NEW STRATEGIES FOR TARGETING ANTIBIOTIC USE IN CLINICAL DENTISTRY

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I. TARGETED INDICATIONS IN DENTAL PRACTICE

A. Therapeutic Indications

1. Acute cellulitis of dental origin
2. Acute pericoronitis with elevated temperature and trismus
3. Deep fascial space infections
4. Open fractures of the mandible and maxilla
5. Extensive, deep, or old (>6hours) orofacial lacerations
6. Dental infection or oral surgery in the compromised host

B. Prophylactic Indications

1. Prosthetic heart valve or valve repair
2. Hx of endocarditis or severe congenital abnormality
3. Total Joint Arthroplasty – www.Orthoguidelines.org/AUC

C. Antibiotics NOT Generally Indicated in Endodontics

Pain Without Signs and Symptoms of Infection
• Symptomatic irreversible pulpitis
• Symptomatic apical periodontitis (Pain to percussion and biting)
Teeth with Necrotic Pulps and a Radiolucency
Teeth with a Sinus Tract/Parulis (Chronic Apical Abscess)
Acute Apical Abscess in Immunocompetent Patients *(When same visit treatment is an option)*
• Localized fluctuant swellings

D. Adjunctive Antibiotics Indicated in Endodontics

Acute Apical Abscess in Immunocompromised Patients
• Localized fluctuant swellings
• Patient with systemic disease causing impaired immunologic function
Acute Apical Abscess in Immunocompetent Patients *(When same visit treatment is not an option)*
• Localized fluctuant swellings
Acute Apical Abscess with Systemic Involvement
• Elevated body temperature >100°F
• Malaise
• Unexplained trismus
• Lymphadenopathy
Progressive Infections
• Rapid onset of swelling <24hrs
• Cellulitis or a spreading infection
• Osteomyelitis
Persistent Infection
• Chronic exudation, which is not resolved by regular intracanal procedures and medications

E. When to Refer to a Specialist and/or Hospital-Based Care

- Rapidly progressive infection
- Difficulty in breathing and/or swallowing
- Fascial space involvement
- Elevated temperature (greater than 101°F)
- Severe Trismus (less than 10 mm)

II. TARGETED PATIENTS AT INCREASED RISK OF OROFACIAL INFECTIONS DUE TO DRUG THERAPY OR DISEASE STATE

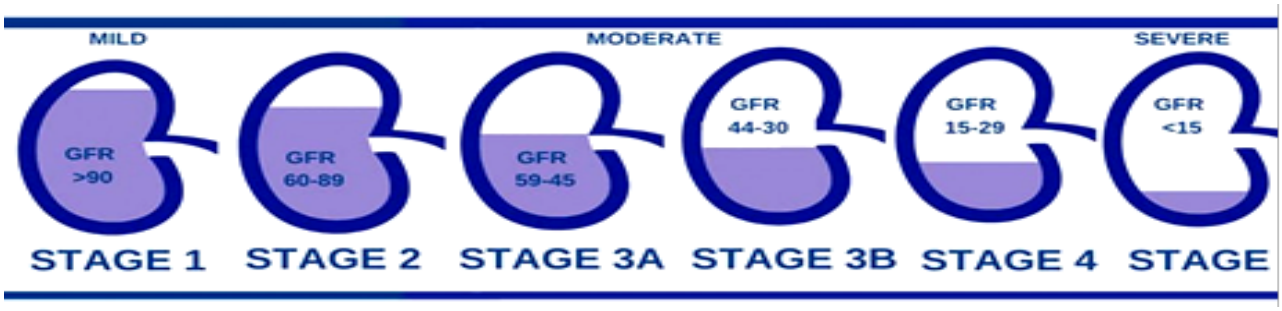
A. Patient-Specific Risk Factors

1. **Immunocompromised** by drug therapy or disease process
   a. drug therapy – TNFIs, Biologics, systemic prednisone > 10mg/day organ transplant rejection drugs, etc.

   b. disease process – SLE, rheumatoid arthritis, malnutrition, neoplastic disease, poor glycemic control in diabetics (A1c > 8%)

2. **Impaired by trauma, surgery, reduced circulation, or implanted device**
   a. hematomas and scar tissue – promote bacterial proliferation
   b. reduced circulation – may prevent antibiotic from reaching site
   c. implanted devices – intravascular devices are the leading cause of nosocomial infections and increase risk of endocarditis in some cases

3. **Renal Insufficiency**
   a. Tetracycline and minocycline are contraindicated in renal failure
   b. Dosage reduction for amoxicillin, cefuroxime, cephalexin, and fluoroquinolones
   c. No dosage reduction necessary for azithromycin, cefaclor, clindamycin, dicloxacillin, doxycycline, erythromycin, metronidazole
   d. **Renal failure is defined by the following stages:**



4. **Diabetic Glycemic Control**

Correlation Between A1c and Mean Plasma Glucose

A1c (%)	Mean plasma glucose	
6	126mg/dl	
7	154mg/dl	
8	183mg/dl	
9	212mg/dl	⇐ **Patient Risks Increased**
10	240mg/dl	
11	269mg/dl	
12	298mg/dl	

Importance of Glycemic Control in Dental Patients

Prevention of hyperglycemia AND hypoglycemia
Nonketotic hypertonicity/ketoacidosis
Impaired wound healing & Increased risk of oral infections
Delayed gastric emptying could lead to aspiration during a procedure

ADA Clinical Practice Guideline on the Use of Antibiotics for the Emergency Management of Symptomatic Irreversible Pulpitis, Symptomatic Apical Periodontitis, and Localized Acute Apical Abscess. Found at www.ada.org/ebd/files/Antibiotics_Recommendations

Setting	Clinical questions	Expert panel recommendations and good practice statements
Emergent situations where dental care is available, but pulpotomy, pulpectomy, root canal debridement, non-surgical root canal treatment, or incision for drainage of abscess are **not** an immediate option (same visit).	1. For immunocompetent adults **with symptomatic irreversible pulpitis[1] with or without symptomatic apical periodontitis,[2]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics to improve health outcomes?	**Recommendation:** The expert panel **does not recommend** dentists prescribe oral systemic antibiotics for immunocompetent adults with symptomatic irreversible pulpitis[1] with or without symptomatic apical periodontitis,[2] due to the lack of improvement in health outcomes and substantial individual and community level harms associated with prescribing antibiotics.[3] Clinicians should refer[4] patients for definitive treatment in a timely manner while providing interim monitoring[5] (Strength of Recommendation: Strong, Certainty in the Evidence: Low).
	2. For immunocompetent adults **with pulp necrosis and symptomatic apical periodontitis[2] or localized acute apical abscess,[6]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics to improve health outcomes?	A. **Recommendation:** The expert panel **does not suggest** dentists prescribe oral systemic antibiotics for immunocompetent adults with pulp necrosis and symptomatic apical periodontitis[2], due to the lack of improvement in health outcomes and substantial individual and community level harms associated with prescribing antibiotics.[3] Clinicians should refer[4] patients for definitive treatment in a timely manner while providing interim monitoring.[5] If definitive treatment is not feasible, a contingency prescription [oral amoxicillin (500 milligrams, three times a day, with or without loading dose of 1,000 mg, 3-7 d) or penicillin VK (500-600 mg, four times a day, 5-7 d)][7,8] (delayed prescribing, watchful waiting) should be provided (Strength of Recommendation: Conditional, Certainty in the Evidence: Very low).
		B. **Recommendation:** The expert panel **suggests** dentists prescribe oral amoxicillin (500 milligrams, three times a day, with or without loading dose of 1,000 mg, 3-7 d) or penicillin VK (500-600 mg, four times a day, 5-7 d)[8] for immunocompetent adults with pulp necrosis and localized acute apical abscess.[6] Clinicians should additionally provide urgent referral[4] as definitive treatment should not be delayed[5] (Strength of Recommendation: Conditional, Certainty in the Evidence: Very low).
	3. For immunocompetent adults **with pulp necrosis and acute apical abscess with systemic involvement,[9]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics to improve health outcomes?	**Good practice statement:** The expert panel **suggests** dentists prescribe oral amoxicillin (500 milligrams, three times a day, with or without loading dose of 1,000 mg, 3-7 d) or penicillin VK (500-600 mg, four times a day, 5-7 d)[8] for immunocompetent adults with pulp necrosis and acute apical abscess with systemic involvement.[9] Clinicians should additionally provide urgent referral[4] as definitive treatment should not be delayed.[5] If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer patient for emergent medical evaluation.
Emergent situations where dental care is available, and pulpotomy, pulpectomy, or root canal debridement, non-surgical root canal treatment, or incision for drainage of abscess **are** an immediate option (same visit).	4. For immunocompetent adults **with symptomatic irreversible pulpitis[1] with or without symptomatic apical periodontitis,[2]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics as an adjunct to dental treatment[10] to improve health outcomes?	**Recommendation:** The expert panel **does not suggest** dentists prescribe oral systemic antibiotics as an adjunct to dental treatment[10] for immunocompetent adults with symptomatic irreversible pulpitis[1] with or without symptomatic apical periodontitis,[2] due to the lack of improvement in health outcomes and substantial individual and community level harms associated with prescribing antibiotics[3] (Strength of Recommendation: Conditional, Certainty in the Evidence: Low).
	5. For immunocompetent adults **with pulp necrosis and symptomatic apical periodontitis[2] or localized acute apical abscess,[6]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics as an adjunct to dental treatment[11] to improve health outcomes?	**Recommendation:** The expert panel **does not recommend** dentists prescribe oral systemic antibiotics as an adjunct to dental treatment[11] for immunocompetent adults with pulp necrosis and symptomatic apical periodontitis[2] or localized acute apical abscess,[6] due to the lack of improvement in health outcomes and substantial individual and community level harms associated with prescribing antibiotics[3] (Strength of Recommendation: Strong, Certainty in the Evidence: Low).
	6. For immunocompetent adults **with pulp necrosis and acute apical abscess with systemic involvement,[9]** should we recommend the use of oral systemic antibiotics compared to the non-use of oral systemic antibiotics as an adjunct to dental treatment[11] to improve health outcomes?	**Good practice statement:** The expert panel **suggests** dentist perform urgent dental treatment[11] in conjunction with prescribing oral amoxicillin (500 milligrams, three times a day, with or without loading dose of 1,000 mg, 3-7 d) or penicillin VK (500 milligrams, four times a day, 5-7 d)[8] for immunocompetent adults with pulp necrosis and acute apical abscess with systemic involvement.[9] If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer for emergent medical evaluation.

