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Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling

A report from the American Dental Association

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ABSTRACT

Background. An expert panel convened by the American Dental Association Council on Scientific Affairs and the Center for Evidence-Based Dentistry conducted a systematic review and formulated clinical recommendations for the urgent management of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and symptomatic apical periodontitis, or pulp necrosis and localized acute apical abscess using antibiotics, either alone or as adjuncts to definitive, conservative dental treatment (DCDT) in immunocompetent adults.

Types of Studies Reviewed. The authors conducted a search of the literature in MEDLINE, Embase, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature to retrieve evidence on benefits and harms associated with antibiotic use. The authors used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty in the evidence and the Evidence-to-Decision framework.

Results. The panel formulated 5 clinical recommendations and 2 good practice statements, each specific to the target conditions, for settings in which DCDT is and is not immediately available. With likely negligible benefits and potentially large harms, the panel recommended against using antibiotics in most clinical scenarios, irrespective of DCDT availability. They recommended antibiotics in patients with systemic involvement (for example, malaise or fever) due to the dental conditions or when the risk of experiencing progression to systemic involvement is high.

Conclusion and Practical Implications. Evidence suggests that antibiotics for the target conditions may provide negligible benefits and probably contribute to large harms. The expert panel suggests that antibiotics for target conditions be used only when systemic involvement is present and that immediate DCDT should be prioritized in all cases.

Key Words. Antibiotics; symptomatic irreversible pulpitis; symptomatic apical periodontitis; pulp necrosis; localized acute apical abscess; clinical practice guideline; antibiotic stewardship.

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Dental pain and intraoral swelling are not only a concern for dental providers but are also the most cited oral health–related reasons for a patient contacting an emergency department (ED) or physician.[1-3] These signs and symptoms are associated with pulpal and periapical conditions, which usually result from caries. Bacteria associated with caries can cause symptomatic irreversible pulpitis (SIP), an inflammation of the pulpal tissue. This condition may manifest as

occasional sharp pain, usually stimulated by temperature change, and can worsen to spontaneous, constant, and dull or severe pain. Progressive pulp inflammation in the apical region (that is, symptomatic apical periodontitis [SAP]) may result in necrotic pulp (that is, pulp necrosis and symptomatic apical periodontitis [PN-SAP]). The infection can continue to move into and through the alveolar bone to the soft tissues surrounding the jaw (that is, localized acute apical abscess). Depending on location and patient status, this can further develop into systemic infection (eTable 1).[4,5]

Dentists and physicians often prescribe antibiotics to relieve dental pain and intraoral swelling. General and specialty dentists are the third highest prescribers of antibiotics in all outpatient settings in the United States.[6] In addition, reports from 2017 through 2019 suggest that 30% through 85% of dental antibiotic prescriptions are "suboptimal or not indicated."[7-9] Owing to major public health and cost-related concerns, the appropriate use of antibiotics has become a critical issue in the health care agenda.

Although a number of countries and clinical practice guideline development groups have produced recommendations on the use of systemic antibiotics to treat pulpal and periapical infections,[10-14] there are no guidelines from the American Dental Association (ADA) for dentists in the United States. Many national and international agencies, including the US federal government and Centers for Disease Control and Prevention, have joined forces with the ADA to help prevent a postantibiotic era in which antibiotics will no longer be effective in treating bacterial infections.[15-19]

The ADA Council on Scientific Affairs convened an expert panel of academic and clinical experts specializing in dentistry, medicine, and pharmacology to develop this guideline and its accompanying systematic review.[20] The ADA Center for Evidence-Based Dentistry (EBD) provided methodological support, drafted manuscripts, and led stakeholder engagement efforts.

SCOPE, PURPOSE, AND TARGET AUDIENCE

The purpose of this guideline is to assist clinicians and patients in determining the appropriate use of systemic antibiotics for the urgent management of the following target conditions: SIP with or without SAP, PN-SAP, and pulp necrosis and localized acute apical abscess (PN-LAAA) with or without access to immediate definitive, conservative (tooth-preserving) dental treatment (DCDT) (that is, pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision and drainage). The scope of this guideline focuses on immunocompetent adult patients (18 years or older) with the target conditions and without additional comorbidities. The management of the care of adults with cellulitis or compromised immune systems (defined as those with the inability to respond appropriately to a bacterial challenge, for example, patients undergoing chemotherapy[21]) and the management the care of adults undergoing tooth extraction are not within the scope of this guideline (Appendix, available online at the end of this article). Although these recommendations are intended primarily for use by general dentists, they also may be used by specialty dentists, dental educators, emergency and primary care physicians, infectious disease specialists, physician assistants, nurse practitioners, pharmacists, and policy makers. These recommendations also might be discussed during chairside conversations with patients (Table).

METHODS

The development of this guideline and article was conducted according to the Appraisal of Guidelines for Research and Evaluation Reporting II Checklist[28] and Guidelines International Network-McMaster Guideline Development Checklist.[29] The expert panel and methodologists met in person twice. They began the first meeting by reviewing panelists' conflicts of interests, followed by defining the scope, purpose, target audience, and clinical questions.[30] The panel defined desirable and undesirable outcomes for decision making. After the first meeting, methodologists at the ADA Center for EBD (L.P., M.P.T., O.U., A.C-.L.) worked with an informationist (K.K.O.) to develop a systematic review of the evidence,[20] which included updating 2 preexisting Cochrane systematic reviews.[31,32] The second in-person meeting was facilitated by a methodologist at the ADA Center for EBD (M.P.T.) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence-to-Decision (EtD) framework.[33-37] During this meeting, the expert panel discussed the evidence to

ABBREVIATION KEY

ADA: American Dental Association.
ANC: Absolute neutrophil count.
CDC: Centers for Disease Control and Prevention.
CDI: *Clostridioides difficile* infection.
DCDT: Definitive, conservative dental treatment.
EBD: Evidence-based dentistry.
ED: Emergency department.
EtD: Evidence-to-decision.
GPS: Good practice statements.
GRADE: Grading of Recommendations Assessment, Development and Evaluation.
PN-LAAA: Pulp necrosis and localized acute apical abscess.
PN-SAP: Pulp necrosis and symptomatic apical periodontitis.
PVP: Patients' values and preferences.
SAP: Symptomatic apical periodontitis.
SIP: Symptomatic irreversible pulpitis.

Table. Summary of clinical recommendations for the urgent management of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and symptomatic apical periodontitis, and pulp necrosis and localized acute apical abscess.

SETTING, CLINICAL QUESTION	EXPERT PANEL RECOMMENDATIONS AND GOOD PRACTICE STATEMENTS
Urgent Situations in Dental Settings in Which Pulpotomy, Pulpectomy, Nonsurgical Root Canal Treatment, or Incision for Drainage of Abscess Are *Not* an Immediate Option (Not On Same Visit)	
1. For immunocompetent* adults **with symptomatic irreversible pulpitis**† **with or without symptomatic apical periodontitis,**‡ should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics to improve health outcomes?	Recommendation 1: The expert panel recommends dentists *do not prescribe* oral systemic antibiotics for immunocompetent adults with **symptomatic irreversible pulpitis**† **with or without symptomatic apical periodontitis**‡ (strong recommendation, low certainty). Clinicians should refer§ patients for DCDT¶ while providing interim monitoring.#
2. For immunocompetent adults with **pulp necrosis and symptomatic apical periodontitis or localized acute apical abscess,**** should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics to improve health outcomes?	Recommendation 2A: The expert panel suggests dentists *do not prescribe* oral systemic antibiotics for immunocompetent adults with **pulp necrosis and symptomatic apical periodontitis** (conditional recommendation, very low certainty). Clinicians should refer patients for DCDT while providing interim monitoring. If DCDT is not feasible, a delayed prescription†† for oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d)‡‡,§§,¶¶,##,*** should be provided. Recommendation 2B: The expert panel suggests dentists prescribe oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d)‡‡,§§,¶¶,##,*** for immunocompetent adults with **pulp necrosis and localized acute apical abscess** (conditional recommendation, very low certainty). Clinicians also should provide urgent referral as DCDT should not be delayed.#
No corresponding clinical question	Good practice statement: The expert panel suggests dentists prescribe oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d)‡‡,§§,¶¶,##,*** for immunocompetent adults with **pulp necrosis and acute apical abscess with systemic involvement.**††† Clinicians also should provide urgent referral as DCDT should not be delayed.# If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer patient for urgent evaluation.‡‡‡
Urgent Situations in Dental Settings and Pulpotomy, Pulpectomy, Nonsurgical Root Canal Treatment, or Incision for Drainage of Abscess *Are* an Immediate Option (Same Visit)	
3. For immunocompetent adults with **pulp necrosis and symptomatic apical periodontitis or localized acute apical abscess,** should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics as adjuncts to DCDT§§§ to improve health outcomes?	Recommendation 3: The expert panel recommends dentists *do not prescribe* oral systemic antibiotics as an adjunct to DCDT§§§ for immunocompetent adults with **pulp necrosis and symptomatic apical periodontitis or localized acute apical abscess** (strong recommendation, very low certainty).
4. For immunocompetent adults with **symptomatic irreversible pulpitis with or without symptomatic apical periodontitis,** should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics as adjuncts to DCDT¶¶¶ to improve health outcomes?	Recommendation 4: The expert panel suggests dentists *do not prescribe* oral systemic antibiotics as an adjunct to DCDT¶¶¶ for immunocompetent adults with **symptomatic irreversible pulpitis with or without symptomatic apical periodontitis** (conditional recommendation, very low certainty).
No corresponding clinical question	Good practice statement: The expert panel suggests dentists perform urgent DCDT§§§ in conjunction with prescribing oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d)‡‡,§§,¶¶,##,*** for immunocompetent adults with **pulp necrosis and acute apical abscess with systemic involvement.**††† If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer for urgent evaluation.‡‡‡

* Immunocompetent is defined as the ability of the body to mount an appropriate immune response to an infection. Immunocompromised patients do not meet the criteria for this recommendation, and they can include, but are not limited to, patients with HIV with an AIDS-defining opportunistic illness, cancer, organ or stem cell transplants, and autoimmune conditions on immunosuppressive drugs.[21] † Symptomatic irreversible pulpitis is characterized by spontaneous pain that may linger with thermal changes due to vital inflamed pulp that is incapable of healing.[5] ‡ Symptomatic apical periodontitis is characterized by pain with mastication, percussion, or palpation, with or without evidence of radiographic periapical pathosis, and without swelling.[5] of § Clinicians including dentists, dental hygienists, and other members of the oral health care team may refer patients to an endodontist, oral and maxillofacial surgeon, or general dentist who is trained to perform definitive, conservative dental treatment (DCDT). ¶ DCDT: Definitive, conservative dental treatment. # Patients should be instructed to call if their condition deteriorates (progression of disease to a more severe state) or if the referral to receive DCDT within 1-2 d is not possible. Evidence suggests that nonsteroidal anti-inflammatory drugs and acetaminophen (specifically, 400-600 milligrams ibuprofen plus 1,000 mg acetaminophen) may be effective in managing dental pain.[22] ** Localized acute apical abscess is characterized by spontaneous pain with or without mastication, percussion, or palpation, with formation of purulent material, localized swelling, and without evidence of fascial space or local lymph node involvement, fever, or malaise (fatigue, reduced energy).[5] †† Dentists should communicate to the patient that *if* their symptoms worsen and they experience swelling or pus formation, the delayed prescription should be filled. Delayed prescribing is defined by the Centers for Disease Control and Prevention as a prescription that is "used for patients with conditions that usually resolve without treatment but who can benefit from antibiotics if the conditions do not improve. [Dentists] can apply delayed prescribing practices by giving the patient a postdated prescription and providing instructions to fill the prescription after a predetermined period or by instructing the patient to call or return to collect a prescription if symptoms worsen or do not improve."[23] ‡‡ Although the expert panel recommends both amoxicillin and penicillin as first-line treatments, amoxicillin is preferred over penicillin because it is more effective against various gram-negative anaerobes and its lower incidence of gastrointestinal side effects. §§ As an alternative for patients with a history of a penicillin allergy, but *without* a history of anaphylaxis, angioedema, or hives with penicillin, ampicillin, or amoxicillin, the panel suggests dentists prescribe oral cephalexin (500 mg, 4 times per d, 3-7d). Of note, the anaerobic activity of cephalexin is not well described for some oral pathogens. Clinicians should have a low threshold to add metronidazole to cephalexin therapy in patients with a delayed response to antibiotics. As an alternative for patients with a history of a penicillin allergy and *with* a history of anaphylaxis, angioedema, or hives with penicillin, ampicillin, or amoxicillin, the panel suggests dentists prescribe oral azithromycin (loading dose of 500 mg on day 1,

