Off-Label Drug Uses

Ampicillin (Parenteral): Prevention of Infective Endocarditis

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@kumc.edu.

BACKGROUND

Infective endocarditis (IE), an uncommon but potentially life-threatening infection, is associated with high mortality and morbidity and is most often caused by *Streptococcus*, *Staphylococcus*, or *Enterococcus* species. Structural heart disease and prosthetic valves are considered risk factors for IE. Antimicrobial prophylaxis for the prevention of IE may be warranted in select dental and surgical procedures. Prior to 2007, national guidelines recommended prophylaxis in a variety of patients undergoing a broad set of dental and surgical procedures. In the current guidelines for the prevention of IE, it has been suggested that IE is more likely to occur from frequent exposure to random bacteremia associated with daily activity than bacteremia caused by dental, gastrointestinal (GI) tract, or genitourinary (GU) procedures. In addition, prophylaxis may prevent only a small number of procedure-related IE cases, and the risk of antibiotic adverse events outweighs the potential benefit associated with such therapy. The maintenance of optimal oral health and hygiene is promoted to reduce the incidence of bacteremia from daily activities. Based on these revised guidelines, fewer patients are eligible for IE prophylaxis.^{1,2}

PATIENT POPULATION

Adults with certain cardiac conditions associated with the highest risk of adverse outcome from IE who are undergoing (a) a dental procedure that involves manipulation of the gingival tissue or the periapical

region of teeth or perforation of the oral mucosa, (b) an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, or (c) a surgical procedure that involves infected skin, skin structures, or musculoskeletal tissue.¹

Cardiac conditions identified by the American Heart Association (AHA) guidelines associated with the highest risk of adverse outcome from IE for which preprocedural prophylaxis is deemed reasonable include patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair or previous IE, specific patients with congenital heart disease, and cardiac transplantation recipients who develop cardiac valvulopathy.¹

DOSAGE AND DURATION

Adults: Parenteral ampicillin (intramuscular [IM] or intravenous [IV]) as a single 2 g dose administered 30 to 60 minutes prior to the procedure.

Children: Parenteral ampicillin (IM or IV) as a single 50 mg/kg dose administered 30 to 60 minutes prior to the procedure.

If dosage is inadvertently not administered prior to the procedure, the dose may be administered up to 2 hours after the procedure. Postprocedural dosing should only be considered in patients who miss the preprocedural dose.¹

RESULTS

The use of parenteral ampicillin as IE prophylaxis prior to certain procedures in highest risk patients with

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certain cardiac conditions or prior IE has been outlined in national guidelines.^{1,2} According to these guidelines, amoxicillin is the preferred oral agent of choice for highest risk patients prior to select dental procedures and it may be used in other procedures where pathogen susceptibility is appropriate. Parenteral ampicillin is an alternative in patients who are unable to tolerate oral medications. Amoxicillin or parenteral ampicillin are preferred agents for use in patients with enterococcal infections who are undergoing urinary tract procedures. It should be noted that there is a lack of data from prospective, randomized, placebo-controlled trials regarding antibiotic prophylaxis prior to procedures.¹

AHA Guidelines for the Prevention of IE

The AHA guidelines for the prevention of IE provide classifications and levels of evidence to their recommendations. Evidence-based classifications include Class I (evidence/agreement that the procedure/treatment is beneficial, useful, and effective), Class IIa (evidence is conflicting but favors effectiveness), Class IIb (evidence is conflicting and effectiveness is not well-established), and Class III (evidence of non-effectiveness or harm). The levels of evidence (LOE) include Level A (multiple randomized trials available), Level B (single randomized trial or nonrandomized trials available), or Level C (expert consensus).

Dental Procedures

AHA guidelines consider antimicrobial IE prophylaxis reasonable in highest risk patients with certain cardiac conditions who undergo any dental procedure that involves the manipulation of the gingival tissue or the periapical region of the teeth or perforation of the oral mucosa. Prophylactic antimicrobial therapy should be directed against viridans group streptococci. Because there is a lack of data from prospective, randomized, placebo-controlled trials regarding antibiotic prophylaxis prior to dental procedures, the guidelines consider the effectiveness of IE prophylaxis as unknown (Class IIa, Level C). Amoxicillin is the preferred oral agent for use prior to dental procedures because it is well absorbed and provides high and sustainable serum concentrations. For those unable to take oral medication, parenteral ampicillin, cefazolin, or ceftriaxone are alternatives. For those allergic to penicillins, the oral use of cephalexin or another first- or second-generation cephalosporin, clindamycin, azithromycin, or clarithromycin is recommended. For patients allergic to penicillins and unable to take

oral medications, parenteral cefazolin, clindamycin, or ceftriaxone is recommended.