6. Reasons Why Antibiotics Fail

- Inadequate drainage or debridement
- Antibiotic does not reach infection site
- Physical obstruction or open access
- Systemic disease alters host response
- Foreign body reaction
- Patient noncompliance
- Inadequate dose or duration

- Wrong antibiotic is chosen
- Development of bacterial resistance
- Concomitant therapy interferes

Pitfalls in Antibiotic Prescribing

Antibiotic adverse effects not considered
Cost of antibiotic not considered
Rapid and inappropriate therapy changes
Patient is not counseled or monitored
Inappropriate drug or dosage regimen
Failure to correct contributing factors
Continuing antibiotics too long after tx

7. Recommended Antibiotics in Endodontics and Dosages

DRUG OF CHOICE	LOADING DOSE *****Conditional recommendation*	ADULT MAINTENANCE DOSE
Amoxicillin w/ clavulanic acid	1000 mg 1000 mg	500 mg q8 h 3-7 days 500/125 mg q8h 7 days
Penicillin VK	1000 mg	500 mg q4-6 h 3-7 days
Azithromycin *Penicillin allergy w/ hx of hives, angioedema, or anaphylaxis	500 mg	250 mg q24h (5 days including loading dose)
Cephalosporins (Cephalexin) *Penicillin allergy w/o hx of hives, angioedema, or anaphylaxis	1000 mg	500 mg q6h 3-7 days
Clindamycin *Penicillin allergy w/ hx of hives, angioedema, or anaphylaxis	600 mg	300 mg q6 h 3-7 days
Metronidazole **Complement antibiotic	1000 mg	500 mg q8h 5-7 days
Erythromycin ***Historical Antibiotic	500 mg	250 mg q4-6h 7-10 days
Ciprofloxacin	500 mg	250-500 mg q6h x 7-10 days

*comparative safety and effectiveness of common antibiotics with Penicillin ***essentially not effective against anaerobic **Provides great gram-negative anaerobic activity ****Facility specific recommendations

III. TARGETED ANTIBIOTIC SELECTION

A. Mechanism of action and spectrum of activity

BACTERIOSTATIC	***BACTERICIDAL***	*SPECTRUM OF ACTIVITY*		
		Narrow	**Extended**	**Broad**
Tetracyclines	**Penicillins**	Penicillin VK	Amoxicillin	Tetracyclines
Sulfonamides	**Cephalosporins**	Azithromycin	Cephalosporins	Sulfonamides
Macrolides	**Metronidazole**	Clarithromycin	Fluoroquinolones	Amox/Clav
Clindamycin(static/Cidal)	**Fluoroquinolones**	Clindamycin		(Augmentin)
		Metronidazole		

B. Activity Against Common Oral Pathogens

Aerobic Bacteria	Frequency	Anaerobic Bacteria	Frequency
Gram-positive cocci		Gram-positive cocci	
Streptococcus		**Peptostreptococcus**	**common**
Viridans (facultative)	**very common**		
B-Hemolytic	unusual	Gram-negative bacilli	
Staphylococcus	rare	**Porphyromonas (Bacteroides)**	**less common**
		Prevotella spp (Bacteroides)	**very common**
Gram-positive bacilli		**Fusobacterium spp**	**common**
Actinomyces (facultative)	less common	Bacteroides fragilis	rare
Lactobacillus (facultative)	less common		

1. The typical odontogenic infection is composed of a mix of aerobic and anaerobic species
2. The timeline of infection may show: AEROBES-------MIXED-------ANAEROBES.
3. Obtain cultures & sensitivities for: antibiotic failures, recalcitrant infections, suspected osteomyelitis, impaired host defenses, post-op wound infections, etc.. REMEMBER-anaerobes outnumber aerobes by a ratio of 3:1.

IV. ANTIBIOTIC THERAPY GUIDELINES

A. Antimicrobial prescribing in the USA is 80 % empirical therapy.

1. Target causative organism -empirical or lab
2. Patient drug and medical history - ALLERGIES vs ADVERSE REACTIONS?? Use Johns Hopkins Flow Chart
3. Patient counseling - adverse effects, compliance, therapeutic endpoints, cost
4. Positive response expected in 48 hours, continue therapy 72 hours after symptom resolution
5. Combination therapy: 3 possible effects - indifferent (additive) - synergism – antagonism
   Cidal + Cidal *or* Static + Static
6. Best combination: penVK qid + metronidazole qid, or amoxicillin tid + metronidazole tid

V. ANTIBIOTIC CLASSES

A. ORAL PENICILLINS – FDA Pregnancy Category B

ORAL PENICILLINS USEFUL IN DENTISTRY

Classification	$t^1/_2$ (h)	OK with food?	Pediatric Dose	Activity against oral pathogens: Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
Natural						
Penicillin G	1	no	150-250K U/kg/d	+	+	+
Penicillin VK	1	yes	25-50mg/kg/day	+	+	+.-
Penicillinase-Resistant						
Dicloxacillin	.75	no	12-25mg/kg/day	staph only	-	-
Nafcillin	.75	no	37mg/kg q 6h	staph+strep	-	-
Aminopenicillins						
Amoxicillin	1.5	yes	40-50mg/kg/day	+	+	-
Amox/potassium clavulanate(Augmentin,G)	1.5	yes	40-45mg/kg/day	+	+	+
Ampicillin	1.5	no	50-100mg/kg/day	+	-	+,-

1. INDIVIDUAL AGENTS

Amoxicillin advantages over penicillin
- more complete absorption
- longer duration of activity
- TID administration

Amoxicillin disadvantages over Pen VK
-broader spectrum
-poor anaerobe activity
-more side effects/less efficacy

2. ADVERSE EFFECTS

Hypersensitivity

- 3 - 10 % of population is allergic to penicillins (more frequently with IV/IM than PO route)
- IgE Mediated acute reaction - PCN binds to protein and acts as a hapten to which Ab develop
- True anaphylactic reactions to penicillin are 1/7,000 to 1/25,000 instances of PCN use
  *mortality occurs once in every 50,000 - 60,000 treatment courses
  * sx. begin 10-20 min. after ingestion, antihistamines are of little effect
-Cross-reactivity to cephalosporins occurs in 3-5% of patients (lowest risk is ceftriaxone)
  *Cephalosporins are contraindicated with pt history of severe or immediate penicillin reaction (urticaria, angioedema, anaphylaxis)