followed by 250 mg for an additional 4 d) or oral clindamycin (300 mg, 4 times per d, 3-7 d).[24] Bacterial resistance rates for azithromycin are higher than for other antibiotics, and clindamycin substantially increases the risk of developing *Clostridioides difficile* infection even after a single dose.[25] Owing to concerns about antibiotic resistance, patients who receive azithromycin should be instructed to closely monitor their symptoms and call a dentist or primary care provider if their infection worsens while receiving therapy. Similarly, clindamycin has a US Food and Drug Administration black box warning for *C. difficile* infection, which can be fatal.[26] Patients should be instructed to call their primary care provider if they develop fever, abdominal cramping, or $\geq$ 3 loose bowel movements per day.[27] An antibiotic with a similar spectrum of activity to those recommended above can be continued if the antibiotic was initiated before the patient sought treatment. As with any antibiotic use, the patient should be informed about symptoms that may indicate lack of antibiotic efficacy and adverse drug events. ¶¶ Clinicians should reevaluate patient within 3 d (for example, in-person visit or phone call). Dentists should instruct patient to discontinue antibiotics 24 h after patient's symptoms resolve, irrespective of reevaluation after 3 d. ## In cases in which patients *without* a penicillin allergy fail to respond to first-line treatment (that is, patient shows no improvement in symptoms or the condition progresses to a more severe state) with oral amoxicillin or oral penicillin V potassium, the panel suggests that dentists should broaden antibiotic therapy to either complement first-line treatment with oral metronidazole (500 mg, 3 times per d, 7d) or *discontinue* first-line treatment and prescribe oral amoxicillin and clavulanate (500/125 mg, 3 times per d, 7 d). Clinicians should reevaluate patient within 3 d (for example, in-person visit or phone call). Dentists should instruct patient to discontinue antibiotics 24 h after patient's symptoms resolve, irrespective of reevaluation after 3 d. *** In cases in which patients *with* a history of a penicillin allergy and *with or without* a history of anaphylaxis, angioedema, or hives with penicillin, ampicillin, or amoxicillin fail to respond to first-line treatment (that is, patient shows no improvement in symptoms or the condition progresses to a more severe state) with oral cephalexin, oral azithromycin, or oral clindamycin, the panel suggests that dentists should broaden antibiotic therapy to complement first-line treatment with oral metronidazole (500 mg, 3 times per d, 7d). Clinicians should reevaluate patient within 3 d (for example, in-person visit or phone call). Dentists should instruct patient to discontinue antibiotics 24 h after patient's symptoms resolve, irrespective of reevaluation after 3 d. ††† Acute apical abscess with systemic involvement is characterized by necrotic pulp with spontaneous pain, with or without mastication, percussion, or palpation, with formation of purulent material, swelling, evidence of fascial space or local lymph node involvement, fever, or malaise. ‡‡‡ Urgent evaluation will most likely be conducted in an urgent care setting or an emergency department. §§§ DCDT refers to nonsurgical root canal treatment or incision for drainage of abscess. Extractions are not within the scope of this guideline. Only clinicians who are authorized or trained to perform the specified treatments should do so. ¶¶¶ DCDT refers to pulpotomy, pulpectomy, or nonsurgical root canal treatment. Extractions are not within the scope of this guideline. Only clinicians who are authorized or trained to perform the specified treatments should do so.

formulate recommendations and good practice statements (GPS), all decisions were developed through consensus, and the panel only voted if consensus was difficult to achieve. Recommendations formulated using GRADE can be strong or conditional with varying implications for different users (eTable 2). Additional efforts to inform this guideline include a robust stakeholder and public engagement process and a plan for updating the guideline whenever the direction and strength of recommendations may be affected by newly published evidence (or within 5 years). Additional details about the methodology we used to develop this clinical practice guideline are available in the appendix (available online at the end of this article) and the associated systematic review.[20]

RESULTS

Recommendations and GPS

Recommendations are informed by a comprehensive search for the best available evidence and a formal process for assessing the certainty of the evidence. In contrast, GPS are appropriate when there is an excess of indirect evidence suggesting that their implementation will result in large and unequivocal net positive or negative consequences. Recommendations are associated with a certainty of the evidence in contrast to GPS (Table).[38]

How to use these recommendations and GPS

The expert panel graded the strength of recommendations (that is, strong or conditional) to provide clinicians, patients, and policy makers with orientation as to how to proceed in the face of the recommendation statement (eTable 2). These recommendations and GPS aim to help clinicians, policy makers, and patients make decisions about antibiotic use for immunocompetent adults (most typical patients) who have the target conditions. Clinicians should use informed clinical judgement[39] to identify the appropriate course of action in situations that deviate from these recommendations and GPS.

RECOMMENDATIONS

Recommendations in settings in which DCDT is *not* immediately available

Question 1. For immunocompetent adults with SIP with or without SAP, should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics to improve health outcomes (Appendix, Methods, available online at the end of this article)?

Desirable and Undesirable Effects From Randomized Controlled Trials

For this comparison, the panel judged anticipated desirable effects as potentially negligible. Evidence suggests that 24 hours after starting antibiotics, pain intensity may increase slightly, but after

7 days, it may reduce slightly (low certainty). In absolute terms, over a range of different time points up through 7 days of follow-up, of 1,000 people taking antibiotics, anywhere from 49 fewer through 100 more people may experience pain (low certainty). In addition, those taking antibiotics also may have one-half of an ibuprofen tablet less and 2 more rescue analgesic tablets than those who did not take antibiotics over 7 days (low certainty) (eTable 3, available online at the end of this article).[40] We identified no randomized controlled trials meeting our selection criteria that reported undesirable effects.

Undesirable Effects From Observational Studies

From observational studies, the panel identified a large burden of anticipated undesirable effects directly or indirectly associated with antibiotic prescriptions, including mortality due to antibiotic-resistant infections (23,000 deaths annually in the United States, low certainty), community-associated *Clostridioides difficile* infection (CDI) (6,400 of 10,000 people with community-associated CDI were exposed to antibiotics, moderate certainty), and community-associated CDI (80 of 10,000 people with community-associated CDI died and were exposed to antibiotics, moderate certainty), as well as anaphylaxis due to antibiotics (46 and 6 of 10,000 hospitalizations were due to anaphylaxis associated with the use of a penicillin and cephalosporin drug classes, respectively), and among others (eTable 4, eTable 5, available online at the end of this article).[6,41-49] The panel is moderately certain that most estimates for critical-harm outcomes represent a large burden, with a high chance for an underestimation. No direct evidence informed the impact of dental antibiotic prescriptions in the outcomes presented above. The panel calculated an adjusted estimate to illustrate the burden of antibiotics prescribed by dentists and rated the certainty of these estimates down owing to serious issues of indirectness[43] (eTable 4, eTable 5, available online at the end of this article).

Values and Preferences

Although patients' values and preferences (PVP) will likely vary owing to access-to-care issues, the panel considered values and preferences a crucial factor for decision making, in part owning to the low certainty of evidence informing beneficial outcomes. Unfortunately, we found no studies on PVPs related to the clinical questions, and we used studies on antibiotic use for other (medical) conditions to inform these factors. For complete details on PVP, see the results section of the appendix, available online at the end of this article.

Acceptability

From the panel's perspective, key stakeholders *will* likely accept a recommendation against the use of antibiotics in most situations for the target conditions. Clinicians and patients may find a recommendation for antibiotics more acceptable in settings and situations in which access to oral health care is an issue and there is the possibility of patients' having high expectations for receiving an antibiotic.

Feasibility

The panel agreed that not prescribing antibiotics for these target conditions in the absence of immediate DCDT *is* feasible if DCDT can be performed shortly (a few days) after the initial visit.

Recommendation

- The expert panel recommends dentists do not prescribe oral systemic antibiotics for immunocompetent adults with SIP with or without SAP (strong recommendation, low certainty). Clinicians should refer patients for DCDT and provide interim monitoring (Table).

Remarks

- The use of antibiotics may result in little to no difference in beneficial outcomes (low certainty) but likely result in a potentially large increase in harm outcomes (moderate certainty), warranting a strong recommendation against their use (second paradigmatic situation from GRADE guidance[34]).

- From a physiopathologic perspective, patient populations with SIP with or without SAP do not require antibiotics, given that the inflamed pulpal tissue associated with this condition is not due to an infection.
- Providers, especially in EDs, other health care settings, or rural settings, should ask patients if they have access to oral health care. If not, clinicians and patients may not find this recommendation acceptable or feasible for implementation given that patients may have high expectations for receiving an antibiotic.

Question 2. For immunocompetent adults with PN-SAP or PN-LAAA, should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics to improve health outcomes (Appendix, Methods, available online at end of this article)?

Desirable and Undesirable Effects from Randomized Controlled Trials

We did not identify any eligible studies to inform this comparison for patients with PN-SAP or PN-LAAA. The panel decided to inform this recommendation with the same body of evidence summarized for Question 1 and rated down the certainty of the evidence for beneficial outcomes from low to very low owing to serious issues of indirectness due to differing patient populations (eTable 3).

Undesirable Effects From Observational Studies

The panel used the same body of evidence informing harm outcomes (moderate certainty) for Question 1 (eTable 4, eTable 5, available online at the end of this article) to inform these factors in Question 2.

Values and Preferences

The same evidence on PVP described for Question 1 informed this recommendation (see Question 1, PVP factor). In addition, the panel identified patients in this comparison to be at higher risk of experiencing systemic involvement because they have necrotic pulp (indicating an infectious process) and because they may not have immediate access to DCDT (see acceptability section under Question 1). Finally, regarding delayed prescribing (that is, "a prescription that is used for patients with conditions that usually resolve without treatment but who can benefit from antibiotics if the conditions do not improve"),[23] Cochrane review reported that there were no statistically significant differences in patient satisfaction when comparing delayed and immediate antibiotic prescriptions (OR: 0.65, 95% CI: 0.39, 1.10, moderate certainty)[50]

Acceptability

According to the panel, given that patients with necrotic pulp are at a higher risk of experiencing disease progression with systemic involvement and DCDT is not an immediate option in this question or patients may lack access to care, clinicians may be less inclined to send patients home without antibiotics compared with patients with SIP with or without SAP (who may be comparatively at lower risk of experiencing disease progression with systemic involvement).

Feasibility

The panel agreed that not providing antibiotics for these patients when DCDT is not immediately available *is* feasible, if DCDT can be performed shortly (1-2 days) after the initial visit.

When formulating recommendations, the panel was more concerned about the risk of disease progression with systemic involvement for patients with PN-LAAA compared with those with PN-SAP and decided to provide separate guidance for each population.

Recommendation 2A

- The expert panel suggests dentists do not prescribe oral systemic antibiotics for immunocompetent adults with PN-SAP (conditional recommendation, very low certainty). Clinicians should refer patients for DCDT and provide interim monitoring. If DCDT is not feasible, a delayed prescription for oral amoxicillin (500 milligrams, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d) should be provided (Table).

Remarks

- For patients with PN-SAP, the panel suggests the use of a delayed antibiotic prescription if patients' symptoms worsen or DCDT has yet to be performed. Clinicians should provide the prescription and instruct patients to fill it 24 through 48 hours after the initial visit.

Recommendation 2B

- The expert panel suggests dentists prescribe oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d) for immunocompetent adults with PN-LAAA (conditional recommendation, very low certainty). In addition, clinicians should provide urgent referral, because DCDT should not be delayed (Table).

Remarks

- Although the evidence on antibiotics suggests both potential negligible benefits and likely substantial harms, there is an increased risk of experiencing disease progression to systemic involvement without immediate access to DCDT compared with patients with PN-SAP. The panel thus judged that prescribing antibiotics in the absence of immediate DCDT may be appropriate for patients with PN-LAAA to reduce the potential risk of a patient's experiencing systemic involvement.

Remarks Applicable to Both Recommendations 2A and 2B

- Indirect evidence suggests that the use of antibiotics may have little to no effect in beneficial outcomes (very low certainty) but likely result in a large increase in harm outcomes (moderate certainty), warranting a conditional recommendation against antibiotic use.
- Providers, especially in EDs, other health care settings, or rural settings, should ask patients if they have access to oral health care. If not, clinicians and patients may find that an immediate antibiotic prescription is the best course of action for patients with PN-SAP in addition to those with PN-LAAA.
- Diagnostic tests readily available to dentists (for example, pulp vitality tests) are usually unavailable in medical settings. Physicians should consider evaluating patients on the basis of their signs and symptoms (eTable 1).
- Resources for discussing delayed prescribing are available online.[51]

Recommendations in settings in which DCDT *is* immediately available

Question 3: For immunocompetent adults with PN-SAP or PN-LAAA, should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics as adjuncts to DCDT to improve health outcomes (Appendix, Methods, available online at the end of this article)?

