Penicillin Allergies: Delabeling, Challenging and Desensitizing

Executive Summary

It is an estimated 10% of the US population self-reports a penicillin allergy. Nearly 90% of those reported cases, the reaction is not considered a true allergy when critically assessed, including patients with serious IgE-mediated reactions. As a result, it is estimated the antibodies that mediate these reactions significantly decrease over time, with 80% of patients who are no longer sensitive after 10 years following a reaction.

Patients should be "delabeled" for penicillin allergy if what they are experiencing is the result of an adverse drug reaction. By conducting careful questioning of the reaction, gathered information may reveal that the patient can safely use penicillin. Penicillin allergy, if not critically evaluated, can lead to prescribing of inferior, toxic, expensive or overly broad agents for infections that are best treated with beta-lactam antimicrobials. Thus, has the potential to significantly impact morbidity and mortality.

Patients Who Report a Penicillin Allergy –

- **A direct oral challenge with amoxicillin for low risk patients** (allergy reported based on family history alone, non-allergic symptoms, itching without a rash, non-urticarial rash >10 years ago, or distant unknown history)
  or
- **A graded challenge with amoxicillin for moderate risk patients** (history of non-anaphylactic IgE mediated reactions, such as urticarial or other pruritic non-blistering rashes or reactions).

Cross-reactivity between penicillin's and cephalosporins or carbapenems is low, estimated at 2% or lower.

When to "delabel" a penicillin allergy from a patient's chart?

Patients often confuse adverse drug reactions, such as an upset stomach and diarrhea with allergy. Careful questioning of reaction details and antimicrobial history often reveals the patient is low risk of reaction and can safely be delabeled. Once patients have been delabeled, this information should be communicated to the patient's primary care physician and/or other appropriate health care providers.

Notification to the patient's pharmacy should also be attempted if possible. Alternatively, a detailed written description of the allergy and actual tolerability of the agent can be clearly documented in the patient's record. Frequent education should be provided to the patient, making sure they understand they are not truly allergic to penicillin.

When to consider a direct oral challenge for a patient with a penicillin allergy?

Most patients reporting penicillin allergies are considered low risk, with the reported allergy based on family history alone or non-allergic symptoms like gastrointestinal distress or headache. These patients can often be challenged with an amoxicillin prescription in or out of a monitored setting. For low risk patients reporting itching with penicillin without a rash, a non-urticarial rash that happened > 10 years ago, or with a distant unknown history, an amoxicillin challenge may also be appropriate, but likely in a monitored setting (e.g. hospital or ambulatory clinic with access to and experience using medications for anaphylaxis).

Amoxicillin is preferred for these challenges, as aminopenicillin allergy (e.g. amoxicillin) can occur in patients that tolerate penicillin alone, but patients that tolerate amoxicillin generally tolerate all penicillin-type agents. Once a patient tolerates amoxicillin after an observation period of one hour, they should be delabeled as described above.

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When could a "graded challenge" be attempted in a patient with a penicillin allergy?

Some patients are at moderate risk based on a history of a non-anaphylactic IgE-mediated reactions to penicillin and may be candidates for a "graded challenge."

These moderate risk features include urticarial or other pruritic non-blistering rashes or reactions, but not anaphylactic reactions. Amoxicillin is generally recommended for graded challenges, with 10 – 25% of the planned dose given with monitoring for 30-60 minutes.

If this dose is tolerated, the full dose is then administered with additional monitoring for 30-60 minutes. Once this is tolerated, the patient can be delabeled from being penicillin allergic and receive any penicillin-type agent in the future. It is important to note, this patient has not been "desensitized" by the challenge. The low initial dose in the two-step graded challenge is used merely to reduce the severity of any reaction elicited by the first dose.

When should I consider "desensitization" for a patient with a penicillin allergy?

Desensitization can be considered for patients with a history of severe, high-risk IgE-mediated reactions to penicillin. This includes anaphylactic reactions resulting in severe immediate itching, flushing, cardiovascular (arrhythmia, syncope, chest tightness), dermatologic (urticaria, angioedema), or respiratory manifestations (rhinitis, wheezing, shortness of breath, bronchospasm).

Desensitization is used when a penicillin-type agent is proven beneficial over alternative therapies and produces only temporary tolerance of penicillins for that specific period of treatment. The desensitization process starts with very low doses (e.g. 1/1000th of treatment dose) and continues with slowly escalating doses over a period of several hours to the full treatment dose. Desensitization can be done with oral or IV penicillin, and some literature suggests oral desensitization results in fewer reactions.

