equipped to treat possible anaphylaxis.

Approach to penicillin allergy



* A penicillin allergy history includes the following:

- Each agent reportedly associated with a reaction and the indication for its use (to make sure that the agent matches the indication).
- The exact signs and symptoms that occurred, in as much detail as the patient and/or medical record can provide.
- When the reaction occurred (ie, how long ago) and at what point in therapy (immediately after starting or later in course).
- The dose and route of medication taken (if known).
- Other concurrent medications, especially if they were new or temporary.
- Any treatment given and response to that treatment (including the duration of reaction).

¶ Allergy can be excluded based upon history if:

- Reaction was not allergic (eg, isolated nausea or diarrhea, yeast vaginitis, other predictable adverse effect of drug) **OR**
- Patient never took a penicillin but has family members with penicillin allergy.

Δ Immediate reactions usually begin within one hour of the last administered dose and may begin within minutes. Some guidelines include reactions beginning up to six hours after the last administered dose. Common symptoms and signs include pruritus, flushing, urticaria, angioedema, bronchospasm (wheezing, repetitive cough, difficulty breathing), laryngeal edema (throat tightness, change in voice quality), abdominal cramping, nausea, vomiting, diarrhea, and hypotension.

◇ Delayed reactions begin later than six hours and more typically days into a course of treatment. A maculopapular or morbilliform eruption is the most common form of delayed reaction, but more serious forms exist. The evaluation and management of delayed reactions are discussed in the UpToDate topic on delayed hypersensitivity reactions to penicillins.

§ Alternative agents include antibiotics that are unrelated to penicillin, such as sulfonamides, tetracyclines, macrolides, or fluoroquinolones. Refer to the discussion of the use of related antibiotics (ie, cephalosporins, carbapenems, and monobactams) in the UpToDate topic on choice of antibiotics in penicillin-allergic patients.

- ✓ For children with mild delayed reaction to penicillin antibiotics, we suggest one of the following:
- **Cefdinir** 14 mg/kg per day orally in one or two doses (maximum 600 mg/day) for 10 days
- **Cefpodoxime** 10 mg/kg per day orally in two doses (maximum 400 mg/day) for 10 days
- **Cefuroxime** suspension 30 mg/kg per day orally divided in two doses (maximum 1 g/day) for 10 days
- **Cefuroxime** tablets 250 mg orally every 12 hours for 10 days
- **Ceftriaxone** 50 mg/kg intramuscularly once per day (maximum 1 g/day) for one to three doses (if there is symptomatic improvement within 48 hours of the first dose, additional doses are not necessary; if symptoms persist, a second and, if necessary, a third dose are administered)

Immediate reaction or serious delayed reaction

- ✓ Macrolides and lincosamides available for the treatment of AOM include:
 - **Azithromycin** 10 mg/kg per day orally (maximum 500 mg/day) as a single dose on day 1 and 5 mg/kg per day (maximum 250 mg/day) for days 2 through 5.
 - **Clarithromycin** 15 mg/kg per day orally divided into two doses (maximum 1 g/day).
 - The optimal dose for **clindamycin** therapy for AOM is uncertain; we suggest 20 to 30 mg/kg per day orally divided in three doses (maximum 1.8 g/day).

Duration of therapy

- ✓ For amoxicillin, amoxicillin-clavulanate, clarithromycin, oral cephalosporins (eg, cefdinir, cefpodoxime, cefuroxime), clindamycin:
 - ❖ 10 days for children <2 years and children (of any age) with tympanic membrane perforation or history of recurrent AOM (see 'First-line therapy' above)
 - ❖ 5-7 days for children ≥ 2 years of age with intact tympanic membrane and no history of recurrent AOM
 - ❖ azithromycin – 5 days
 - ❖ ceftriaxone – One to three doses, depending upon persistence of symptoms

Persistent symptoms

- ✓ Children who fail to improve after 48 to 72 hours of antibiotic therapy should be seen in follow-up to confirm the diagnosis of AOM, evaluate other causes of persistent symptoms, and determine whether a change in antibacterial therapy is warranted

TREATMENT FAILURE

- ✓ Treatment failure is defined by lack of improvement in symptoms by 48 to 72 hours in a patient treated with antimicrobial therapy.
- ✓ We suggest that patients who fail treatment with high-dose amoxicillin be treated with amoxicillin-clavulanate.(high dose)

TREATMENT FAILURE

- ✓ Patients who fail initial treatment with **high-dose amoxicillin-clavulanate** or **oral cephalosporins** may be treated with:
 - ✓ parenteral ceftriaxone (preferred) or
 - ✓ oral levofloxacin(?)

Levofloxacin should be reserved for children with contraindications to ceftriaxone or AOM refractory to other drugs(not FDA approved in children)

Antibiotic resistance



Other common conditions:

- ✓ Cough
- ✓ Diarrhea
- ✓ UTI