Desirable and Undesirable Effects From Randomized Controlled Trials

The panel judged that the anticipated desirable effects of antibiotics as adjuncts to DCDT for patients with PN-SAP or PN-LAAA to be negligible. The evidence suggests that, during the first 72 hours, pain intensity may be slightly higher in patients taking antibiotics compared with patients not taking antibiotics (very low certainty). Up through 7 days, antibiotics might result in a slight reduction in pain intensity (low certainty). The results over a range of different time points, up through 7 days of follow-up, suggest that of 1,000 people taking antibiotics, anywhere from 88 fewer people through 128 more people may experience pain (very low-low certainty). In addition, the evidence regarding the effect of antibiotics on intraoral swelling may suggest both a slight increase and reduction in the outcome over 7 days. Of 1,000 patients taking antibiotics, anywhere from 0 through 175 more people may experience intraoral swelling (very low-low certainty). In addition, those taking antibiotics may take 2 more ibuprofen tablets and approximately one-half tablet less of rescue analgesic than those who did not take antibiotics over 7 days (low certainty) (eTable 6, available online at the end of this article).[52,53] The panel judged that the anticipated undesirable effects of antibiotics as adjuncts to DCDT for patients with PN-SAP or PN-LAAA may be negligible. When taking antibiotics, adverse events such as endodontic flare-up and diarrhea may infrequently occur (all very low certainty) (eTable 6, available online at the end of this article).

Undesirable Effects From Observational Studies

The panel applied the same interpretation of the anticipated adverse effects in settings in which DCDT is not immediately available to this clinical setting (see the undesirable effects section in Question 1) (eTable 4, eTable 5, available online at the end of this article).

Values and Preferences

The same evidence for PVP previously described informed this recommendation (see Question 1, PVP factor; Appendix, Results, available online at the end of this article). In addition, the panel acknowledged that for patients with PN-SAP or PN-LAAA, procedures for DCDT may take 1 hour or more to complete. They hypothesized that implementing these procedures may reduce patients' expectations for receiving antibiotics.

Acceptability

The panel agreed that not prescribing antibiotics as adjuncts to DCDT for this population will probably be acceptable to key stakeholders. They hypothesized that stakeholders would be willing to accept a recommendation for implementing DCDT alone, given the biological mechanism underlying these conditions (oral antibiotics may not reach to the affected tooth owning to the lack of vascular supply, or the antibiotics prescribed empirically may not be effective for the dominant microflora in the infection) and the balance between benefits and harms favoring the nonuse of antibiotics as adjuncts.

Feasibility

The panel judged that not using antibiotics as adjuncts to DCDT would be feasible.

Recommendation

- The expert panel recommends dentists do not prescribe oral systemic antibiotics as an adjunct to DCDT for immunocompetent adults with PN-SAP or PN-LAAA (strong recommendation, very low certainty) (Table).

Remarks

- The use of antibiotics may result in little to no difference in beneficial outcomes (very low certainty) but likely result in a potentially large increase in harm outcomes (moderate certainty), warranting a strong recommendation against their use (second paradigmatic situation from GRADE guidance[34]).

Question 4. For immunocompetent adults with SIP with or without SAP, should we recommend the use of oral systemic antibiotics compared with the nonuse of oral systemic antibiotics as adjuncts to DCDT to improve health outcomes (Appendix, Methods, available online at the end of this article)?

Desirable and Undesirable Effects From Randomized Controlled Trials

We did not identify any studies specific to patients with SIP with or without SAP who have immediate access to DCDT. The panel decided to use the same body of evidence (eTable 6, available online at the end of this article) used for Question 3 to inform this recommendation. The panel rated down the certainty of the evidence owning to serious issues of indirectness due to differing patient populations, resulting in very low certainty.

Undesirable Effects From Observational Studies

The panel used the same body of evidence summarized above (eTable 4, eTable 5, available online at the end of this article) to inform the undesirable effects of antibiotics as adjuncts to DCDT.

Values and Preferences

The panel used the same evidence on PVP previously described (see Question 1, PVP factor; Appendix, Results, available online at the end of this article) to inform this factor. One additional consideration specific to this patient population is that removing the pulp tissue by means of DCDT may alleviate symptoms, and the panel hypothesized that these procedures may reduce patients' expectations for receiving antibiotics.

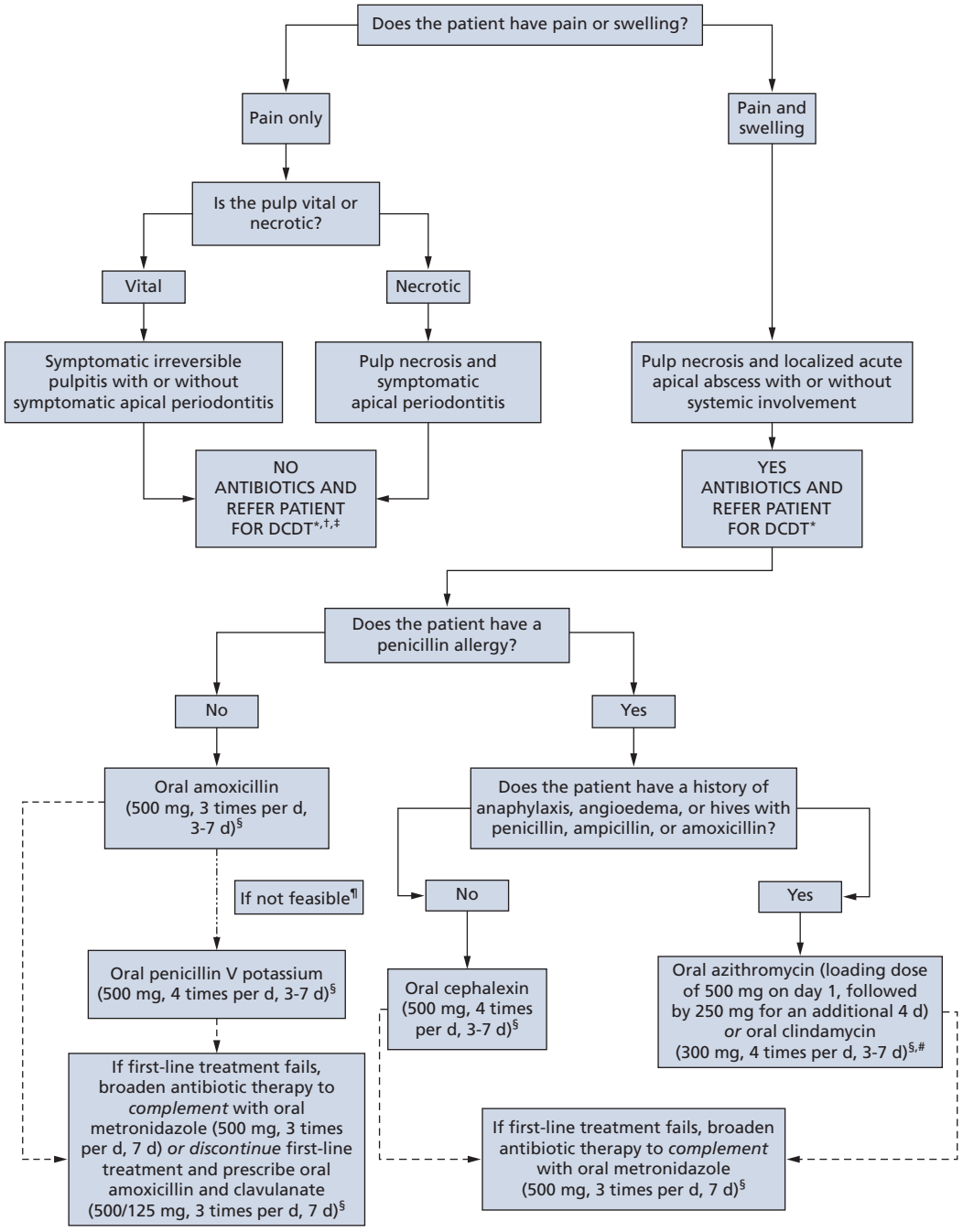

Figure 1. Clinical pathway for treatment of immunocompetent adult patients seeking treatment in a dental setting with a pulpal or periapical condition, in which definitive, conservative dental treatment (DCDT) is not immediately available. * DCDT refers to pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision for drainage abscess. Only clinicians who are authorized or trained to perform the specified treatment should do so. † Adult patients with pulp necrosis and symptomatic apical periodontitis should be instructed to call if their condition deteriorates (progression of disease to a more severe state) or if the referral to receive DCDT within 1-2 d is not possible. ‡ For adult patients with pulp necrosis and symptomatic apical periodontitis, a delayed prescription should be provided if DCDT is *not* immediately available. Dentists should communicate to the patients that if their symptoms worsen and they experience swelling or formation of purulent material, the delayed prescription should be filled. A delayed prescription is defined by the Centers for Disease Control and Prevention as a prescription that is used for patients with conditions that usually resolve without treatment but who can benefit from antibiotics if the conditions do not improve. Source: Sanchez and colleagues.[23] § Clinicians should reevaluate within 3 d (for example, in-person visit or phone call). Dentists should instruct patients to discontinue antibiotics 24 h after their symptoms resolve, irrespective of reevaluation after 3 d. ¶ Although the expert panel recommends both amoxicillin and penicillin as first-line treatments, amoxicillin is preferred over penicillin because it is more effective against various gram-negative anaerobes and is associated with lower incidence of gastrointestinal adverse effects. # Bacterial resistance rates for azithromycin are higher than for other antibiotics, and clindamycin substantially increases the risk of developing *Clostridioides difficile* infection even after a single dose. Owing to concerns about antibiotic resistance, patients who receive azithromycin should be instructed to

Acceptability

The panel agreed that not prescribing antibiotics as adjuncts to DCDT will be highly acceptable to key stakeholders, given that these patients have vital pulp and the risk of experiencing disease progression with systemic involvement is low.

Feasibility

The panel does not anticipate feasibility issues regarding implementing a recommendation against using antibiotics as adjunct to DCDT.

Recommendation

- The expert panel suggests dentists do not prescribe oral systemic antibiotics as an adjunct to DCDT for immunocompetent adults with SIP with or without SAP (conditional recommendation, very low certainty) (Table).

Remarks

- Indirect evidence suggests that the use of antibiotics may have little to no effect in beneficial outcomes (very low certainty) but likely will result in a potentially large increase in harm outcomes (moderate certainty), warranting a conditional recommendation against their use.
- From a physiopathologic perspective, patient populations with SIP with or without SAP, especially those with the option of DCDT, do not require antibiotics, given that the inflamed pulpal tissue associated with this condition is not due to an infection.

Patients with pulp necrosis and acute apical abscess with systemic involvement

The panel provided GPS for the use of antibiotics in patients with systemic involvement (fever, malaise, and so forth) given that the role of antibiotics for this population, irrespective of whether they are provided alone or as adjuncts to DCDT, has been extensively studied and the balance between benefits and harms when systemic involvement is present has been well established.

For adults with PN-AAA with systemic involvement, when considering the use of antibiotics alone or as adjuncts to DCDT, the panel formulated 2 GPS.

GPS

The expert panel suggests dentists prescribe oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d) for immunocompetent adults with PN-LAAA with systemic involvement. In addition, clinicians should provide urgent referral because DCDT should not be delayed. If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer patient for urgent evaluation (Table).

The expert panel suggests dentists perform urgent DCDT in conjunction with prescribing oral amoxicillin (500 mg, 3 times per d, 3-7 d) or oral penicillin V potassium (500 mg, 4 times per d, 3-7 d) for immunocompetent adults with PN-LAAA with systemic involvement. If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer for urgent evaluation (Table).