3. **JOHNS HOPKINS PENICILLIN ALLERGY SCREENING TOOL WITH PICTURES**

https://www.hopkinsmedicine.org/antimicrobial-stewardship/_doc/_nursing_toolkit/penicillin-allergy-algorithm-with-pictures.pdf

***Useful Corresponding Article: JAMA.* 2019;321(2):188-199. doi:10.1001/jama.2018.19283**

4. DRUG INTERACTIONS

Bacteriostatic antibiotics
Oral contraceptives
Methotrexate

B. ORAL CEPHALOSPORINS – FDA Pregnancy Category B

Oral Cephalosporins Useful in Dentistry						
Classification	$t^1/_2$(min)	OK with food?	Pediatric Dose	activity against oral pathogens Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
First Generation						
Cephalexin (Keflex,g)	50-80	yes	25-50mg/kg/d (4)	+	+	-
Cefadroxil(Duricef,Ultracef,g)	78-96	yes+	30mg/kg/day (1)	+	+	-
Second Generation						
Cefaclor (Ceclor,G)	35-54	yes	20-40mg/kg/day (3)	+	+	-
Cefuroxime-Axe (Ceftin,G))	80	yes+	10-15mg/kg bid (2)	+	+	-
Cefprozil (Cefzil,G)	78	yes+	15-30mg/kg/day (2)	-	+	-
Third Generation						
Cefdinir (Omnicef)	100	yes	14mg/kg/day (1-2	+	-	-
Cefixime (Suprax)	180-240	yes	8mg/kg/day (1-2)	+	+	-
Cefpodoxime (Vantin)	120-180	yes+	10mg/kg/day (2)	+	+	-
Ceftibuten (Cedax)	144	no	4.5mg/kg bid	-	+	-
Cefditoren (Spectracef)	96	yes	None given	+	-	-

1. INDIVIDUAL AGENTS

1st generation: best gram + coverage of all cephalosporins
2nd generation: best anaerobe coverage of all cephalosporins
3rd generation: oral agents provide variable degrees of oral anaerobe activity

2. ADVERSE EFFECTS

Hypersensitivity and oral candidiasis

3. DRUG INTERACTIONS

Bacteriostatic antibiotics
Anticoagulants
Antacids, H_2 blockers, PPIs (cefdinir, cefuroxime)

C. ORAL MACROLIDES – FDA Pregnancy Category B (except clarithromycin = C)

Oral Macrolides Useful in Dentistry						
Drug	Tpeak(h)	OK with food?	Pediatric Dose	activity against oral pathogens Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
Erythromycin Base						
Abbott Filmtab	3	no	30-40mg/kg/day	+,-	+	-
Boots E-Mycin (EC)	6	yes	(3-4)	+,-	+	-
Abbott Ery-Tab (EC)	3f, 2nf	yes	(3-4)	+,-	+	-
Abbott PCE (PC)	3	no?	(3-4)	+,-	+	-
P-D ERYC (EC)	3	no		+,-	+	-
Erythromycin Ethylsuccinate						
Abbott E.E.S., generic	2	yes	Base dose x 1.6	+,-	-	-
Erythromycin Stearate						
Abbott Erythrocin	3	no	30-40mg/kg/day	+,-	-	-
Azithromycin (Zithromax,g)	2-3	Caps-no Tabs-yes	Day 1: 10mg/kg Days 2-5: 5mg/kg	+,-	+	+,-
Clarithromycin (Biaxin,g) Preg C	1.7	yes	15mg/kg/day (1-2)	+,-	+,-	+,-
Telithromycin (Ketek)	1	yes	Not approved	+	-	-

1. INDIVIDUAL AGENTS

Clarithromycin (Biaxin) advantages over erythromycin base:
- 3% GI irritation as opposed to 30% for older agents, BID dosing
- better activity against *S. pyogenes* than erythromycin, cefaclor or doxycycline
- better anaerobe coverage than erythromycin

Azithromycin (Zithromax): 2-4 fold less active than erythromycin against most strains of strep.HAS risk of QT interval prolongation. Azalide has limited drug interactions compared to macrolides

2 ADVERSE EFFECTS

Cholestatic jaundice (estolate salt = Ilosone)
Gastrointestinal disturbances
Taste disturbances (Clarithromycin)
Oral candidiasis

3. DRUG INTERACTIONS

Alfentanil	Carbamazepine	Ergotamine
Anticoagulants	CCBs (diltiazem, verapamil)	"Statins"
Azole antifungals	Cyclosporine	Theophylline
Bromocriptine	Disopyramide	Tolterodine

D. ORAL FLUOROQUINOLONES – FDA Pregnancy Category C

Oral Fluoroquinolones Available in the USA						
Drug*	$t^1/_2$ (h)	OK with food?	Usual Adult Dose	activity against oral pathogens Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
Ciprofloxacin (Cipro, G)	5	yes	500mg bid	-	-	-
Delafloxacin (Baxdela)	5	yes	450mg bid	+	+	+,-
Gemifloxacin (Factive,G)	7	yes	320mg qd	+	-	-
Levofloxacin (Levaquin,G)	8	yes	500mg q24 h	++	+	+,-
Moxifloxacin (Avelox,G)	10	yes	400mg qd	+	+	+,-
Ofloxacin (Floxin)	8	yes	400mg q12h	+,-	-	-

*not indicated for children or adolescents except for cystic fibrosis

1. BLACK BOX WARNING: TENDONITIS & ACHILLES TENDON RUPTURE, WORSENING MYASTHENIA GRAVIS, IRREVERSIBLE PERIPHERAL NEUROPATHY, CNS EFFECTS. AVOID IN UNCOMPLICATED INFECTIONS.

2. ADVERSE EFFECTS

Arthropathies: contraindicated for children, adolescents, pregnant or lactating women
CNS stimulation/toxicity
Gastrointestinal disturbances
QT interval prolongation risk

3. DRUG INTERACTIONS

Antacids (Fe, sucralfate, zinc)	Cyclosporine
Antiarrhythmics (Spar)	NSAIDS (increased CNS stimulation)
Anticoagulants	Probenecid
Antineoplastics	Theophylline
Cimetidine	Caffeine (Cipro)

E. MISCELLANEOUS AGENTS

Miscellaneous Oral Agents						
Drug	$t^1/_2$ (h)	OK with food?	Pediatric Dose	activity against oral pathogens Gm^+ Aerobes	Gm^+ Anaerobes	Gm^- Anaerobes
Clindamycin (Cleocin,g) FDA B	2	yes	15-30mg/kg/day (3-4)	+	+	+
Metronidazole (Flagyl,g) FDA B	8	yes	30mg/kg/day (3-4)	-	+	+
Tetracyclines FDA D						
Tetracycline HCL(Sumycin,g)	6-12	no	25-50mg/kg/d (4)	-	+	+,-
Doxycycline (Vibramycin,g)	15-25	yes	2-4mg/kg/day (2)	-	+	+,-
Minocycline (Minocin,g)	11-18	yes	4mg/kg x 1 day, 2mg/kg/day	-	+	+,-

1 . CLINDAMYCIN is Pregnancy Category B

a). Cross-reaction with erythromycins because they are all "mycins"?? – doesn't happen
b). Adverse effects:
Gastrointestinal disturbances & morbilliform skin eruptions
c)BLACK BOX WARNING: ***Clostridia Difficile Induced Colitis (CDIC)***
d). Drug interactions

Succinylcholine	Erythromycin	Kaolin-Pectin

Take Home Points

- The **biggest risk factor** for CDI is antibiotics and the most common offenders include clindamycin, fluoroquinolones, cephalosporins (3rd/4th gen), and penicillins.

- **Nosocomial CDI** occurs within 1 year of hospitalization.

→ A medication that is a **risk factor for both nosocomial and community** acquired CDI is PPI.

- **50%** of Pts have positive stool PCR for as long as 6 weeks **after abx completion**.

- **2 main lab tests** that differentiate non-severe from severe infection are WBC >15 and Cr >1.5x baseline.

- New **2018 first line Tx** for an initial, non-severe infection is Vancomycin PO or Fidaxomycin PO x10 days.

→ Metronidazole PO can still be used if these are not available.

- **For fulminant colitis**, Vancomycin PO AND Metronidazole IV are given x14 days.

→ One can also consider Vancomycin enemas vs surgery in appropriate clinical situations.

- **Recurrent infection** is thought to result from persistent spores from the initial infection.