For highest risk patients taking long-term penicillin for prevention of rheumatic fever, it is likely that penicillin-resistant viridans group streptococci will be found in the oral cavity. In these cases, clindamycin, azithromycin, or clarithromycin should be used for IE prophylaxis. Cephalosporins should be avoided due to possible cross-resistance.

Antibiotic prophylaxis for dental procedures is not recommended for patients with coronary artery stents (Class III, Level C). IE prophylaxis for dental procedures in cardiac transplant patients who develop cardiac valvulopathy is considered reasonable, but the usefulness is not established (Class IIa, Level C).

Respiratory Tract Procedures

The guidelines consider IE prophylaxis reasonable for highest risk adults who are undergoing an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa (Class IIa, Level C). Antibiotic regimens mentioned previously for dental procedures are considered reasonable in this patient population. If the respiratory procedure is to treat an established infection, antibiotic selection should include an agent active against viridans group streptococci. If *S. aureus* is suspected, the regimen should include an agent active against this pathogen, such as an antistaphylococcal penicillin or cephalosporin, or vancomycin in patients unable to tolerate a B-lactam. Vancomycin should be used in cases of infection caused by known or suspected methicillin-resistant *S. aureus*.

GU or GI Tract Procedures

The administration of IE prophylaxis solely to prevent endocarditis is no longer recommended for patients who undergo GU or GI tract procedures (Class III, Level B). This represents a significant change compared to previous AHA guidelines. The current guidelines state that there is no conclusive link between these procedures and the development of IE. For highest risk patients who have an established infection of the GI or GU tract or receive antibiotic therapy to prevent wound infection or sepsis associated with a GI or GU procedure, an antibiotic regimen should include an agent active against enterococci (eg, penicillin, ampicillin, piperacillin, or vancomycin) (Class IIb, Level B). It is noted that no published studies demonstrate that such therapy prevents enterococcal IE. Amoxicillin and ampicillin are preferred agents for

use in patients with enterococcal infections who are undergoing urinary tract procedures (Class IIb, Level B). Vancomycin may be used in patients unable to tolerate ampicillin. If a resistant strain of enterococcus is suspected, expert opinion is recommended.

Surgical Procedures of Infected Skin, Skin Structures, or Musculoskeletal Tissue

For highest risk patients undergoing a surgical procedure that involves infected skin, skin structures, or musculoskeletal tissue, guidelines state that it is reasonable to treat with a regimen that contains an agent active against staphylococci and B-hemolytic streptococci, such as an antistaphylococcal penicillin or cephalosporin. (Class IIb, Level C). Vancomycin or clindamycin may be administered to patients unable to tolerate a B-lactam or who have an infection related to methicillin-resistant staphylococcus.

American College of Cardiology /AHA Guideline Update on Valvular Heart Disease

In 2008, the American College of Cardiology (ACC)/AHA published revised guidelines on valvular heart disease (VHD) with a focused update on IE prevention based on recent changes in the AHA guidelines. Changes in the VHD guidelines were consistent with AHA recommendations.^{1,2}

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, warnings/precautions, adverse reactions, drug interactions).

Intramuscular injections for IE prophylaxis should be avoided in patients who are receiving anticoagulant therapy (Class I, Level A). Orally administered regimens should be administered whenever possible. Intravenously administered antibiotics should be

used in persons unable to tolerate or absorb oral medications.¹

Common adverse effects seen with ampicillin administration include skin rashes, urticaria, exfoliative dermatitis, and erythema multiforme. The medication should be discontinued if a hypersensitivity reaction occurs.³

THERAPY CONSIDERATIONS

According to national guidelines, parenteral ampicillin is an alternative to oral amoxicillin for the highest risk patients prior to select dental procedures and may be used in other procedures where appropriate coverage is known or suspected. Amoxicillin and parenteral ampicillin are preferred agents for use in patients with enterococcal infections who are undergoing urinary tract procedures. There is a lack of data from prospective, randomized, placebo-controlled trials regarding antibiotic prophylaxis prior to procedures.

REFERENCES

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