Summary of the rationale for the type of antibiotic and regimen

To inform the current status of antibiotic prescribing behaviors of dentists, including antibiotic types, doses, and durations, we used a 2018 scoping review.[24] We also included input from stakeholders and expert panelists and data on antibiotic sensitivity[54-58] to determine the most appropriate course of action when first-line treatment fails, guidance to avoid recommending antibiotics

closely monitor their symptoms and call a dentist or primary care provider if their infection worsens while receiving therapy. Similarly, clindamycin has a US Food and Drug Administration black box warning for *Clostridioides difficile* infection, which can be fatal.[26] Patients should be instructed to call their primary care provider if they develop fever, abdominal cramping, or $\geq$ 3 loose bowel movements/d. If the patient currently is taking an antibiotic within the same spectrum as the one indicated, additional antibiotics do not need to be prescribed. If the patient currently is taking an antibiotic outside of the spectrum as the one indicated, the intended antibiotic still can be prescribed, considering potential contraindications. An antibiotic with a similar spectrum of activity to those recommended can be continued if the antibiotic was initiated before the patient sought treatment. As with any antibiotic use, the patients should be informed about symptoms that may indicate lack of antibiotic efficacy and adverse drug events. Sources: Thornhill and colleagues,[25] Leffler and Lamont.[27]

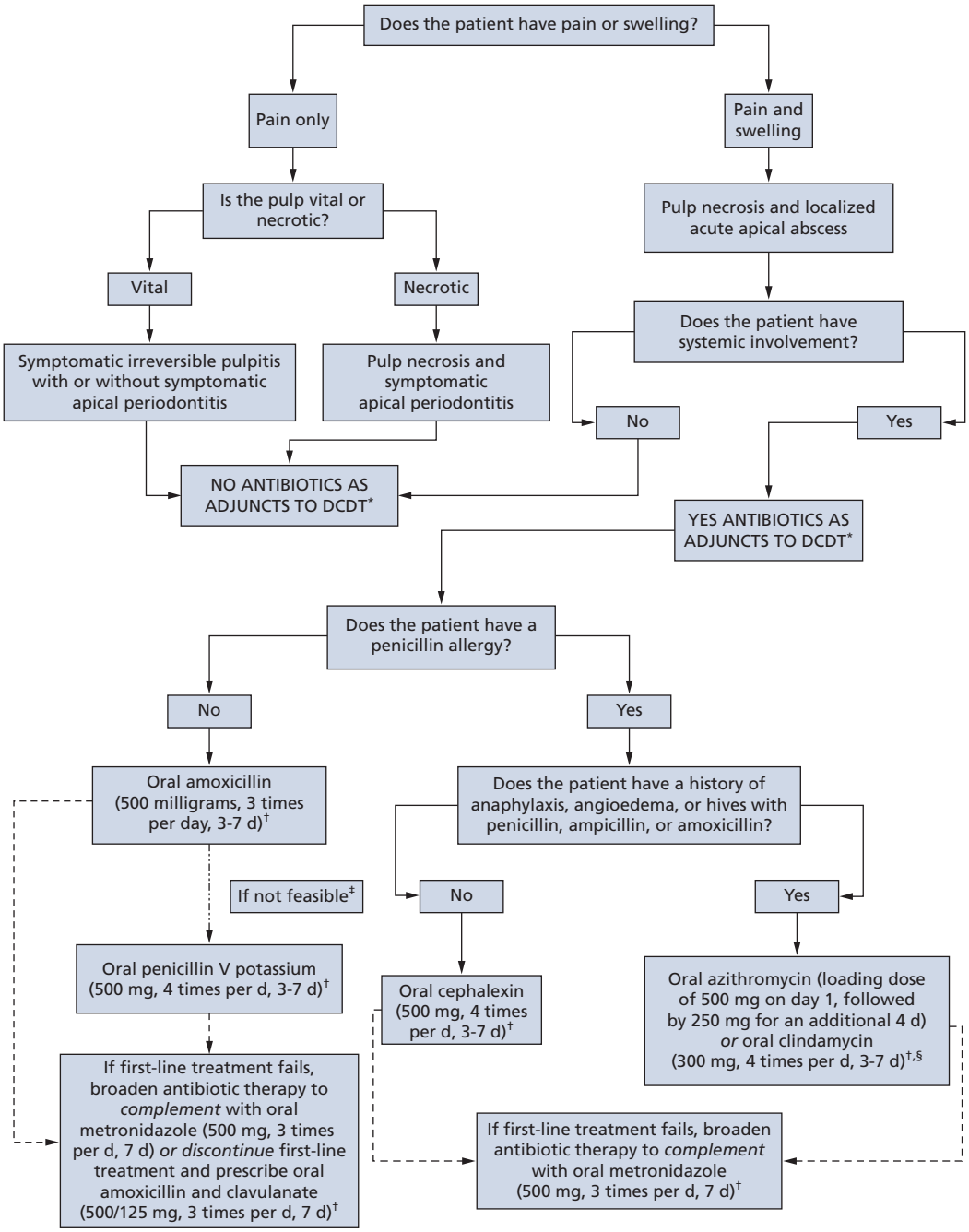

Figure 2. Clinical pathway for treatment of immunocompetent adult patients seeking treatment in a dental setting with a pulpal or periapical condition, in which definitive, conservative dental treatment (DCDT) is immediately available. * DCDT refers to pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision for drainage abscess. Only clinicians who are authorized or trained to perform the specified treatment should do so. † Clinicians should reevaluate within 3 d (for example, in-person visit or phone call). Dentists should instruct patients to discontinue antibiotics 24 h after their symptoms resolve, irrespective of reevaluation after 3 d. ‡ Although the expert panel recommends both amoxicillin and penicillin as first-line treatments, amoxicillin is preferred over penicillin because it is more effective against various gram-negative anaerobes and is associated with lower incidence of gastrointestinal adverse effects. § Bacterial resistance rates for azithromycin are higher than for other antibiotics, and clindamycin substantially increases the risk of developing *Clostridioides difficile* infection even after a single dose. Owing to concerns about antibiotic resistance, patients who receive azithromycin should be instructed to closely monitor their symptoms and call a dentist or primary care provider if their infection worsens while on therapy. Similarly, clindamycin has a US Food and Drug Administration black box warning for *Clostridioides difficile* infection, which can be fatal.[26] Patients should be instructed to call their primary care provider if they develop fever, abdominal cramping, or $\geq$ 3 loose bowel movements/d. If the patient currently is taking an antibiotic within the same spectrum as the one indicated, additional antibiotics do not need to be prescribed. If the patient currently is taking an antibiotic outside of the spectrum as the one indicated, the intended antibiotic still can be prescribed, considering potential contraindications. An antibiotic with a similar

prone to cause severe drug-drug interactions, and guidance to balance the potential efficacy of a selected antibiotic with its potential serious adverse events.

General Remarks

- To facilitate the implementation of these recommendations and GPS in practice, the expert panel integrated them in an algorithm (Figure 1, Figure 2).
- In the case of a reported penicillin allergy, the panel detailed nonpenicillin drug class antibiotics for this patient population (Table).
- Although approximately 10% of the population self-reports having a penicillin allergy, less than 1% of the entire population is truly allergic.[59,60] Clinicians should proceed with nonpenicillin drug class antibiotics until further confirmation of a true penicillin allergy. The panel suggests prescribing oral cephalexin, oral azithromycin, or oral clindamycin.
- Some antibiotics may be less effective or carry a greater risk of harming patients through allergic reactions (penicillin) or CDI (clindamycin).[25,27] Therefore, the list of antibiotics presented in this guideline is ordered balancing desirable and undesirable consequences of the use of each antibiotic.[61]
- The prevention of CDI should be a community priority in addition to a hospital priority.[41] According to a United Kingdom–based study, the incidence of CDI can be reduced through the appropriate use of antibiotics.[62]
- The panel acknowledges that other antibiotics have a reasonable spectrum of activity for the treatment of oral infections, such as moxifloxacin; however, there are US Food and Drug Administration black box warnings (indicating a serious safety hazard) for this antibiotic.[26,63]
- For cases that do not respond promptly to antibiotics, clinicians may consider either complementing first-line treatment with oral metronidazole or discontinuing first-line treatment and prescribing oral amoxicillin and clavulanate to enhance the efficacy against gram-negative anaerobic organisms.
- An antibiotic with a spectrum of activity similar to those recommended in Table can be continued if the antibiotic was initiated before the patient sought treatment. As with any antibiotic use, the patient should be informed about symptoms that may indicate lack of antibiotic efficacy and adverse drug events.
- There is little to no evidence supporting the common belief that a shortened course of antibiotics contributes to antimicrobial resistance.[61,64] Clinicians should reevaluate or follow up with their patient after 3 days to assess if there is resolution of systemic signs and symptoms. If the patient's signs and symptoms begin to resolve, clinicians should instruct the patient to discontinue antibiotics 24 hours after complete resolution, irrespective of reevaluation after 3 days.
- Prescription medications, including antibiotics, should not be saved for later use nor shared with others. The panel emphasizes the importance of patients' discarding antibiotics safely at local disposal centers.[65]
- Estimates for pain outcomes reported in this review may be influenced by the use of analgesics in both intervention and control groups; therefore, when considering the effect of antibiotics on pain experience and intensity, the panel interpreted any improvement in pain as *additional* pain relief attributable to antibiotics.
- Providers often prescribe antibiotics even when they are not appropriate owning to the patient's being in severe pain and expecting antibiotics to relieve this pain. The best available evidence for the management of acute pain can be found in a 2018 overview of 5 systematic reviews.[22] The evidence suggests that nonsteroidal anti-inflammatory drugs (specifically, 400-600 mg ibuprofen plus 1,000 mg acetaminophen) could be effective and less harmful than any opioid-containing medication or medication combination for the temporary relief of dental pain.[22]

DISCUSSION

Studies have suggested that clinicians often prescribe antibiotics for patients with dental pain and intraoral swelling to reduce the uncertainty associated with the "watch and wait" model,

spectrum of activity to those recommended can be continued if the antibiotic was initiated before the patient sought treatment. As with any antibiotic use, the patients should be informed about symptoms that may indicate lack of antibiotic efficacy and adverse drug events. Sources: Thornhill and colleagues,[25] Leffler and Lamont.[27]

barriers in the health system, gaps in knowledge or disagreement with existing guidelines, diagnostic and prognostic uncertainties, patient expectations, or access-to-care issues.[66-70] However, a shift in the paradigm of antibiotic prescribing in dentistry is necessary; the profession is encouraged to move from a "just in case" approach of antibiotic prescribing to a "when absolutely needed" approach.[17]

If there are no signs or symptoms of systemic involvement and if DCDT is immediately available, evidence suggests antibiotics may not provide substantial, additional improvement in pain intensity and experience and probably cause large harms or undesirable effects (for example, serious adverse events, antibiotic resistance, CDI, and high costs). In contrast, if systemic involvement such as fever and malaise are present, good practice indicates that antibiotics should be prescribed in conjunction with DCDT or referral for DCDT. Ultimately, for the management of pain, other strategies such as the use of nonsteroidal anti-inflammatory drugs and acetaminophen (400-600 mg ibuprofen plus 1,000 mg acetaminophen) should be considered.[22]

Patients with the target dental conditions usually refer to pain as their chief symptom. Even though there is no physiopathologic rationale for the use of antibiotics for the management of inflammatory conditions and even the management of pain for patients with a dental infection, patients and clinicians still would be interested in learning the extent to which antibiotics would play any role in offering pain relief. To make sure that these recommendations are informed by a complete set of patient-important outcomes, the panel decided to include pain as 1 of the potential desirable effects of antibiotics.

Comparison with other guidelines

This article is the first guideline on the antibiotic use for the urgent management of immunocompetent patients with pulpal and periapical conditions from the ADA, the first developed by a multidisciplinary panel, and the first intended primarily for general dentists in the United States. Reports from other groups provide similar recommendations to ours; the American Association of Endodontists,[11] Scottish Dental Clinical Effectiveness Programme,[10] Faculty of General Dental Practice,[14] and *Journal of the Canadian Dental Association*[12,13] have provided recommendations against antibiotic use for pulpal and periapical conditions, unless there is systemic involvement. Unlike ours, they omitted guidance on first- and second-line antibiotic regimens, did not use GRADE methodology to assess certainty in the evidence and strength of recommendations, and did not incorporate a robust stakeholder engagement process. Guidelines from other associations have not been formally assessed or endorsed by the ADA.

Although broader and more medical in scope, a guideline from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America[61] also presents a wide range of clinical questions and recommendations related to antibiotic stewardship in inpatient settings. The authors of that guideline provided recommendations for facility-specific recommendations and algorithms for antibiotic prescribing (conditional recommendation, low certainty), shorter duration of antibiotics (strong recommendation, moderate certainty), and stewardship interventions designed to reduce CDI (strong recommendation, moderate certainty), among others.

Implications for research

At the moment, there is a dearth of published evidence on the effect of antibiotic prescribing in outpatient and dental care settings on population-level harms; most published research is based on inpatient medical care settings. Also, national observational studies on the harms of antibiotic use presented in both absolute and relative terms would allow guideline developers to better summarize and use this evidence to make decisions.