→ **1st recurrence** can be treated with fidaxomicin or a prolonged PO vancomycin pulse taper.

2. METRONIDAZOLE

a.) **BLACK BOX WARNING**: Metronidazole has been shown to be carcinogenic when given chronically to rats and mice. Avoid use in children except for approved indication (amebiasis).

b.) Adverse effects – taste disturbances, peripheral neuropathy, GI irritation
- mutagenic effect demonstrated with in vitro assays as well, turns urine reddish

c.) Interaction with ethanol and disulfuram (Antabuse) may lead to gastrointestinal distress and N/V. Avoid alcohol during and for 1 day after discontinuing metronidazole.Preg Category B

d). Drug interactions

Anticoagulants	Disulfuram	Ethanol (IV diazepam, IV SMZ/TMP)
Lithium	Phenytoin	

3 . TETRACYCLINES

a). Adverse effects
Esophageal ulceration
Toxicity -outdated tetracycline is potentially renal toxic
Pregnancy – hepatotoxicity. Pregnancy Category D due to pediatric tooth discoloration

b). Drug interactions

ALL TETRACYLINES	*DOXYCYCLINE*	*TETRACYCLINE*
Antacids, bismuth	Phenobarbital	Food (milk, dairy)
Iron salts	Phenytoin	Cholestipol
Oral contraceptives		Zinc sulfate

c). Periodontal infections
Advantages in periodontal infections:
- high concentration in GCF
- good activity against A.A
- binds to root surfaces
- anticollagenase activity

d). Periodontal abscesses – tetracyclines are NOT the drugs of choice

e). Compliance considerations: cost, GI irritation, doses per day

4. **OXALODINONES – Linezolid (Zyvox) 400mg and 600mg tablets**
    a) **reserved for resistant gram positive pneumonias and CA-MRSA**
    b) **IS effective for gram positive oropharyngeal anaerobes**

F. PATIENT-SPECIFIC ANTIBIOTIC SELECTION CRITERIA

1. History of allergy to penicillin
    a. Avoid all penicillins and don't prescribe clarithromycin due to cardiotoxicity concerns.
    b. Avoid cephalosporins if hives, angioedema, anaphylaxis, or unknown history is reported

2. History of antibiotic-associated diarrhea
    a. Use narrow spectrum agent if possible-consider flora support with Florajen3 probiotic supplement
    Best choice is pen VK with /without metronidazole
    b. Avoid 2nd and 3rd generation cephalosporins
    c. Avoid clindamycin, fluoroquinolones, and amoxicillin/clavulanic acid (Augmentin,G)

3. Inadequate response to penicillin VK
    a. Add metronidazole 1000-2000mg/day in four divided doses to pen VK
    b. Stop pen VK and initiate clindamycin 300mg qid or q 6h.
    c. Stop pen VK and initiate Augmentin 500/125 tid or q 8h.

4. Allergy or intolerance to penicillins, cephalosporins, macrolides, clindamycin
    a. Reserve agents include levofloxacin or moxifloxacin but be aware of toxicities and new warnings.
    b. May combine fluoroquinolone with metronidazole for resistant anaerobic infections

5. Patient may be pregnant
    a. Use penicillins, cephalosporins, clindamycin, azithromycin
    b. Avoid clarithromycin, all fluoroquinolones and tetracyclines

G. APPROACH TO PRESCRIBING ANTIBIOTCS FOR ODONTOGENIC INFECTIONS

1. **Establish a clear need for antibiotics**
    Patient presents with malaise, fever, chills, trismus, rapid respirations, swelling, lymphadenopathy, or hypotension
    Signs an sx of infection have escalated rapidly over the past 24 to 48 hours
    Oral soft tissue swelling appears to be spreading
    Patients presenting with signs of impending airway obstruction, marked trismus (<25mm), dehydration, malaise, disorientation, tachycardia, and hypotension SHOULD BE ADMITTED TO THE HOSPITAL for urgent care.
2. **Determine the Patient's Health Status**
    Systemic Considerations
    History of Adverse Drug Reactions
    Potential Drug-Drug Interactions
3. **Select appropriate agent with narrow spectrum and limited toxicity (if you can)**
    Immune status of patient determines static vs cidal
    Empiric therapy based on most likely organisms associated with odontogenic infections
    Culture and sensitivity testing if patient compromised or resistance is suspected
    Establish a dosage regimen based on Sanford Guide, Dental Lexi-Drugs, Micromedex,etc
    Consider severity and compliance issues
    Follow up in 48 hours to check compliance and response to treatment
    Monitor patient for adverse effects
    Duration of therapy typically 3-5 days post definitive dental treatment
    Patient should continue therapy 24 hours past symptom resolution

Antimicrobial Adult Regimens for Odontogenic Infections-2024

PENICILLINS

NAME	USUAL DOSAGES	USUAL REGIMENS
PENICILLIN VK (generic)	**Tablet**: 250MG, 500MG	500MG TAB QID OR Q 6 HOURS FOR 3-7 DAYS.
AMOXICILLIN (generic)	**Capsules**: 250MG,500MG **Tablets**:250MG CHEWABLE **Tablets**: 875MG	500MG CAP TID OR Q 8 HOURS UNTIL GONE. DON'T USE 875mg BID DUE TO SHORT DURATION.
AMOXICILLIN/POTASSIUM CLAVULANATE (AUGMENTIN,G)	**Tablets**: 250 mg amoxicillin with 125 mg clavulanate, 500 mg amoxicillin with 125 mg clavulanate, 875 mg amoxicillin with 125 mg clavulanate.	500MG/125MG TID OR Q 8 HOURS FOR 3-7 DAYS. DON'T USE 875mg BID DUE TO SHORT DURATION OF AMOXICILLIN

CEPHALOSPORINS

NAME	USUAL DOSAGES	USUAL REGIMENS
Cefaclor (Ceclor, generic)	**Capsule**: 250 MG, 500 MG **Powder for Suspension**: 125 MG/5 ML, 187 MG/5 ML, 250 MG/5 ML, 375 MG/5 ML **Tablet, Extended Release**: 500 MG	250mg-500mg TID OR Q 8 HOURS FOR 3-7 DAYS.
Cefuroxime (Ceftin, generic)	**Powder for Suspension**: 125 MG/5 ML, 250 MG/5 ML **Tablet**: 125 MG, 250 MG, 500 MG	250mg-500mg BID OR Q 12 HOURS FOR 3-7 DAYS.
Cefzil (Cefprozil,generic)	**Powder for Suspension**: 125 MG/5 ML, 250 MG/5 ML **Tablet**: 250 MG, 500 MG	250mg-500mg BID OR Q 12 HOURS FOR 3-7 DAYS.

MISCELLANEOUS

Clindamycin (Cleocin, generic)	***Capsules:***75mg,150mg,300mg **Suspension:**	150-450mg QID OR Q 6 HOURS FOR 3-7 D.
Metronidazole (Flagyl,generic)	**Capsules**: 375mg **Tablets**: 250mg, 500mg	1-2 GRAMS DAILY AS: 250MG QID OR 375MG TID OR 500MG TID – QID.

MACROLIDES

Name	Usual Dosages	Usual Regimens
Azithromycin (Zithromax Z-Pak)	**Oral Powder for Suspension:** 1 GM/Packet, 100 MG/5 ML, 200 MG/5 ML **Oral Tablet**: 250 MG, 500 MG, 600 MG	500mg on Day 1, followed by 250mg daily for 4 more days.