Once the course of treatment with the penicillin-type agent completes, the patient is still considered penicillin-allergic. The desensitization process would need to be repeated again should the patient require another treatment with a penicillin in the future. Desensitization is generally performed in the hospital setting under the direction of an infectious disease specialist and/or allergy specialist.

When should penicillin skin testing be considered over desensitization?

Penicillin skin testing is an option for assessment and possible delabeling in a patient with a history of an IgE-mediated reaction if they do not react to the skin testing procedure. It is less expensive and resource-intensive than desensitization and may be done under supervision in both the inpatient and outpatient setting. While becoming a more widespread option than in the past, many health systems do not have the resources to perform standardized skin testing procedures.

Other beta-lactams and cross-reactivity

Overall cross-reactivity between penicillins and cephalosporins is now estimated at 2% risk, lower than previous estimates. Cross-reactivity in penicillin allergic patients with some early generation cephalosporins was historically thought to be as high as 40% due to similar side chains. Fortunately, the commonly used first generation cephalosporin, cefazolin, has a unique side chain and very low cross-reactivity with penicillin. Later generation cephalosporins also have unique side chains compared to penicillin, resulting in a low rate of cross reaction. Cross reactivity between penicillins and carbapenems is also low, estimated at less than 1%.

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Asymptomatic Bacteriuria: When to Treat and When NOT to Treat

Asymptomatic bacteriuria is very common in clinical practice; however, most patients should not be treated with antibiotics. Randomized controlled trials demonstrate a lack of benefits to antibiotic treatment for asymptomatic bacteriuria. Additionally, risks often associated with treating asymptomatic bacteriuria include antimicrobial resistance, adverse drug reactions and Clostridioides difficile infections.

There are some instances that allow treatment of asymptomatic bacteriuria, such as pregnancy and patients undergoing endoscopic urologic procedures, but limit screening and treating to these patient populations.

Pharmacy Pearls Recommendations: What can be done to prevent treatment of asymptomatic bacteriuria?

Takeaway #1: Only screen and treat patients for asymptomatic bacteriuria in patients who experience BENEFITS from treating asymptomatic bacteriuria, including patients who are:

1. **Pregnant**
   - ☐ Screen and treat to prevent pyelonephritis, pre-term labor, and infant low birth weight
   - ☐ See Avera Guideline UTIs and Asymptomatic Bacteruria in Pregnant Adults

2. **Undergoing endoscopic urologic procedures associated with mucosal trauma** (This does NOT include placement of a urinary catheter)
   - ☐ Screen and treat prior to surgery to prevent urosepsis

Takeaway #2: Send urine culture ONLY when you suspect UTI based on CLINICAL SYMPTOMS

- ☐ See Avera Guideline: UTIs in Adults (Non-Pregnant)

Takeaway #3: Do not start antibiotics in patients with a positive UA and/or culture until asking about symptoms.

What is Asymptomatic Bacteriuria?

Asymptomatic bacteriuria is the presence of 1 or more species of bacteria growing at least 100,000 colony-forming units (CFU)/mL, WITHOUT signs or symptoms attributable to urinary tract infection (UTI).

Common Symptoms of:	Signs Include:
Cystitis:	Dysuria, urinary frequency, urinary urgency, suprapubic pain
Pyelonephritis:	Fever, flank pain
Catheter-associated UTI (CAUTI):	Fever, suprapubic tenderness

Additional Notes:

- Mental status changes alone → do not indicate a UTI.
- Foul smelling or cloudy urine → does not indicate a UTI.

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Randomized, controlled trials demonstrated a lack of benefits to antibiotic treatment of asymptomatic bacteriuria in the following populations:

- Healthy, non-pregnant women aged 18 to 40 years
- Older females
- Elderly nursing home residents
- Diabetic females
- Patients with long-term indwelling catheters
- Patients with renal transplant
- Patients undergoing orthopedic surgery

What harm can be done with treating asymptomatic bacteriuria?