Furthermore, evidence informing benefits of antibiotics for the target conditions was limited. High-quality, powered studies, especially those using validated scales for measuring patient-reported outcomes like pain and being careful to provide DCDT to all patients, may provide more trustworthy evidence to inform beneficial outcomes. Also, future studies providing a robust evaluation of antibiotic sensitivity for dental infections, comparative safety and effectiveness of common antibiotic regimens, and optimal antibiotic prescription duration would be useful for decision making.

Finally, an initial study on antibiotic stewardship programming in an *academic* dental setting suggests a 73% decrease in antibiotic prescribing.[7] Guideline and policy developers would benefit from more research on the implementation of guidelines and antibiotic stewardship programs in *community* dental practices to better inform decisions.

Implications for practice

In many cases, some patients with target conditions may seek treatment in dental clinics in which DCDT is not immediately available and may need repeat visits or a referral to a specialist. Other patients may seek treatment in EDs, which may not have easy access to DCDT nor the possibility for further monitoring.[71,72] Clinicians may find that for patients with access-to-care issues, this guideline's recommendations may be difficult to implement. However, additional system-level changes to increase access to oral health care, a task outside of the scope of our guideline, is needed to resolve this disparity.[73]

Patient expectation for antibiotics may also present a substantial barrier for clinicians implementing these recommendations. The ADA is supplementing this clinical practice guideline with additional materials, including an Oral Health Topic[74] and a For the Patient page[75] to provide additional insight into antibiotic stewardship and facilitate shared decision making, respectively (both available at ebd.ada.org). National, state, and local health policies; additional community-level partnerships between dentists, pharmacists, and physicians; and the increased use of electronic health records and clinical decision support systems (with the right training, time, and resources) can also assist in the implementation of our recommendations.[61,66]

CONCLUSIONS

The ADA expert panel suggests prescribing antibiotics for immunocompetent adult patients (patients with an ability to respond to a bacterial challenge) with PN-LAAA in settings in which DCDT is *not* available. This recommendation is specific to situations in which the risk of experiencing systemic involvement is high and a patient may lack immediate access to care. The expert panel suggests *not* prescribing antibiotics for immunocompetent adult patients with SIP with or without SAP, PN-SAP, or PN-LAAA in settings in which DCDT *is* available owning to potentially negligible benefits and likely large harms associated with their use. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2019.08.020.

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APPENDIX

Scope, purpose, target audience

The scope of this guideline is limited to immunocompetent adults. Immunocompetence is broadly defined as the ability of a patient to respond to a bacterial challenge. For practical reasons, clinicians may benefit from specific diagnoses that are not within the scope of this guideline (that is, those applicable to immunocompromised patients). We have adapted a list of conditions that may constitute an immunocompromised patient, although it is possible to have 1 of the below conditions and be able to respond to a bacterial challenge:[21]

- patients with AIDS, which is defined as HIV with a CD4 T cell count below 200 cells per cubic millimeter or HIV with an AIDS-defining opportunistic illness.[e1]
  - AIDS-defining opportunistic infections, as defined by the Centers for Disease Control and Prevention, include[e2]
    - bacterial infections, multiple or recurrent;
    - candidiasis of bronchi, trachea, or lungs;
    - candidiasis of esophagus;
    - cervical cancer, invasive;
    - coccidioidomycosis, disseminated or extrapulmonary;
    - cryptococcosis, extrapulmonary;
    - cryptosporidiosis, chronic intestinal (> 1 month's duration);
    - cytomegalovirus disease (other than liver, spleen, or nodes), onset at age above 1 month;
    - cytomegalovirus retinitis (with loss of vision);
    - encephalopathy attributed to HIV;
    - herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month);
    - histoplasmosis, disseminated or extrapulmonary;
    - isosporiasis, chronic intestinal (> 1 month's duration);
    - Kaposi sarcoma;
    - lymphoma, Burkitt (or equivalent term);
    - lymphoma, immunoblastic (or equivalent term);
    - lymphoma, primary, of brain;
    - *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary;
    - *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary;
    - *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary;
    - *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia;
    - pneumonia, recurrent;
    - progressive multifocal leukoencephalopathy;
    - salmonella septicemia, recurrent;
    - toxoplasmosis of brain, onset at age above 1 month;
    - wasting syndrome attributed to HIV;
- patients with cancer undergoing immunosuppressive chemotherapy with febrile (39° C) neutropenia (absolute neutrophil count < 2,000) OR severe neutropenia irrespective of fever (absolute neutrophil count < 500);
- patients with autoimmune conditions with concomitant use of potent immunosuppressive drugs, such as biologic agents (for example, tumor necrosis factor alpha inhibitors) or steroids (for example, prednisone > 10 milligrams per day). Note, methotrexate, hydroxychloroquine, azathioprine, and other medications with a similar potency should not be considered immunocompromising agents;
- patients with solid organ transplant on immunosuppressants;
- inherited diseases of immunodeficiency (for example, congenital agammaglobulinemia and congenital immunoglobulin A deficiency);
- patients with bone marrow transplant in 1 of the following phases of treatment:
  - pretransplantation period;
  - pre-engraftment period (approximately 0-30 days posttransplantation);
  - postengraftment period (approximately 30-100 days posttransplantation);

- Late posttransplantation period (≥ 100 days posttransplantation) while still on immunosuppressive medications to prevent graft-versus-host disease (typically 36 months posttransplantation).

METHODS

Panel configuration and conflicts of interest

In 2018, the American Dental Association (ADA) Council on Scientific Affairs convened a multidisciplinary panel of subject matter experts from general and public health dentistry, endodontics, oral and maxillofacial surgery, oral medicine, infectious diseases, emergency medicine, pharmacology, and epidemiology. Panel nominees completed financial and intellectual conflict of interest forms that were reviewed by methodologists from the ADA Center for Evidence-Based Dentistry. Conflict of interests were disclosed and updated at the beginning of each panel meeting. When relevant conflicts were identified in relation to a particular recommendation, the panel member was asked to abstain from discussion and not participate in formulating that recommendation. In the first panel meeting in April 2018, we defined the scope, purpose, clinical questions and outcomes, and target audience. In the second panel meeting in December 2018, we formulated recommendations.

Body of evidence and outcomes informing this guideline

A complete list of outcomes for total analgesics used refers to total number of nonsteroidal anti-inflammatory drugs used and total number of rescue analgesics used. A complete list of outcomes for progression of disease to more severe state refers to malaise, trismus, fever, cellulitis, additional dental visit, and additional medical visit.

A complete list of outcomes for community-associated *Clostridioides difficile* infection (CDI) includes community-associated CDI, community-associated CDI related to a dental prescription for antibiotics, and mortality due to community-associated CDI.

A complete list of outcomes for antibiotic-resistant infections includes antibiotic-resistant infections and mortality due to antibiotic-resistant infections.

A complete list of outcomes for costs includes community-associated CDI related costs, community-associated CDI related costs associated with a dental prescription for antibiotics, antibiotic-resistant infections related costs, antibiotic-resistant infections related costs associated with a dental prescriptions for antibiotics, and cost-effectiveness of antibiotics to treat symptomatic irreversible pulpitis with or without symptomatic apical periodontitis (SIP: Symptomatic irreversible pulpitis (SAP), pulp necrosis and SAP, or pulp necrosis and localized acute apical abscess.

A complete list of outcomes of hospitalizations includes admission to hospital due to community-associated CDI, admission to hospital due to community-associated CDI related to a dental prescription for antibiotics, admission to hospital due to antibiotic-resistant infection, admission to hospital due to antibiotic-resistant infection associated with a dental prescription for antibiotics, length of hospital stay due to community-associated CDI, length of hospital stay due to community-associated CDI related to a dental prescription for antibiotics, length of hospital stay due to antibiotic-resistant infection, and length of hospital stay due to antibiotic-resistant infections associated with a dental prescription for antibiotics.

A complete list of outcomes of anaphylaxis includes allergic reaction to antibiotics, allergic reaction to antibiotics associated with a dental prescription, anaphylaxis due to antibiotics, anaphylaxis due to antibiotics associated with a dental prescription, fatal anaphylaxis due to antibiotics, and fatal anaphylaxis due to antibiotics associated with a dental prescription. The panel ranked allergic reaction due to antibiotics, anaphylaxis due to antibiotics, and fatal anaphylaxis due to antibiotics as critical outcomes.

The panel defined and ranked (critical, important, not important for decision making) outcomes *a priori*. The panel ranked pain and intraoral swelling as a critical outcomes. The panel ranked total number of nonsteroidal anti-inflammatory drugs used and total number of rescue analgesics used, malaise, trismus, fever, cellulitis, additional dental visit, and additional medical visit, allergic reaction, endodontic flare-up, diarrhea, CDI, and repeat procedure as important outcomes. The panel ranked community-associated CDI and mortality due to community-associated CDI as critical outcomes and community-associated CDI related to a dental prescription for antibiotics as an

important outcome. The panel ranked mortality due to antibiotic-resistant infections as a critical outcome and antibiotic-resistant infections as an important outcome.

The panel ranked community-associated CDI related costs, antibiotic-resistant infections related costs, and cost-effectiveness of antibiotics to treat symptomatic irreversible pulpitis with or without SAP, pulp necrosis and SAP, or pulp necrosis and localized acute apical abscess as critical outcomes. The panel ranked community-associated CDI related costs associated with a dental prescription for antibiotics and antibiotic-resistant infection related costs associated with a dental prescriptions for antibiotics as important outcomes. The panel ranked all hospitalization and anaphylaxis outcomes as important.

Anticipating limited evidence to inform harm outcomes from randomized controlled trials, the panel decided to include evidence from randomized controlled trials and observational studies to inform this guideline, in that order of priority.

Retrieving the evidence

For beneficial outcomes, the informationist (K.K.O.), methodologists (M.P.T., L.P., O.U., A.C.L.), and the expert panel updated a 2014 and 2016 Cochrane systematic review.[31,32] The published search strategy for the 2016 systematic review[31] was adapted for inclusivity via combining the antibiotics search string used in the 2014 systematic review[32] with a new, simple pulpectomy and dental pulp concept. Other outcomes required additional evidence, and considering the scope of the Cochrane reviews, we conducted a search for systematic reviews on antibiotic resistance to identify primary studies related to these outcomes. All searches were conducted in MEDLINE via PubMed, Embase via embase.com, the Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature in May and early June 2018. In addition, we searched the gray literature and national health care agency Web sites and databases and contacted the Centers for Diseases Control and Prevention to retrieve evidence that may not be available from the electronic databases cited above.[20] Using similar methods, we also searched for systematic reviews and primary studies on patients' values and preferences as well as provider acceptability and feasibility related to the use of antibiotics for the target conditions in dentistry, and if not available, from its use in medicine.

Pairs of reviewers (E.K., L.P., M.P.T., O.U., and an author of the related systematic review) independently screened titles and abstracts and full-text articles and determined final eligibility. Reviewers (L.P., M.P.T., O.U.) then independently and in duplicate extracted data from included studies. We prioritized data specific to outpatient dental settings over inpatient medical settings. When dealing with population-level harm outcomes accounting for all prescriptions in the health system, we adjusted our estimates by 10% to illustrate the impact of antibiotic prescription rate from dentistry in regard to the total outpatient antibiotic prescriptions in the United States in 2011.[43]

Evidence synthesis and measures of association

Using a random-effects model, we pooled data and calculated relative risk and 95% confidence intervals for dichotomous data and mean difference and 95% confidence intervals for continuous data. When meta-analysis was not possible, we reported data at an individual-study level. When comparative effect estimations (for example, measures of association) were not possible to obtain, we calculated frequency estimates.

Certainty in the evidence

We assessed the certainty in the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[35] The certainty in the evidence represents the panel's confidence that the treatment effects are appropriate to inform the recommendations (eTable 2).

Moving from evidence to decisions

The expert panel formulated recommendations using the GRADE evidence-to-decision framework, facilitated by a methodologist (M.P.T.) during the second panel meeting. The evidence-to-decision framework allows for a structured display of the pros and cons of implementing an intervention, allowing for guided discussion when formulating recommendations.[36] This framework considers 8 factors: importance of the health care problem, magnitude of desirable effects, magnitude of undesirable effects, certainty in the evidence, patient's values and preferences, balance of desirable versus undesirable effects, acceptability, and feasibility. Once judgments were made for each factor, the expert panel decided the direction and strength of the recommendation (Table).[33-35]

Stakeholder and public engagement

We contacted internal and external stakeholders and invited them to participate in the development of the guideline. Using an electronic survey, we solicited feedback on 2 occasions. First, we requested input regarding the initial draft of the guideline's scope, purpose, clinical questions, outcomes, and target audience; second, we requested input on the final draft of the recommendations and GPS. We also invited the general public to provide input on the recommendations and GPS through social media and the ADA Center for EBD's Web site (ebd.ada.org). Methodologists classified and prioritized all comments for discussion and resolution with the panel.