FLUOROQUINOLONES

Name	Usual Dosages	Usual Regimens
Levofloxacin (Levaquin,generic)	Oral Tablet: 250 MG, 500 MG, 750 MG	250mg-500mg QD FOR 3-7 DAYS
Moxifloxacin (Avelox,generic)	Oral Tablet: 400mg	400mg QD FOR 3-7 DAYS

Antimicrobial Prescribing for Odontogenic Infections Decision Criteria

1. **Assess the nature and severity of the infection**
    a. **Small, isolated, non-progressive with no systemic spread**
        i. **Definitive dental treatment alone may be adequate**
    b. **Large, rapidly progressive with systemic spread**
        i. **Definitive dental treatment PLUS antibiotic therapy**

2. **Assess the patient's immunocompetence**
    a. **Immune system normal-static or cidal antibiotic effective**
    b. **Immune system suppressed-cidal antibiotic preferred**

3. **Assess the patient's disease states & corresponding chronic drug therapy**
    a. **Any disease interactions with dental antibiotics?**
    b. **Any patient drug interactions with dental antibiotics?**

4. **Antibiotic Selection Based on Above Factors**
    a. **First line less aggressive therapy**
        i. **Penicillin VK 500mg qid**
        ii. **Amoxicillin 500mg tid**
        iii. **Azithromycin 500mg, the 250mg daily x 4 days**
    b. **First line aggressive therapy for large rapidly progressive infections with signs and symptoms of systemic spread**
        i. **Amoxicillin/clavulanate 500mg/125mg tid**
        ii. **Penicilin VK 500mg plus metronidazole 250or500mg both qid**
        iii. **Clindamycin 300mg qid**
        iv. **Moxifloxacin 400mg qd**
    c. **Patients at increased risk of CDIC**
        i. **Pen VK 500mg plus metronidazole 250-500mg both qid**
        ii. **Azithromycin 500mg, then 250mg days 2-5**
        iii. **AVOID Amox/clav, Clindamycin, levofloxacin,moxifloxacin**
    d. **Remember, failure of less aggressive first line therapy indicates proliferation of resistant gram negative anaerobes so make changes to antimicrobial therapy with this in mind. You will need to start or add a drug that is effective against most oral anaerobes. This means starting clindamycin as a single agent or adding metronidazole to the previous failing beta lactam.**
    e. **Typical duration of antibiotic therapy after definitive treatment is 3-7 days and tell patient to stop the antibiotic when symptom free for 24 hours. This duration is usually about 5 days but may be 7 days.**

AN UPDATE ON ANTIBIOTIC PROPHYLAXIS IN DENTAL PRACTICE

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I. ANTIMICROBIAL PROPHYLAXIS: for prevention of infection pre-&postop

A. RISK FACTORS FOR POST-OPERATIVE INFECTIONS:

1. Proportional to the degree of bacterial contamination during surgery – dirty vs. clean surgeries
2. Virulence of the infective organism – HA-MRSA or CA-MRSA?
3. Host factors – immunocompromised? Type I Diabetics

B. TIMING OF PRE- & PERISURGICAL PROPHYLAXIS

IV REGIMENS: Recommend a single dose given just prior to surgery
Give follow-up dose when: drug has short $t_{1/2}$, for prolonged surgeries, ↑ blood loss
PO REGIMENS: Peak plasma concentration of antibiotic should occur when surgery begins

C. SOURCES OF BACTERIAL CONTAMINATION

EXOGENOUS: Due to poor aseptic technique, high O.R. traffic, colonized surgeons

ENDOGENOUS: Flora from patient's skin, GI, GU, or respiratory tract, dirty wounds (pus)
most common cause of post-op infections

D. ANTIMICROBIAL AGENTS-how does a single pre-procedural dose prevent distant site infection?

MECHANISM OF ACTION ??: ↓ Level of bacteremia and bacterial growth after adherence
Prevents adherence of bacteria to defect or prosthetic device

- Direct prophylaxis against the <u>most likely</u> infective organisms:
  - Usually normal skin flora
  - Target specific organisms

- For dental procedures: Coverage of Viridans streptococci
  - Amoxicillin preferred by A.H.A. (American Heart Association) over penicillin VK citing better absorption & more prolonged serum levels

E. PROPHYLACTIC ANTIBIOTICS PRIOR TO IMPLANT PLACEMENT AND IMPLANT FAILURE RATES

Efficacy of preoperative antibiotics in prevention of dental implant failure: a Meta-analysis of randomized controlled trials *Oral Maxillofac Surg* 24, 469–475 (2020). https://doi.org/10.1007/s10006-020-00872-5

Considering the results of our study, we conclude that preoperative amoxicillin 1 h prior to surgery significantly reduces the rate of implant failure. But, the potential of this conclusion is limited due to various confounding factors, the varied methodologies of the included studies, the difference in surgical techniques, and the difference in patients' data. Furthermore, research is required in the direction where more complicated implant surgeries are conducted like implant placement with maxillary sinus lift, alveolar ridge splits, bone grafting, and soft tissue grafting.

F. ESSENTIAL REFERENCES:

Circulation. 2021;143:e963–e978 (May 2021 J of the AHA Prevention of VGS Endocarditis Guidelines)

J Bone Joint Surg Am. 2017;99:161-3 (January 2017 AAOS AUC App for Joint Replacement Premed)

CID 2020:71 (15 July) (Reviews The History of Antibiotic Prophylaxis and How to Resolve Conflicts)

II. ANTIBIOTIC PROPHYLAXIS FOR PATIENTS WITH TOTAL JOINT REPLACEMENTS

A. GUIDELINES FOR ANTIMICROBIAL PROPHYLAXIS – TIMELINE FROM 2003 THROUGH 2016

- Advisory statement adopted by the ADA and the AAOS (American Academy of Orthopedic Surgeons), published JADA 134:895-899, July 2003. AAOS "retired" that advisory statement in February of 2009.

- February 2009 AAOS Information Statement recommends lifelong antimicrobial prophylaxis for all patients with total replacements of large weight-bearing joints even though no new evidence for the change exists.

- *Given this new "Information Statement", Orthopedic Surgeons now bear prescriptive responsibility if the dentist does not deem premedication to be appropriate. See* ***Clinical Infectious Diseases****,1/1/10 and* **JADA***;141;667-671. (Position Paper from the AAOM on Dental Treatment of Joint Patients);Also see JADA December 2011.*

- **Evidence-based recommendation issued December 18, 2012 with guideline writing committee appointed.**

This clinical practice guideline, with three recommendations, is based on a systematic review of the correlation between dental procedures and prosthetic joint infection (PJI).

• Recommendation one, which is based on limited evidence, supports that practitioners consider changing their longstanding practice of prescribing prophylactic antibiotics for patients who undergo dental procedures. Limited evidence shows that dental procedures are unrelated to PJI.

• Recommendation two addresses the use of oral topical antimicrobials (topical antibiotic administered by a dentist) in the prevention of PJI in patients undergoing dental procedures. There is no direct evidence that the use of oral topical antimicrobials before dental procedures will prevent PJI.

• Recommendation three is the only consensus recommendation in the guideline, and it supports the maintenance of good oral hygiene.

B. ADA Constitutes 2014 Committee and Publishes Clinical Recommendations in January 2015

Management of patients with prosthetic joints undergoing dental procedures

Clinical Recommendation:

In general, for patients with prosthetic joint implants, prophylactic antibiotics are *not* recommended prior to dental procedures to prevent prosthetic joint infection.

For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, prophylactic antibiotics should only be considered after consultation with the patient and orthopedic surgeon.* To assess a patient's medical status, a complete health history is always recommended when making final decisions regarding the need for antibiotic prophylaxis.

Clinical Reasoning for the Recommendation:

- There is evidence that dental procedures are not associated with prosthetic joint implant infections.
- There is evidence that antibiotics provided before oral care do not prevent prosthetic joint implant infections.
- There are potential harms of antibiotics including risk for anaphylaxis, antibiotic resistance, and opportunistic infections like *Clostridium difficile*.
- The benefits of antibiotic prophylaxis may not exceed the harms for most patients.
- The individual patient's circumstances and preferences should be considered when deciding whether to prescribe prophylactic antibiotics prior to dental procedures.

ADA. Center for Evidence-Based Dentistry™

* In cases where antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the appropriate antibiotic regimen and when reasonable write the prescription.

C. AAOS Appropriate Use Criteria (AUC) for Total Hip and Knee Replacement Patients Undergoing Dental Procedures (Approved September 23, 2016 and published September 28, 2016)

We recognize that in the office setting, some specific laboratory values and other patient data are not always readily available. This also may include timely access to published scientific studies that can support clinical decision-making. Appropriate Use Criteria (AUC) specify when it is appropriate to perform a clinical procedure or service. An "appropriate" procedure is one for which the expected health benefits greatly exceed the expected health risks. Ideally, AUC are evidence-based, but in the absence of sufficient evidence, may be derived from a "consensus of expert opinion" and "accepted practice".

With this AUC, we have attempted to define clinical situations in which antibiotic prophylaxis in certain at-risk dental patients could reduce a theoretical risk of post-surgical prosthetic joint infection. This AUC was developed as a decision support tool to facilitate the treatment of defined "high risk" and "immune compromised" patients who are on the more severe end of the clinical spectrum of disease. In the absence of readily available laboratory data or suggestive clinical suspicion, it would be reasonable to assume that most patients will fall outside of these criteria and therefore lay outside the confines of our strict definitions. As always, sound judgment should guide clinical decisions about when it may be necessary or prudent to delay a dental procedure until more information is available.