1. **Antimicrobial Resistance:** Antimicrobial use drives antimicrobial resistance in the community as well as in the individual treated. Antimicrobial stewardship programs, including Avera's, have identified the treatment of asymptomatic bacteriuria as an important contributor to inappropriate antimicrobial use, which promotes resistance.
2. **Adverse Effects:** All antibiotics have the risk for adverse effects. These effects can be mild to severe. Exposing an individual patient to an antibiotic when there is no likelihood of benefit only puts that patient at risk for adverse effects.
3. ***Clostridioides difficile* infection (CDI):** Antibiotics commonly used to treat UTIs have risks for developing CDI which include:
   a. Amoxicillin-Clavulanate
   b. Cephalosporins
   c. Fluoroquinolones
   d. Trimethoprim-Sulfamethoxazole

How Common is Asymptomatic Bacteriuria?

Patient Population:	% Prevalence
Healthy Pre-menopausal Females	< 5%
Females 65 to 90 years old	6 to 16%
Females > 90 years old	22 to 43%
Female LTC Residents	25 to 50%
Male LTC Residents	15 to 35%
Diabetic Females	9 to 27%
People Receiving Hemodialysis	28%
People with Indwelling Urinary Catheters	100%

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- Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteruria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):e83-110.
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Procedural Prophylaxis Against Infective Endocarditis

Content Author: Kyle Dvoracek, PharmD

Executive Summary

Infective endocarditis (IE) is an uncommon life-threatening infection where prophylaxis is integral and the preferred treatment. Certain underlying cardiac conditions predispose patients to endocarditis and bacteremia with organisms known to cause infective endocarditis, commonly associated to invasive dental, gastrointestinal and/or genitourinary tract procedures. Currently, antimicrobial prophylaxis has been proven to be effective for prevention of experimental infective endocarditis in animals; however, there is limited data in humans. As a result, below is a summary of recommendations from clinical experts associated to multiple national organizations, including the Infectious Diseases Society of America, American Dental Association, American Academy of Pediatrics and American Heart Association.

Table 1.1

When Antibiotic Prophylaxis May Be Considered For Prevention of IE
Prosthetic cardiac valve or material ▪ Presence of cardiac prosthetic valve. ▪ Transcatheter implantation of prosthetic valves. ▪ Cardiac valve repair with devices, including annuloplasty, rings or clips. ▪ Left ventricular assist devices or implantable heart.
Previous, Relapse or Recurrent IE
Congenital Heart Disease (CHD) ▪ Unrepaired cyanotic congenital CHD, including palliative shunts and conduits. ▪ Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 months after the procedure. ▪ Repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device. ▪ Surgical or transcatheter pulmonary artery valve or conduit placement such as Melody valve and Contegra conduit.
Cardiac Transplant Recipients Who Develop Cardiac Valvulopathy

Antibiotic Regimens for Prophylaxis Against Infective Endocarditis:

Give a single dose 30 to 60 minutes before procedure.

Situation	Agent	Adults	Children
Oral:	Amoxicillin	2g	50 mg/kg
Unable to take Oral Meds:	Ampicillin **OR**	2g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1g IM or IV	50 mg/kg IM or IV
If Allergic to Penicillin or Ampicillin:			
Oral:	Cephalexin **OR**	2g	50 mg/kg
	Azithromycin or clarithromycin	500mg	15 mg/kg
	OR Doxycycline	100mg	≤ 45 kg, 4.4 mg/kg > 45kg, 100 mg
Unable to take Oral Meds:	Cefazolin or ceftriaxone*	1g IM or IV	50 mg/kg IM or IV

*Cephalosporins should not be used for patients with history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin. In such cases, vancomycin may be used (adults: 15 to 20 mg/kg, not to exceed 2 g per dose; children: 15 mg/kg to a maximum dose of 1g).

Note: The situations below are only addressing prophylaxis for patients with the above underlying conditions that put them at a higher risk for infective endocarditis. This document does not address prophylaxis for patients without the conditions outlined in Table 1.1

Dental Procedures

Dental procedures where antibiotic prophylaxis is suggested include all dental procedures involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

Prophylaxis is NOT Suggested for:

- Anesthetic injections through non-infected tissue
- Taking dental radiographs
- Placement of removable prosthodontic or orthodontic appliances
- Adjustment of orthodontic appliances
- Placement of orthodontic brackets
- Shedding of primary teeth and bleeding from trauma to the lips or oral mucosa

Other Counseling Points

- IE is much more likely to develop as a result of transient bacteremia attributable to routine daily activities such as chewing food and toothbrushing than from a dental procedure.
- Maintenance of good oral health and regular access to dental care are considered more important to prevent infective endocarditis than antibiotic prophylaxis for a dental procedure. Suggest that patients have biannual dental examinations.