Updating process

The ADA Center for EBD continuously monitors relevant literature. We will update this guideline every 5 years or when new evidence may affect the direction and strength of the recommendations. Any updated versions of this guideline will be available at ebd.ada.org.

RESULTS

Values and preferences

From the patient perspective, antibiotic use is often considered a noninvasive, inexpensive treatment option. Though this is often true, patients may be unaware of the magnitude of harms associated with antibiotic use.[e3,e4] On the basis of results from a focus group,[e3,e5] participants did not believe that antibiotic resistance affected them as individuals[e5] and did not know that methicillin-resistant *Staphylococcus aureus* could be community-acquired.[e3] There was general consensus among participants that the other patients' and general practitioners' indiscriminate use and prescription of antibiotics were to blame for antibiotic resistance; they were less aware of the impact of *their own* antibiotic use. Finally, these participants were confident that science would resolve any issues related to antibiotic resistance.[e3]

Clinicians often encounter patients with expectations for receiving antibiotics. This is a common reason clinicians deviate from clinical practice guidelines recommending against antibiotic use.[e6,e7] During the panel meeting, experts discussed that antibiotics may be considered an appropriate treatment choice owing to access-to-care issues affecting many communities. For example, if a patient is visibly in pain, upset, and unable to receive definitive, conservative dental treatment within a short time, a clinician may consider antibiotics as an option, regardless of the potential negligible benefits and likely large harms.

A report from the United Kingdom proposes that increasing public awareness of antibiotic resistance could decrease patient expectations for antibiotics.[e8] As many professional dental and medical organizations and federal agencies continue investing in antibiotic stewardship, evidence suggests that health care providers should also consider shared decision making as a way to incorporate their patients' values into treatment planning.[e9]

e1. US Department of Health and Human Services. Glossary of HIV/AIDS-related terms. Available at: https://aidsinfo.nih.gov/contentfiles/glossaryhivrelatedterms_english.pdf. Accessed May 25, 2019.

e2. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection: United States, 2014. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm. Accessed May 25, 2019.

e3. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. *Fam Pract*. 2008;25(5):341-348.

e4. Wagstaff B. Impact of antibiotic restrictions: the patient's perspective. *Clin Microbiol Infect*. 2006;12(suppl 5):10-15.

e5. Ancillotti M, Eriksson S, Veldwijk J, Nihlén Fahlquist J, Andersson DI, Godskesen T. Public awareness and individual responsibility needed for judicious use of antibiotics: a qualitative study of public beliefs and perceptions. *BMC Public Health*. 2018;18(1):1153.

e6. Dempsey PP, Businger AC, Whaley LE, Gagne JJ, Linder JA. Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. *BMC Fam Pract*. 2014;15:194.

e7. Lopez-Vazquez P, Vazquez-Lago JM, Figueiras A. Misprescription of antibiotics in primary care: a critical systematic review of its determinants. *J Eval Clin Pract*. 2012;18(2):473-484.

e8. Cope AL, Wood F, Francis NA, Chestnutt IG. General dental practitioners' perceptions of antimicrobial use and resistance: a qualitative interview study. *Br Dent J*. 2014;217(5):E9.

e9. Centers for Disease Control and Prevention. Antibiotic prescribing and use in doctor's offices. Available at: https://www.cdc.gov/antibiotic-use/community/for-hcp/index.html. Accessed May 25, 2019.

eTable 1. Pulpal and periapical target conditions and their clinical signs and symptoms.

TARGET CONDITION	CHARACTERISTICS OF CLINICAL SIGNS AND SYMPTOMS
Symptomatic Irreversible Pulpitis	Spontaneous pain that may linger with thermal changes owing to vital inflamed pulp that is incapable of healing
Symptomatic Apical Periodontitis	Pain with mastication, percussion, or palpation, with or without evidence of radiographic periapical pathosis, and without swelling
Pulp Necrosis and Symptomatic Apical Periodontitis	Nonvital pulp, with pain with mastication, percussion, or palpation, with or without evidence of radiographic periapical pathosis, and without swelling
Pulp Necrosis and Localized Acute Apical Abscess	Nonvital pulp, with spontaneous pain with or without mastication, percussion, or palpation; with formation of purulent material and localized swelling; and without evidence of fascial space or local lymph node involvement, fever, or malaise
Acute Apical Abscess with Systemic Involvement	Necrotic pulp with spontaneous pain, with or without mastication, percussion, or palpation, with formation of purulent material, swelling, evidence of fascial space or local lymph node involvement, fever, or malaise

eTable 2. Definitions of certainty in the evidence and strength of recommendations and implications for patients, clinicians, and policy makers.*

CATEGORY	DEFINITION
Definition of Certainty (Quality) in the Evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Definition of Strong and Conditional Recommendations and Implications for Users	
Implications for patients	
Strong recommendations	Most patients in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
Conditional recommendations	Most patients in this situation would want the suggested course of action, but many would not.
Implications for clinicians	
Strong recommendations	Most patients should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
Conditional recommendations	Recognize that different choices will be appropriate for individual patients and that the clinician must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping patients make decisions consistent with their values and preferences.
Implications for policy makers	
Strong recommendations	The recommendation can be adapted as policy in most situations.
Conditional recommendations	Policy making will require substantial debate and involvement of various stakeholders.

* Sources: Andrews and colleagues,[33,34] Guyatt and colleagues.[35]

eTable 3. Relative and absolute desirable and undesirable effects (95% confidence interval) from randomized controlled trials and certainty in the evidence for systemic antibiotics compared with no systemic antibiotics for symptomatic irreversible pulpitis with or without symptomatic apical periodontitis in immunocompetent adults when definitive, conservative dental treatment is not available.

OUTCOMES*	PARTICIPANTS (STUDIES), NO.	CERTAINTY OF THE EVIDENCE ACCORDING TO GRADE†	RR‡ (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECTS	
				Risk With No Systemic Antibiotic§ (No. of People)	Risk Difference With Systemic Antibiotics (Range)
Pain Intensity at 24 H	40 (1 RCT¶,#)	Low**	Not applicable	Mean pain intensity at 24 h, 1.35	MD,†† 0.35 higher (0.21 lower - 0.91 higher)
Pain Experience at 24 H	40 (1 RCT#)	Low‡‡	RR, 1.20, (0.68 to 2.11)§§	500 per 1,000	100 more per 1,000 (160 fewer - 555 more)§§
Pain Intensity at 48 H	40 (1 RCT#)	Low**	Not applicable	Mean pain intensity at 48 h, 1.35	MD, 0.2 higher (0.35 lower - 0.75 higher)
Pain Experience at 48 H	40 (1 RCT#)	Low‡‡	RR, 1.22 (0.65 to 2.29)§§	450 per 1,000	99 more per 1,000 (158 fewer - 581 more)§§
Pain Intensity at 72 H	40 (1 RCT#)	Low**	Not applicable	Mean pain intensity at 72 h, 1.35	MD, 0 (0.5 lower - 0.5 higher)
Pain Experience at 72 H	40 (1 RCT#)	Low‡‡	RR, 1.00 (0.47 to 2.14)§§	400 per 1,000	0 fewer per 1,000 (212 fewer - 456 more)§§
Pain Intensity at 7 D	40 (1 RCT#)	Low**	Not applicable	Mean pain intensity at 7 d, 1.35	MD, 0.15 lower (0.75 lower - 0.45 higher)
Pain Experience at 7 D	40 (1 RCT#)	Low‡‡	RR, 0.89 (0.43 to 1.83)§§	450 per 1,000	49 fewer per 1,000 (257 fewer - 374 more)§§
Total Number of Nonsteroidal Anti-inflammatory Drugs (Tablets) Used	40 (1 RCT#)	Low**	Not applicable	Mean total number of nonsteroidal anti-inflammatory drugs (tablets) used, 9.6	MD, 0.4 lower (4.23 lower - 3.43 higher)
Total Number of Acetaminophen with Codeine (Tablets) Used	40 (1 RCT#)	Low¶¶	Not applicable	Mean total number of acetaminophen with codeine (tablets) used, 4.45	MD 2.45 higher (1.23 lower - 6.13 higher)

* Selection criteria: patient or population: immunocompetent adults with symptomatic irreversible pulpitis with or without symptomatic apical periodontitis; setting: dental settings in which definitive, conservative dental treatment is not immediately available; intervention: systemic antibiotics; comparison: no systemic antibiotic. No studies meeting the selection criteria reported data on malaise, trismus, fever, cellulitis, additional dental visit, additional medical visit, allergic reaction, endodontic flare-up, diarrhea, *Clostridioides difficile* infection, or repeat procedure for this population. Nagle and colleagues[40] did report intraoral swelling, but owing to symptom inconsistencies with a clinical diagnosis of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, the guideline authors did not extract this data. † GRADE: Grading of Recommendations Assessment, Development and Evaluation. GRADE Working Group grades of evidence: high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. ‡ RR: Risk ratio. § For dichotomous outcomes, the guideline authors calculated absolute treatment effects via using the control group's baseline risk as the assumed control intervention risk. ¶ RCT: Randomized controlled trial. # Nagle and colleagues.[40] ** Serious issues of imprecision due to small sample size. †† MD: Mean difference. ‡‡ There were serious issues of imprecision due to small sample size, and the confidence interval suggests a large benefit and a large harm. §§ For Nagle and colleagues,[40] the data for the outcome of pain were dichotomized (visual analog scale from 0-3) as follows: "no pain" and "mild pain" were coded as "no pain," and "moderate pain" and "severe pain" were coded as "pain." ¶¶ There were serious issues of imprecision due to small sample size, and the confidence interval suggests both a small benefit and a large harm.

eTable 4. Magnitude of undesirable effects related to use of any systemic antibiotic by any patient in any setting from observational studies and certainty in the evidence.

OUTCOME*	STUDIES, NO.	CERTAINTY OF THE EVIDENCE ACCORDING TO GRADE†	IMPACT
Community-Associated *Clostridioides difficile* Infections	2 observational studies‡,§	Moderate¶	Of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 6,400 probably were exposed to antibiotics.#
Community-Associated *C. difficile* Infection Related to a Dental Prescription for Antibiotics	3 observational studies‡,§,**	Very low††	Of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 640 may have been exposed to antibiotics received from a dentist.#,‡‡,§§
Mortality Due to Community-Associated *C. difficile* Infections	2 observational studies‡,§	Moderate¶	Of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 80 people probably died due to exposure to antibiotics.#
Antibiotic-Resistant Infections	1 observational study¶¶	Low	At least 2 million people may experience an antibiotic-resistant infection annually in the United States.
Mortality Due to Antibiotic-Resistant Infections	1 observational study¶¶	Low	Annually, there may have been approximately 23,000 deaths due to antibiotic-resistant infections.
Community-Associated *C. difficile* Infection Related Costs	2 observational studies‡,##	Moderate¶	In 2011, the mean community-associated *C. difficile*–attributable cost was likely $3 billion.
Community-Associated *C. difficile* Infection Costs Associated With a Dental Prescription for Antibiotics	2 observational studies‡,**	Very low††	The guideline authors approximated that in 2011 $300 million may have been related to community-associated *C. difficile* infections that were associated with a dental prescription for antibiotics.‡‡,§§,***
Antibiotic-Resistant Infection Related Costs	1 observational study¶¶	Low	In 2008, antibiotic resistance may have caused $20 billion in direct costs with an additional $35 billion associated with productivity losses.
Antibiotic-Resistant Infection Related Costs Associated With a Dental Prescription for Antibiotics	2 observational studies**,¶¶	Very low††	The guideline authors approximate that $2 billion in direct costs with an additional $3.5 billion associated with productivity losses may have been related to antibiotic resistance associated with a dental prescription for antibiotics.‡‡,§§,***
Admission to Hospital Due to Community-Associated *C. difficile* Infection	2 observational studies‡,§	Moderate¶	Of 10,000 people with a community-associated *C. difficile* infection, 1,270 patients probably listed community-associated *C. difficile* infection as the primary reason for admission to the hospital.
Admission to Hospital Due to Antibiotic-Resistant Infection	1 observational study†††	Low	In 2006, infection-related hospitalizations associated with antibiotic-resistant infections may have accounted for 2.4% of all infection-related hospitalizations.
Admission to Hospital Due to Antibiotic-Resistant Infection Associated With a Dental Prescription for Antibiotics	2 observational studies**,†††	Very low††	The guideline authors approximated that in 2006, 0.24% of infection-related hospitalizations due to antibiotic-resistant infections may have been associated with a dental prescription for antibiotics.‡‡,§§,***
Length of Hospital Stay Due to Community-Associated *C. difficile* Infection	1 observational study##	Low	The average community-associated *C. difficile*–attributable length of stay due to community-associated *C. difficile* infection may be 5.7 d (range, 2.1-33.4).
Length of Hospital Stay Due to Antibiotic-Resistant Infections	1 observational study‡‡‡	Low	In 2014, the average (standard deviation) length of hospital stay due to bacterial infections and infections associated with multidrug-resistant organisms (that is, methicillin-resistant *Staphylococcus aureus* and other multidrug-resistant organisms) may have ranged from 9.45 (11.81) d to 9.47 (11.59) d.
Anaphylaxis Due to Antibiotics	1 observational study§§§	Low	Of 10,000 hospitalizations from 1995 through 2013, approximately 46 patients may have reported anaphylaxis due to a penicillin drug class; 2 patients may have reported anaphylaxis due to amoxicillin; 6 patients may have reported anaphylaxis due to a cephalosporin drug class#; and 1 patient may have reported anaphylaxis due to cephalexin.#
Anaphylaxis Due to Antibiotics Associated with a Dental Prescription	2 observational studies**,§§§	Very low††	Of 100,000 hospitalizations from 1995 through 2013, approximately 46 patients may have reported anaphylaxis due to a penicillin drug class and received the antibiotic from a dentist; 2 patients may have reported anaphylaxis due to amoxicillin and received the antibiotic from a dentist; 6 patients may have reported anaphylaxis due to a cephalosporin drug class and received the antibiotic from a dentist; and 1 patient may have reported anaphylaxis due to cephalexin and received the antibiotic from a dentist.#,‡‡,§§