Assumptions:
Planned Dental Procedures

- **The chance of oral bacteremia being related to joint infections is extremely low, with no evidence for an association.**
- **Oral bacteremia frequently occurs secondary to activities of daily living such as tooth brushing and eating.**
- **Virtually all dental office procedures have the potential to create bacteremia.**

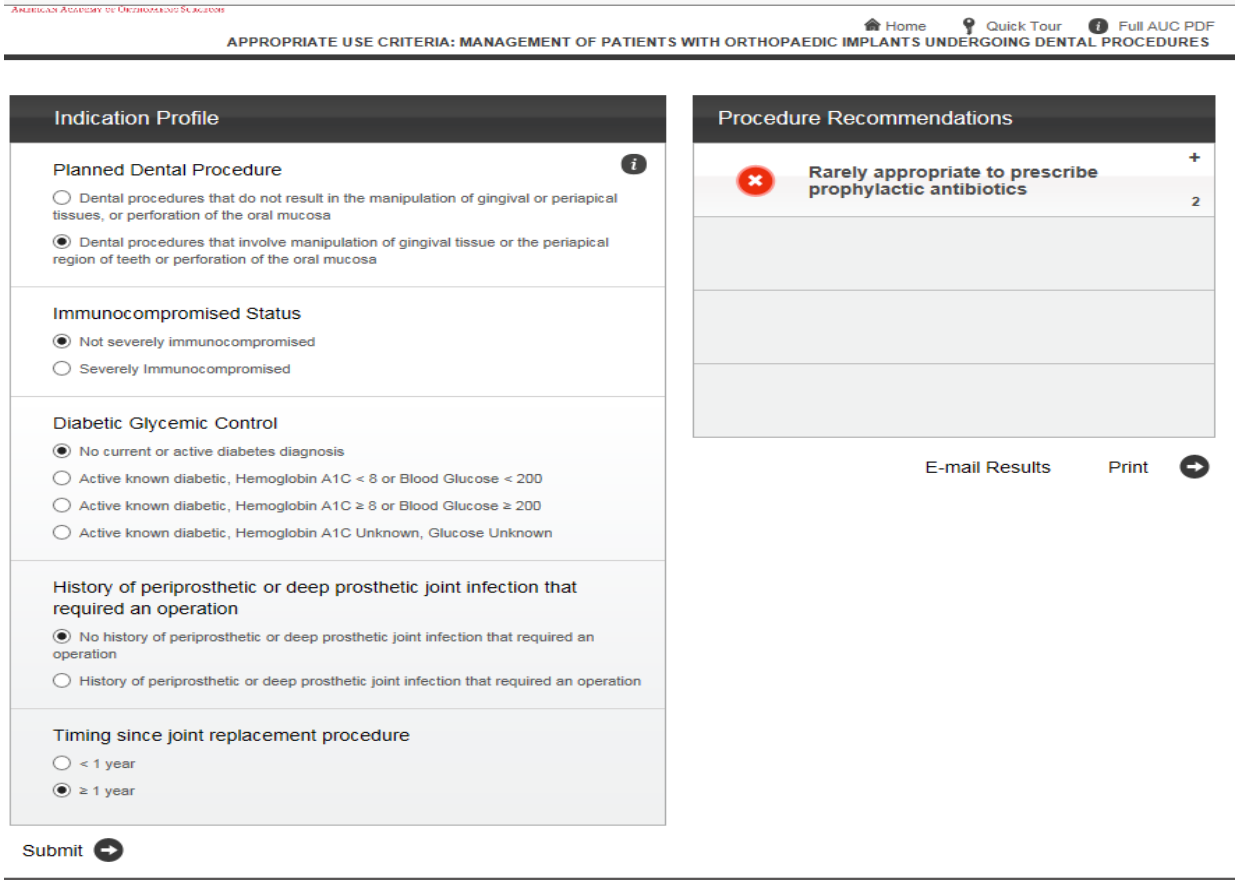
Immunocompromised Status

1. **Severely immunocompromised patients include:**
    a. **Patient with Stage 3 AIDS as defined by the Centers for Disease Control and Prevention (CDC) Guidelines when the immune system becomes severely compromised due to reduced CD4 T lymphocyte counts (<200) or opportunistic infection as defined by CDC[8] see list of diseases below.**
    b. **Cancer patient undergoing immunosuppressive chemotherapy with febrile (Celsius 39) neutropenia (ANC <2000) OR severe neutropenia irrespective of fever (ANC <500)**
    c. **Rheumatoid arthritis with use of biologic disease modifying agents including tumor necrosis factor alpha or prednisone >10 mg per day. Methotrexate, Plaquenil not considered immunocompromising agents.**
    d. **Solid organ transplant on immunosuppressants**
    e. **Inherited diseases of immunodeficiency (e.g., congenital agammaglobulinemia, congenital IgA deficiency)**
    f. **Bone marrow transplant recipient in one of the following phases of treatment:**
        i. **Pretransplantation period**
        ii. **Preengraftment period (approximately 0-30 d posttransplantation)**
        iii. **Postengraftment period (approximately 30-100 d posttransplantation)**
        iv. **Late posttransplantation period (≥100 d posttransplantation) while still on immunosuppressive medications to prevent GVHD (typically 36 months post transplantation) (see Table reference below)**

*Opportunistic illness in AIDS: (as per CDC[6])

Glycemic Control

1. **A1C scores should be recent within 3-6 months.**
2. **Acucheck spot check in dental office blood glucose level is equivalent to a patient self-report.**
3. **Blood glucose tests are assumed to be random (not necessarily fasting).**
4. **Every Dental Office should be able to take an ambient blood glucose or HgA1c Chairside.**



D. PRESCRIPTIONS

Rx: Amoxicillin 500 mg capsules
or
Cephalexin 500 mg capsules
Disp: # 4
Sig: Take 4 capsules p.o. 1 hr. prior to dental appointment

- **Amox Is for patients <u>NOT</u> allergic to penicillin**
- Cephalexin is a 1st generation cephalosporin with good strep. coverage and active against staphylococcal organisms

Rx: Azithromycin 250mg tablets
Disp: # 2
Sig: Take 2 tablets p.o. 1 hr. prior to dental appointment

- For patients with penicillin allergy
- Doesn't inhibit P450 3A4
- Does prolong QT interval

Rx: Cefazolin 1 gram **<u>or</u>** Ampicillin 1 gram
Administer: I.M. or I.V.
Sig: 1 hr. prior to procedure

- For patients unable to take oral medications AND NOT allergic to penicillin

Rx: Ceftriaxone 1 gram
Administer: I.V. **or I.M.**
Sig: 1 hr. prior to procedure

- For patients unable to take oral medications AND penicillin allergic
-Give IM injection with lidocaine 1% solution added

E. BEST PRACTICES FOR DENTAL MANAGEMENT OF PATIENTS WITH TOTAL JOINT REPLACEMENTS

- Updated health history with each visit and explain why you ask at every visit
- Reinforce home-care procedures and use chemotherapeutic measures to reduce bleeding
- Immediate and aggressive treatment of acute and newly recognized chronic infections
- Avoidance of regular daily bacteremia

III. PROPHYLAXIS FOR OTHER IMPLANTS AND DEVICES

A. NO PROPHYLAXIS NECESSARY:

- Breast implants
- **Intraocular lenses**
- Deep Brain Stimulators
- Cochlear implants
- Cardiac Pacemakers
- **A.I.C.D. (Artificially Implanted Cardiac Defibrillators)**
- Orthopedic Plates, Pins, Screws, and Wires
- Hernia Repair Mesh, Vascular Screens

B. PENILE PROSTHESES

BACKGROUND: 30% of men over 40 yrs. have erectile problems due to:
- arteriosclerotic disease, endocrine problems
- medications (25%) e.g. antihypertensives, diuretics alcohol, tobacco

MANAGEMENT: Defer elective dental treatment until 3 months post-op
ANTIBIOTIC *PROPHYLAXIS?? Not unless immunosuppressant co-morbidities are present*

C. VASCULAR GRAFTS-only consider prophylaxis for large grafts in the thoracic cavity

BACKGROUND: 1 – 5 % incidence of infections
- varies with the site of graft placements
- organisms often originate from bowel or skin

MANAGEMENT: Antibiotic prophylaxis is indicated for grafts < 6 months old
- pseudointima (connective tissue & fibrin) forms on the inner surface of the graft
- physician consult to determine size, type and location of graft