Respiratory Tract Procedures:

- No published data conclusively demonstrate a link between respiratory tract procedures and IE.
- Antibiotic regimens above may be reasonable to provide for patients with high-risk underlying conditions (same conditions as for dental procedures above).

Procedures - Prophylaxis Reasonable for:

- Incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy

Procedures - Prophylaxis NOT Suggested for:

- Bronchoscopy unless involving incision of the respiratory mucosa.

Gastrointestinal or Genitourinary Tract Procedures

- Patients undergoing an elective cystoscopy or other urinary tract manipulation who have an enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure may be reasonable. Thus, amoxicillin or ampicillin are recommended agents.

Prophylaxis NOT Suggested for:

- The administration of prophylactic antibiotics solely to prevent IE *is not recommended* for patients undergoing gastrointestinal or genitourinary procedures, including diagnostic EGD or colonoscopy.

Skin, Skin Structure, or Musculoskeletal Tissue

- Patients undergoing a surgical procedure that involves INFECTED skin, skin structure or musculoskeletal tissue, it may be reasonable that the therapeutic regimen contain an agent active against staphylococci and beta-hemolytic streptococci.

Prophylaxis NOT Suggested for:

- Non-infected skin, skin structure or musculoskeletal tissue.

References:

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- Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. *Circ.* 2007;116(15):1736-54.

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Maybe 7 Isn't Lucky for Antibiotic Treatment Duration

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Executive Summary:

Longer antibiotic courses come with risks such as C. Diff, hypersensitivity reactions, nephrotoxicity, hepatotoxicity, drug-drug interactions and antibiotic resistance. An individualized approach to treatment duration vs fixed duration can be used to reduce unnecessary antibiotic exposure. It may be more appropriate to stop treatment early if symptoms resolve for certain infections such as community-acquired pneumonia, COPD exacerbation, bacterial sinusitis or cellulitis.

The seven-day week is a nearly 1700-year-old convention that still defines the rhythm by which modern humans live. As a result, it heavy-handedly influences our behaviors and habits - including antibiotics prescription practices. 7, 14, 21 days and other multiples thereof remain our primary reference point for duration of therapy. The result can be rigidly defined antibiotic courses guided more by dogma than data. Many such conventions are challenged by recent literature which show shorter treatment durations are equivalent to longer courses in many disease states.

Consequences of Longer Antibiotic Courses:

The frequently stated risks of antibiotic treatment to include C. Diff, immune-mediate hypersensitivity reactions, nephrotoxicity, hepatotoxicity, drug-drug interactions among others - are all relevant. Another important and widely known consequence is driving antibiotic resistance. The population level epidemiological consequences of this are well established. However, there are also data to suggest that individual patients with frequent intermittent antibiotic use, when compared to occasional users, observed reduced antibiotic effectiveness and increased risk of treatment failure. As such, the risk of antibiotic resistance doesn't just apply at the population level, but can also affect the single patient by driving individualized resistance.

Fixed Duration vs. Treatment Response

A less dogmatic and more individualized approach to antibiotic treatment duration is recommended. A widely accepted convention is to instruct the patient to take all of the antibiotics once prescribed. However, this may not be necessary if the patient's symptom appear to resolve prior to completing all the antibiotics. As a result, depending on a patient's disease diagnosis, it may be more clinically appropriate to instruct a patient after being prescribed antibiotics to communicate back to their health care provider if their symptoms have resolved to see if treatment can be stopped early.

Infections for which shorter courses have been shown to be equivalent in efficacy to longer treatment:

Disease	Treatment Days (Short)	Treatment Days (Long)
Community-acquired Pneumonia • **View:** Avera CAP Treatment Guideline	3 to 5	7 to 10
Nosocomial Pneumonia	≤ 8	10 to 15
Intraabdominal Infection	4	10
Acute Exacerbation of Chronic Bronchitis and COPD • **View:** Avera COPD Exacerbation Treatment Guideline	≤ 5	≥ 7
Acute Bacterial Sinusitis • **View:** Avera Sinusitis Treatment Guideline	5	10
Cellulitis • **View:** Avera Cellulitis Treatment Guideline	5 to 6	10
Chronic Osteomyelitis	42	84

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- Palin V, Welfare W, Ashcroft DM, van Staa TP. Shorter and Longer Courses of Antibiotics for Common Infections and the Association With Reductions of Infection-Related Complications Including Hospital Admissions. *Clin Infect Dis*. 2021;73(10):1805-1812. doi:10.1093/cid/ciab159
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