* Selection criteria: patient or population: any person of any age seeking treatment in any dental setting in the United States; setting: any dental setting in the United States; exposure: any systemic antibiotics; nonexposure: no systemic antibiotic. No studies meeting the selection criteria reported data on mortality due to community-associated *Clostridioides difficile* infections related to a dental prescription for antibiotics; mortality due to antibiotic-resistant infections associated with a dental prescription for antibiotics; cost-effectiveness of antibiotics to treat symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and symptomatic apical periodontitis, or pulp necrosis and localized acute apical abscess; admission to hospital due to community-associated *C. difficile* infections related to a dental prescription for antibiotics; length of hospital stay due to community-associated *C. difficile* infection related to a dental prescription for antibiotics; length of hospital stay due to antibiotic-resistant infections associated with a dental prescription for antibiotics; allergic reaction due to antibiotics; allergic reaction due to antibiotics associated with a dental prescription; fatal anaphylaxis due to antibiotics; or fatal anaphylaxis due to antibiotics associated with a dental prescriptions. † GRADE: Grading of Recommendations Assessment, Development and Evaluation. GRADE Working Group grades of evidence: high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. ‡ Considerations for Lessa and colleagues[41]: the case definition of *C. difficile* infection relying only on positive test results for *C. difficile* toxin or molecular assay from unformed samples sent to laboratories may lead to an underestimation of the true burden (that is, partially formed samples being untested); there is the possibility for an underestimation of "both recurrence and mortality, given that [they] assessed only first recurrences and deaths that were documented in the medical record"; there is a potential overdiagnosis or an overestimation of the burden of *C. difficile* infection owing to diagnostic tests being highly sensitive (that is, a poor distinction between colonization and the disease); The authors estimated the recurrence of and mortality due to *C. difficile* infection via using a random sample of cases that may or may not be representative of the US rates. § Considerations for Chitnis and colleagues[42]: there are potential issues of generalizability to the US population given that patients included in the analysis with community-associated *C. difficile* infection were more likely to be white and female; only a convenience sample of stools were sent for definitive testing (40%); although antibiotic use within 12 weeks was adjudicated on the basis of a telephone interview (self-reported) and medical records, it is unclear as to how many cases were confirmed using both methods; hospitalization in which *C. difficile* infection was the primary reason for admission was ascertained through medical records. ¶ Upgraded due to a large effect on the basis of observational studies without important risk of bias or other limitations. # This is likely an overestimation of the effect of dental prescriptions for antibiotics because the provided information and data did not differentiate between inpatient and outpatient antibiotic prescriptions. The guideline authors assume that prescribing for dental conditions rarely occurs in inpatient settings. ** Considerations for Hicks and colleagues[43]: dentistry accounts for 10% of the total outpatient antibiotic prescriptions in the United States; the magnitude of antibiotic prescriptions may not necessarily represent the magnitude of antibiotic consumption by patients; there is possible underestimation owing to the total number of prescriptions from other nondental professionals (for example, emergency medicine services) for any dental condition not being included in the estimate; estimates related to antibiotic prescribing practices reported by Hicks and colleagues[43] correspond to that of general dentists and dental specialties combined. †† Downgraded owing to serious issues of indirectness related to estimates being extrapolated to illustrate the burden in a dental setting. ‡‡ Data were adjusted considering that dentistry accounts for 10% of total outpatient antibiotic prescriptions in the United States. §§ The presented estimate assumes that dental prescriptions for any antibiotic has the same potential of inducing antibiotic resistance as nondental related prescriptions. ¶¶ Considerations for Centers for Disease Control and Prevention[44]: no reports containing methods or results are linked to this report; estimates used from this report are likely an underestimation of the true burden of antibiotic resistance related outcomes; the magnitude of antibiotic resistance related outcomes may not necessarily represent the magnitude of antibiotics prescribed for and consumed by patients. ## Considerations for Zhang and colleagues[45]: all included studies in the review reported direct medical costs from a hospital perspective; indirect costs to patients and society and costs of additional care after hospital discharge have not been captured (for example, productivity loss due to work day losses and costs in long-term care facilities). Approximately 9% of patients with *C. difficile* infections were discharged to a long-term care facility for an average of 24 d of after-care, which would result in an additional $141 million burden on the health care system and society due to long-term care facility transfers; primary *C. difficile* infections were not separated for the estimation of recurrent *C. difficile* infection costs; there was discrepancy in case definitions in cost studies versus surveillance and epidemiological studies (for example, community- versus health care–associated *C. difficile* infections); the total costs of *C. difficile* infection in the United States may be higher than the reported estimate. *** This is likely an overestimation of the effect of dental prescriptions for antibiotics owing to the primary study not measuring or reporting antibiotic exposure. ††† Considerations for Mainous and colleagues[46]: the methods did not allow the guideline authors to determine whether the infection arose in the hospital or the patients were colonized or infected before admission; *International Classification of Diseases*, Ninth Revision, Clinical Modification diagnosis codes were used instead of laboratory results on bacterial cultures; "Greater awareness of drug resistance among hospital coding departments may have prompted more attention to adding these codes to discharge records of patients who were relatively healthy and discharged without incident." ‡‡‡ Considerations for Johnston and colleagues[47]: *International Classification of Diseases*, Ninth Revision, Clinical Modification diagnosis codes were used instead of laboratory results on bacterial cultures; the authors were unable to distinguish between hospital-acquired and community-acquired infections; 10% of the eligible population was excluded due to missing data. §§§ Considerations for Dhopeshwarkar and colleagues[48]: the estimates presented in this study only included penicillin and cephalosporin drug classes and amoxicillin and cephalexin drugs and did not include other individual drugs commonly prescribed by dentists such as clindamycin. Considerations for: Durkin and colleagues:[6] there may be issues of generalizability as only patients from 2 Boston-area hospitals were included in this analysis, which may not be representative of inpatient populations admitted to other US hospitals; there was a potential overestimate of the occurrence of anaphylaxis owing to reported cases not being confirmed by tryptase tests; there was possible underestimation owing to exclusion of codes listed in electronic health records not directly linking to anaphylaxis; there was uncertainty surrounding whether the estimates of the reported or observed cases of anaphylaxis resulted in death.

eTable 5. Calculations of the magnitude of undesirable effects related to use of any systemic antibiotic by any patient in any setting.

OUTCOME*	STUDIES, NO.	CERTAINTY OF THE EVIDENCE ACCORDING TO GRADE†	CALCULATION OF IMPACT
Community-Associated *Clostridioides difficile* Infections	2 observational studies‡,§	Moderate¶	Of the estimated cases of community-associated *C. difficile* infections, approximately 64% were exposed to antibiotics in 2011. This represents 102,409 cases of 159,700 total *C. difficile* infections (95% CI,# 85,056 to 119,040).**
Community-Associated *C. difficile* Infection Related to a Dental Prescription for Antibiotics	3 observational studies‡,§,††	Very low‡‡	The guideline authors approximated that 6.4% of people with community-associated *C. difficile* infections who were exposed to antibiotics received the prescription from a dentist. This represents 10,221 cases of 159,700 total *C. difficile* infections in 2011 (95% CI, 8,506 to 11,904).**,§§,¶¶
Mortality Due to Community-Associated *C. difficile* Infections	2 observational studies‡,§	Moderate¶	In 2011, approximately 2,000 of 159,700 people infected with community-associated *C. difficile* infection died within 30 d of diagnosis (95% CI, 1,200 to 2,800). Of the estimated cases of community-associated *C. difficile* infection, approximately 64% were exposed to antibiotics, and 1,280 people died due to community-associated C. difficile infection related to exposure to antibiotics (95% CI, 768 to 1,792). This represents a 0.8% mortality rate due to community-associated *C. difficile* infection related to exposure to antibiotics.**
Antibiotic-Resistant Infections	1 observational study##	Low	Estimate taken directly from report.
Mortality Due to Antibiotic-Resistant Infections	1 observational study##	Low	Estimate taken directly from report.
Community-Associated *C. difficile* Infection Related Costs	2 observational studies‡,***	Moderate¶	The estimated cost due to community-associated *C. difficile* infection in 2015, as reported by Zhang and colleagues,[45] was $20,085. The estimated cases of community-associated *C. difficile* infection in 2011, as reported by Lessa and colleagues,[41] was 159,700 cases. The US Department of Labor[49] inflation calculator was used to convert the value of a 2015 US dollar to the value of a 2011 US dollar, which equates to $19,163.40. $19,163.40 x 159,700 cases of *C. difficile* infection in 2011 = $3,060,394,980.
Community-Associated *C. difficile* Infection Costs Associated with a Dental Prescription for Antibiotics	2 observational studies‡,††	Very low‡‡	The total cost due to community-associated *C. difficile* infections was adjusted by 10%.§§,¶¶,†††
Antibiotic-Resistant infection Related Costs	1 observational study##	Low	Estimate taken directly from report.
Antibiotic-Resistant Infection Related Costs Associated with a Dental Prescription for Antibiotics	2 observational studies††,##	Very low‡‡	The total cost related to antibiotic-resistance infections was adjusted by 10%.§§,¶¶,†††
Admission to Hospital Due to Community-Associated *C. difficile* Infection	2 observational studies‡,§	Moderate¶	Of the estimated cases of community-associated *C. difficile* infections in 2011, approximately 12.7% of the patients were admitted to the hospital owing to community-associated *C. difficile* infections being the primary reason for admission. This represents 20,287 (95% CI, 16,878 to 23,622) of 159,700 total cases with community-associated *C. difficile* infections.
Admission to Hospital Due to Antibiotic-Resistant Infection	1 observational study‡‡‡	Low	Estimate taken directly from report.
Admission to Hospital Due to Antibiotic-Resistant Infection Associated with a Dental Prescription for Antibiotics	1 observational study‡‡‡	Very low‡‡	Admissions to the hospital due to antibiotic-resistant infections was adjusted by 10%.§§,¶¶,†††
Length of Hospital Stay Due to Community-Associated *C. difficile* Infection	1 observational study***	Low	Estimate taken directly from report.
Length of Hospital Stay Due to Antibiotic-Resistant Infections	1 observational study§§§	Low	Estimate taken directly from report.
Anaphylaxis Due to Antibiotics	1 observational study¶¶¶	Low	Estimates taken directly from report.**
Anaphylaxis Due to Antibiotics Associated with a Dental Prescription	2 observational studies††,¶¶¶	Very low‡‡	Reported anaphylaxis due to antibiotics occurrences was adjusted by 10%.**,§§,¶¶