D. INTRAVASCULAR ACCESS DEVICES

BACKGROUND:

Central (tunnel) I.V. lines

- Broviac or Hickman lines - for chemotherapy (chemo port, PICC lines)
- Uldall catheters - for hemodialysis-do NOT premedicate per 2021 AHA, plasmaphoresis

- Infections primarily due to skin contamination
- Increased risk with newer grafts

MANAGEMENT: No invasive procedures within 6 weeks of graft placement or revision

- Hemodialysis patients NO LONGER REQUIRE ANTIBIOTIC PROPHYLAXIS per 2021 AHA
  - **home maintenance of oral hygiene is crucial to avoid shunt infection**

E. CEREBROSPINAL FLUID SHUNTS – NO PROPHYLAXIS RECOMMENDED PER 2021 AHA

- **Ventricluoatrial shunts (ventriculoatriostomy)– DO NOT premedicate per May 2021 AHA**
- Lumboperitoneal shunts – negligible risk, no prophylaxis needed
- Ventriculoperitoneal shunts – negligible risk, no prophylaxis needed
  - Most common procedure performed today
  - Used to treat hydrocephalus, post-stroke injury
  - Used to treat normal pressure hydrocephalus (NPH) which is a reversible cause of dementia

IV. PREVENTION OF VIRIDANS GROUP STREPTOCOCCAL INFECTIVE ENDOCARDITIS – A Scientific Statement from the American Heart Association CIRCULATION, MAY 18, 2021

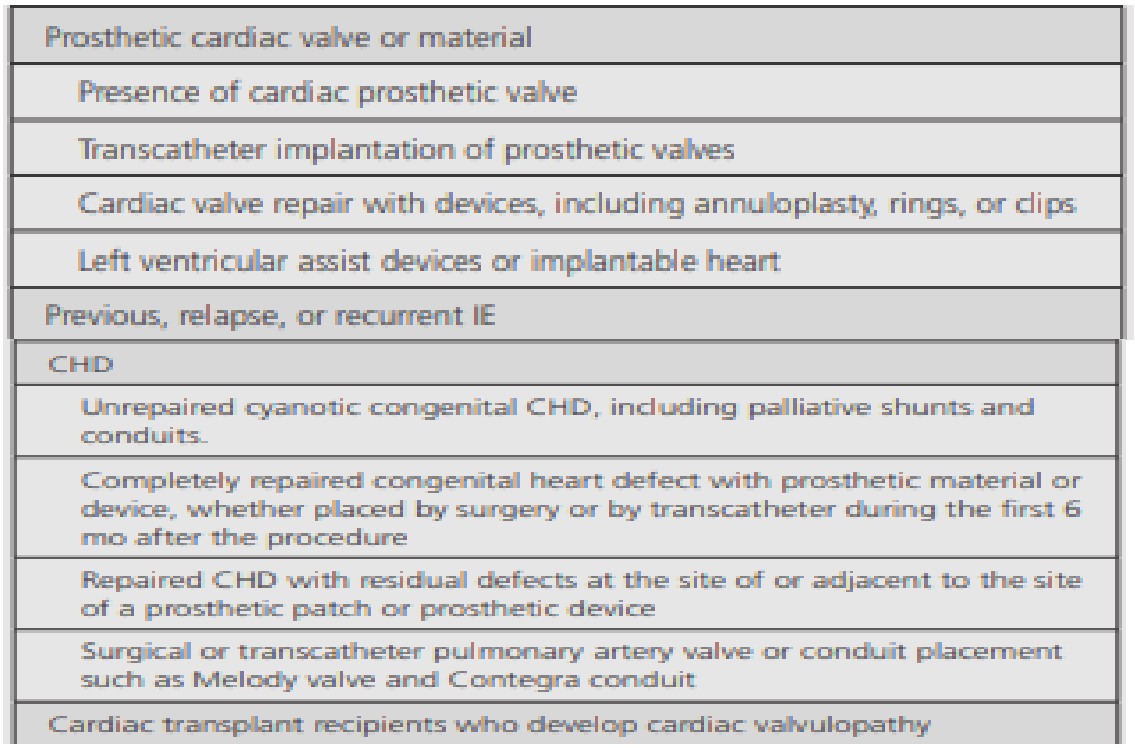
2021 AHA Guidelines for the Prevention of Infective Endocarditis

A. Regimens for a Dental Procedure

Situation	Agent	Regimen – Single dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Oral Allergic to penicillins or ampicillin	Cephalexin**† *OR* Azithromycin *OR* Doxycycline	2 g 500 mg 100 mg	50 m/kg 15 mg/kg <45kg - 4.4mg/kg
Unable to take oral medication	Ampicillin *OR* Cefazolin or ceftriaxone	2 g IM or IV* 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins & unable to take oral med	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV

*IM – intramuscular; IV – intravenous.
**or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

B. AP for a Dental Procedure Underlying Conditions for Which AP is Suggested (Table 3.)



C. AP for a Dental Procedure IS NOT RECOMMENDED

Implantable electronic devices such as a pacemaker or similar devices
Septal defect closure devices when complete closure is achieved
Peripheral vascular grafts and patches, including those used for hemodialysis
Coronary artery stents or other vascular stents
CNS ventriculoatrial shunts
Vena cava filters
Pledgets

D. Dental Procedures for which Antibiotic Prophylaxis is Reccommended for Patients

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa *
***The following procedures and events do not need prophylaxis**: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of primary teeth and bleeding from trauma to the lips or oral mucosa.

E. SAMPLE ADULT ANTIBIOTIC PREMEDICATION PRESCRIPTIONS

RX: Amoxicillin 500 mg capsules
Disp. # 4
Sig: Take 4 capsules p.o. 1 hour before dental Appointment

- **For patients NOT penicillin allergi**c
- Pediatric dose: 50 mg/kg not to exceed adult dose!
- Amoxicillin is available in 500 and 250 mg **capsules**, and 250 mg chewable tablets and 250 mg/5 ml susp.

RX: Cefaclor 500 mg capsules
Disp. # 4
Sig: Take 4 capsules p.o. 1 hour before dental appointment

- Pediatric dose: 50 mg/kg
- Cefaclor (generic Ceclor®) is second generation ceph
- Also comes in a 250 mg/5ml suspension
- Avoid ALL cephalosporins if patients allergic reaction was either – urticarial, angioedema, anaphylaxis or unknown

RX: Azithromycin (Zithromax®) 250 mg tablets
Disp. #2
Sig: Take 2 tablets p.o. 1 hour before appointment.

- Pediatric dose: 15 mg/kg
- Less drug interactions than macrolides, low incidence of GI irritation

Oral liquids for adults who have forgotten to take AP at home:

RX: Amoxicillin 250 mg/5 ml suspension
Disp. # 40 ml
Sig: Take 40 ml one-half to one hour before dental appointment

- Suspension is a powder that must be reconstituted prior to use- tastes good
- Reconstituted suspension expires in 14 days with or without refrigeration. Tastes good!

RX: Azithromycin 200 mg/5 ml susp.
Disp. # 15 ml (pour out 12.5ml for 500mg)
Sig: Take 12.5 ml one-half hour before dental appointment

- Suspension is commercially available as 600mg/15ml
- 12.5ml is 500mg of azithromycin
- Tastes good!

V. OTHER CONDITIONS THAT MAY REQUIRE ANTIMICROBIAL PROPHYLAXIS

A. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

BACKGROUND:

- SLE is an inflammatory autoimmune disease whereby pathogenic antigen-antibody complexes harm a variety of organs & systems including the skin, kidneys, blood vessels, joints and the heart
- 50% of SLE patients demonstrate cardiac valve abnormalities at autopsy
- SLE patients have an increased prevalence of cardiovascular abnormalities
- **Incidence of *Infective Endocarditis***: SLE = 1 - 7%
  RHD = 0.8 - 1.2%
  Prosthetic heart valve = 1.1%

MANAGEMENT: Progressive SLE patients should be regularly evaluated for the detection of new heart murmurs And patients should be questioned about cardiac valve disease at dental visits.