* Selection criteria: patient or population: any person of any age seeking treatment in any dental setting in the United States; setting: any dental setting in the United States; exposure: any systemic antibiotics; nonexposure: no systemic antibiotic. No studies meeting the selection criteria reported data on mortality due to community-associated *Clostridioides difficile* infections related to a dental prescription for antibiotics, length of hospital stay due to community-associated *C. difficile* infection related to a dental prescription for antibiotics, length of hospital stay due to antibiotic-resistant infections associated with a dental prescription for antibiotics, allergic reaction due to antibiotics, allergic reaction due to antibiotics associated with a dental prescription, fatal anaphylaxis due to antibiotics, or fatal anaphylaxis due to antibiotics associated with a dental prescriptions. † GRADE: Grading of Recommendations Assessment, Development and Evaluation. GRADE Working Group grades of evidence: high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. ‡ Considerations for Lessa and colleagues[41]: the case definition of *C. difficile* infection relying only on positive test results for *C. difficile* toxin or molecular assay from unformed samples sent to laboratories may lead to an underestimation of the true burden (that is, partially formed samples being untested); there is the possibility for an underestimation of "both recurrence and mortality, given that [they] assessed only first recurrences and deaths that were documented in the medical record"; there is a potential over-diagnosis or an overestimation of the burden of *C. difficile* infection owing to diagnostic tests being highly sensitive (that is, a poor distinction between colonization and the disease); the authors estimated the recurrence of and mortality due to *C. difficile* infection via using a random sample of cases that may or may not be representative of the US rates. § Considerations for Chitnis and colleagues[42]: there are potential issues of generalizability to the US population given that patients included in the analysis with community-associated *C. difficile* infection were more likely to be white and female; only a convenience sample of stools were sent for definitive testing (40%); although antibiotic use within 12 weeks was adjudicated on the basis of a telephone interview (self-reported) and medical records, it is unclear as to how many cases were confirmed using both methods; hospitalization in which *C. difficile* infection was the primary reason for admission was ascertained through medical records. ¶ Upgraded due to a large effect based on observational studies without important risk of bias or other limitations. # CI: Confidence interval. ** This is likely an overestimation of the effect of dental prescriptions for antibiotics because the provided information and data did not differentiate between inpatient and outpatient antibiotic prescriptions. The guideline authors assume that prescribing for dental conditions rarely occurs in inpatient settings. †† Considerations for Hicks and colleagues[43]: dentistry accounts for 10% of the total outpatient antibiotic prescriptions in the United States; the magnitude of antibiotic prescriptions may not necessarily represent the magnitude of antibiotic consumption by patients; there is possible underestimation owing to the total number of prescriptions from other nondental professionals (for example, emergency medicine services) for any dental condition not being included in the estimate; estimates related to antibiotic prescribing practices reported by Hicks and colleagues[43] correspond to that of general dentists and not all dental specialties combined. ‡‡ Downgraded owing to serious issues of indirectness related to estimates being extrapolated to illustrate the burden in a dental setting. §§ Data were adjusted considering that dentistry accounts for 10% of total outpatient antibiotic prescriptions in the United States. ¶¶ The presented estimate assumes that dental prescriptions for any antibiotic has the same potential of inducing antibiotic resistance as nondental related prescriptions. ## Considerations for Centers for Disease Control and Prevention[44]: no reports containing methods or results is linked to this report; estimates used from this report are likely an underestimation of the true burden of antibiotic resistance related outcomes; the magnitude of antibiotic resistance related outcomes may not necessarily represent the magnitude of antibiotics prescribed for and consumed by patients. *** Considerations for Zhang and colleagues[45]: all included studies in the Zhang and colleagues review reported direct medical costs from a hospital perspective; indirect costs to patients and society and costs of additional care after hospital discharge were not captured (for example, productivity loss due to work day losses and costs in long-term care facilities). Approximately 9% of patients with *C. difficile* infections were discharged to a long-term care facility for an average of 24 d of after-care, which would result in an additional $141 million burden on the health care system and society due to long-term care facility transfers; primary *C. difficile* infections were not separated for the estimation of recurrent *C. difficile* infection costs; there was discrepancy in case definitions in cost studies versus surveillance and epidemiologic studies (for example, community- versus health care–associated *C. difficile* infections); the total costs of *C. difficile* infection in the United States may be higher than the reported estimate. ††† This is likely an overestimation of the effect of dental prescriptions for antibiotics owing to the primary study not measuring or reporting antibiotic exposure. ‡‡‡ Considerations for Mainous and colleagues[46]: the methods did not allow the guideline authors to determine whether the infection arose in the hospital or if patients were colonized or infected prior to admission, *International Classification of Diseases*, Ninth Revision, Clinical Modification diagnosis codes were used instead of laboratory results on bacterial cultures; "Greater awareness of drug resistance among hospital coding departments may have prompted more attention to adding these codes to discharge records of patients who were relatively healthy and discharged without incident." §§§ Considerations for Johnston and colleagues: *International Classification of Diseases*, Ninth Revision, Clinical Modification diagnosis codes were used instead of laboratory results on bacterial cultures; the authors were unable to distinguish between hospital-acquired and community-acquired infections; 10% of the eligible population was excluded owing to missing data. ¶¶¶ Considerations for Dhopeshwarkar and colleagues[48]: the estimates presented in this study only included penicillin and cephalosporin drug classes and amoxicillin and cephalexin drugs and did not include other individual drugs commonly prescribed by dentists such as clindamycin. Source: Durkin and colleagues;[6] there may be issues of generalizability as only patients from 2 Boston-area hospitals were included in this analysis, which may not be representative of inpatient populations admitted to other US hospitals; there was a potential overestimate of the occurrence of anaphylaxis owing to reported cases not being confirmed by tryptase tests; there was possible underestimation owing to exclusion of codes listed in electronic health records not directly linking to anaphylaxis; there was uncertainty surrounding whether the estimates of the reported or observed cases of anaphylaxis resulted in death.

eTable 6. Relative and absolute desirable and undesirable effects (95% confidence interval) from randomized controlled trials and certainty in the evidence for systemic antibiotics as adjuncts to definitive, conservative dental treatment compared with no systemic antibiotics as adjuncts to definitive, conservative dental treatment for pulp necrosis and symptomatic apical periodontitis and pulp necrosis and localized acute apical abscess in immunocompetent adults.

OUTCOMES*	PARTICIPANTS (STUDIES), NO.	CERTAINTY OF THE EVIDENCE ACCORDING TO GRADE†	RR‡ (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECTS	
				Risk With No Systemic Antibiotic as Adjuncts to Definitive, Conservative Dental Treatment§ (No. of People)	Risk Difference With Systemic Antibiotics as Adjuncts to Definitive, Conservative Dental Treatment (Range)
Pain Intensity at 24 H	72 (2 RCTs)¶,#,**	Very low††,‡‡	Not applicable	The mean pain intensity at 24 h ranged from 0.67-1.68	MD,§§ 0.09 higher (0.37 lower to 0.55 higher)
Pain Experience at 24 H	72 (2 RCTs)#,**	Very low††,¶¶	RR, 0.80 (0.49 to 1.30)##	442 per 1,000	88 fewer per 1,000 (225 fewer to 133 more)
Pain Intensity at 48 H	72 (2 RCTs)#,**	Very low††,‡‡	Not applicable	The mean pain intensity at 48 h ranged from 0.52-0.96	MD, 0.39 higher (0.13 lower to 0.91 higher)
Pain Experience at 48 H	72 (2 RCTs)#,**	Very low††,¶¶	RR, 1.55 (0.75 to 3.21)##	233 per 1,000	128 more per 1,000 (58 fewer to 514 more)
Pain Intensity at 72 H	72 (2 RCTs)#,**	Very low††,‡‡	Not applicable	The mean pain intensity at 72 h ranged from 0.29-0.82	MD, 0.12 higher (0.32 lower to 0.56 higher)
Pain Experience at 72 H	72 (2 RCTs)#,**	Very low††,¶¶	RR, 1.38 (0.50 to 3.82)##	116 per 1,000	44 more per 1,000 (58 fewer to 328 more)
Pain Intensity at 7 D	41 (1 RCT)#	Low‡‡	Not applicable	The mean pain intensity at 7 d was 0.32	MD, 0.05 lower (0.41 lower to 0.3 higher)
Pain Experience at 7 D	41 (1 RCT)#	Low¶¶	RR, 5.75 (0.29 to 112.83)##	23 per 1,000	108 fewer per 1,000 (16 fewer to 2,542 more)
Intraoral Swelling at 24 H	67 (2 RCTs)#,**,***	Very low††,¶¶	RR, 1.70 (0.55 to 5.24)†††,‡‡‡	250 per 1,000	175 more per 1,000 (112 fewer to 1,060 more)
Intraoral Swelling at 48 H	66 (2 RCTs)#,**,§§§	Very low††,¶¶	RR, 1.36 (0.62 to 2.98)†††,‡‡‡	282 per 1,000	102 more per 1,000 (107 fewer to 558 more)
Intraoral Swelling at 72 H	59 (2 RCTs)#,**,§§§	Very low††,###	RR, 1.00 (0.05 to 20.81)†††,‡‡‡	189 per 1,000	0 fewer per 1,000 (180 fewer to 3,748 more)
Intraoral Swelling at 7 D	40 (1 RCT)#	Low###	RR, 1.11 (0.07 to 16.47)‡‡‡	48 per 1,000	5 more per 1,000 (44 fewer to 737 more)
Total Number of Nonsteroidal Anti-inflammatory Drugs (Tablets) Used	41 (1 RCT)#	Low###	Not applicable	The mean total number of nonsteroidal anti-inflammatory drugs (tablets) used was 8.42	MD, 1.58 higher (4.55 lower to 7.71 higher)
Total Number of Acetaminophen with Codeine (Tablets) Used	41 (1 RCT)#	Low###	Not applicable	The mean total number of acetaminophen with codeine (tablets) used was 5.58	MD, 0.31 lower (3.94 lower to 3.32 higher)
Endodontic Flare-up	30 (1 RCT)**	Very low††,¶¶	RR, 0.28 (0.02 to 4.76)	182 per 1,000	131 fewer per 1,000 (178 fewer to 684 more)
Diarrhea	31 (1 RCT)**,****	Very low††,¶¶	RR, 0.40 (0.02 to 7.63)	95 per 1,000	57 fewer per 1,000 (93 fewer to 631 more)
Malaise	32 (1 RCT)**,****	Very low††,¶¶	RR, 6.79 (0.25 to 182.33)	24 per 1,000	138 fewer per 1,000 (18 fewer to 4,317 more)

* Selection criteria: patient or population: immunocompetent adults with pulp necrosis and symptomatic apical periodontitis or pulp necrosis and localized acute apical abscess; setting: dental setting in which definitive, conservative dental treatment is immediately available; intervention: systemic antibiotics as adjuncts to definitive, conservative dental treatment; comparison: no systemic antibiotic as adjunct to definitive, conservative dental treatment. No studies meeting the selection criteria reported data on trismus, fever, cellulitis, additional dental visit, additional medical visit, allergic reaction, *Clostridioides difficile* infection, or repeat procedure for this population. † GRADE: Grading of Recommendations Assessment, Development and Evaluation. GRADE Working Group grades of evidence: high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect

is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. ‡ RR: Risk ratio. § For dichotomous outcomes, the guideline authors calculated absolute treatment effects via using the control group's baseline risk as the assumed control intervention risk. ¶ RCT: Randomized controlled trial. # Henry and colleagues.[52] ** Fouad and colleagues[53] †† Serious issues of risk of bias (attrition bias and selective reporting). ‡‡ Serious issues of imprecision due to small sample size. §§ MD: Mean difference. ¶¶ Very serious issues of imprecision owing to small sample size and the confidence interval suggests a large benefit and a large harm. ## For included studies, the data for the outcome of pain were dichotomized (visual analog scale from 0-3) as follows: "no pain" and "mild pain" were coded as "no pain" and "moderate pain" and "severe pain" were coded as "pain." *** In Fouad and colleagues,[53] 14 participants were excluded from the analysis because they either did not report their baseline swelling or they did not report swelling data at follow up. ††† In Fouad and colleauges,[53] the data for the outcome of intraoral swelling were dichotomized (visual analog scale from 0-4) as follows: "no swelling," "much less swelling," and "slightly less swelling," when compared with swelling at baseline, were coded as "no swelling." The options of "same swelling" and "more swelling," when compared with swelling at baseline, were coded as "swelling." ‡‡‡ In Henry and colleagues,[52] the data for the outcome of swelling were dichotomized (visual analog scale from 0-3) as follows: "no swelling" and "mild swelling" were coded as "no swelling" and "moderate swelling" and "severe swelling" were coded as "swelling." §§§ In Fouad and colleagues,[53] 15 participants were excluded from the analysis because they either did not report their baseline swelling or they did not report swelling data at follow up. ### Serious issue of imprecision owing to small sample size and the confidence interval suggests both a small benefit and a small harm. **** Owing to the total number of participants in Fouad and colleagues[53] informing this outcome, the total number of participants for the outcome of pain at 72 h was used.