B. ASPLENIC PATIENTS

BACKGROUND (JADA: Dental Considerations in Asplenic Patients. 127:1359-1363, 1996)

- Patients who are functionally or anatomically asplenic fail to clear organisms from the bloodstream and are at an increased risk of overwhelming bacteremia
- Reasons for splenectomy
- Encapsulated organisms pose the highest risk - primary pathogens of concern are *S. pneumoniae, H. influenzae, N. meningitidis, β-* hemolytic streptococci
- Splenectomy confers life-long risk from sepsis in <u>both</u> adults and children (2 - 4%)
- Recommend dental prophylaxis with current AHA regimen when needed

C. SOLID ORGAN TRANSPLANTATION

BACKGROUND: (Clin Transplant. A Survey of Dental Care Protocols. 19: 15-18, 2005)

- Infectious Disease Rates of Patients
  - 80% have “normal” rate of infections
  - 10% chronic or progressive viral infections
  - Hepatitis B or C, cytomegalovirus, EPV etc.
- Theoretically at ⇑ risk from transient bacteremias
- 5-10% recurrent or chronic rejection
  - Increased immunosuppressive dosages (tacrolimus,mycophenolate, prednisone)
  - Most likely to develop opportunistic infections

MANAGEMENT:

- Defer elective dental treatment until at least 6 months after transplantation

D. CORONARY ARTERY STENTS

The report published in *JADA* can be summarized for the dental professional as follows:

1. Dental professionals and other healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postoperative bleeding must be made aware of the potential catastrophic risks of premature discontinuation of antiplatelet (thienopyridine) therapy. The dental professional should contact the patient’s physician if issues regarding the patient’s antiplatelet therapy are unclear, in order to discuss optimal patient management strategy.

2. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy. The course of this therapy is suggested as 12 months after drug-eluting stent implantation if they are not at high-risk of bleeding.

WHAT ABOUT ANTIBIOTIC PREMEDICATION??

* **According to the 2021 AHA guidelines, antibiotic prophylaxis is not indicated as stated in previously listed Table 3.**

Advances in Dental Pain Management

I. AMBULATORY DENTAL PAIN CONTROL STRATEGY

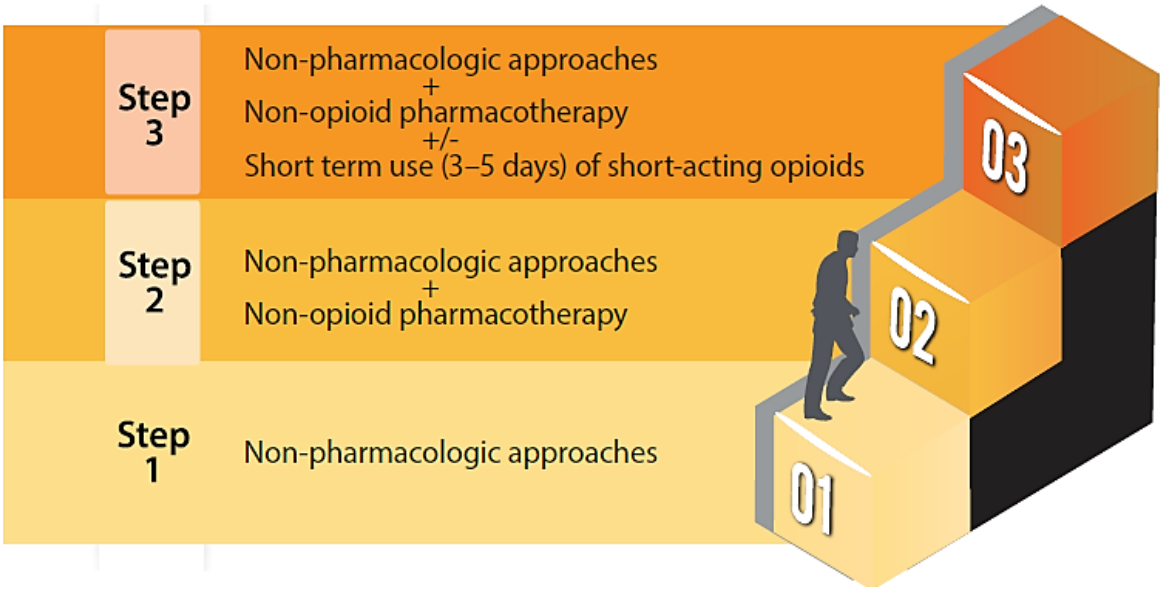
Pain Control Strategy		
	NSAIDs Indicated (Patients who Can take ASA-like Drugs)	NSAIDs CONTRA Indicated (Patients who Can't take ASA-like Drugs)
Mild Pain	Ibu 200 mg-400mg scheduled four times a day	APAP 650 – 1000 mg up to 4000mg per day
Moderate Pain	NSAID – Up to maximum Effective Dose	APAP 650 – 1000 mg With equivalent of Hydrocodone 5-10mg scheduled four times a day
	NSAID Plus APAP Or NSAID Plus APAP/HC.	
Severe Pain	NSAID – Max Dose and APAP/Oxycodone 10 mg Combination	Acetaminophen 1000 mg with equivalent of Oxycodone 10 mg scheduled four times a day

II. VETERANS HEALTH ADMINISTRATION ACUTE PAIN LADDER

Managing Acute Pain Safely and Effectively[2]

To manage acute pain safely and effectively, first evaluate the severity of the pain based on the evaluation of the patient, diagnosis, and the patient's feedback about the pain and impact of the pain on their functioning.

Figure 4. Step-wise Approach to Acute Pain Management[2]



Dose-Response for Three Types of Oral Analgesics

- ☐ Opioids provide unlimited pain relief but side effects and abuse potential limit their use in ambulatory patients
- ☐ Ibuprofen and equi-analgesic oral doses of other NSAIDs provide a ceiling analgesic effect. Increasing beyond ibuprofen 400mg DOES increase anti-inflammatory effect which is an essential component of acute dental pain.
- ☐ ASA/APAP provide a lower ceiling analgesic effect which reaches maximum analgesic at 1000mg.
- ☐ APAP combined with NSAIDs shows a synergistic effect on acute dental pain and these two agents should be dosed concomitantly to maximize non-opoid pain control for acute dental pain.

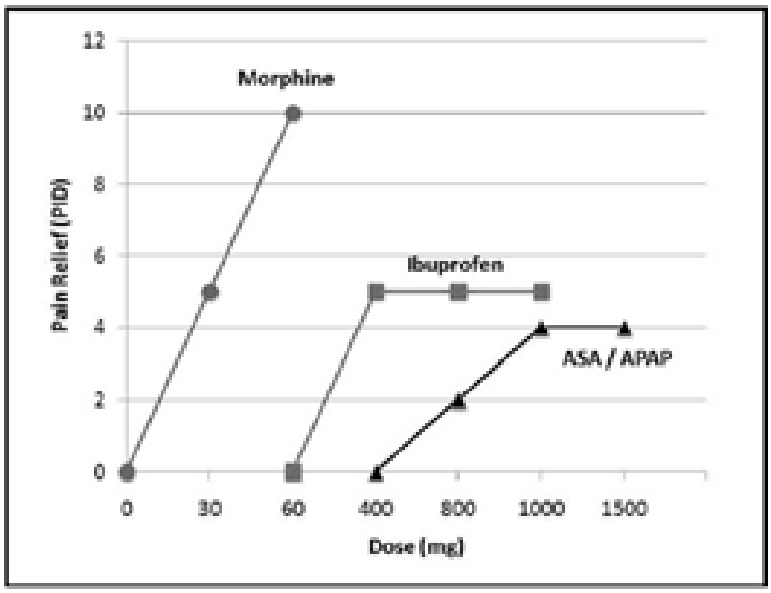


Figure 2. Analgesic efficacy. This graph illustrates a typical dose-response curve for orally administered (PO) analgesics. The dose-response curve for opioids such as morphine demonstrates unlimited efficacy in which greater doses provide greater analgesia. At equipotent doses, all opioids demonstrate a similar dose response. In contrast, nonopioids demonstrate a "ceiling" effect that generally is adequate for relief of mild to moderate pain (pain relief rating of 4–5 in this scale). For ibuprofen, doses greater than 400 mg do not provide further analgesia. For aspirin (ASA) and acetaminophen (APAP), this ceiling effect is achieved at 1000 mg and is somewhat lower than that provided by nonsteroidal anti-inflammatory drugs (NSAIDs).

III. ACETAMINOPHEN (APAP, Tylenol, g)

Maximum daily dosage:

- *ACUTE THERAPY*: Maximum of 4 g/day monitored and 3g/day unmonitored
- *CHRONIC THERAPY +/or ELDERLY PATIENT*: Maximum of 2.6 grams APAP/day

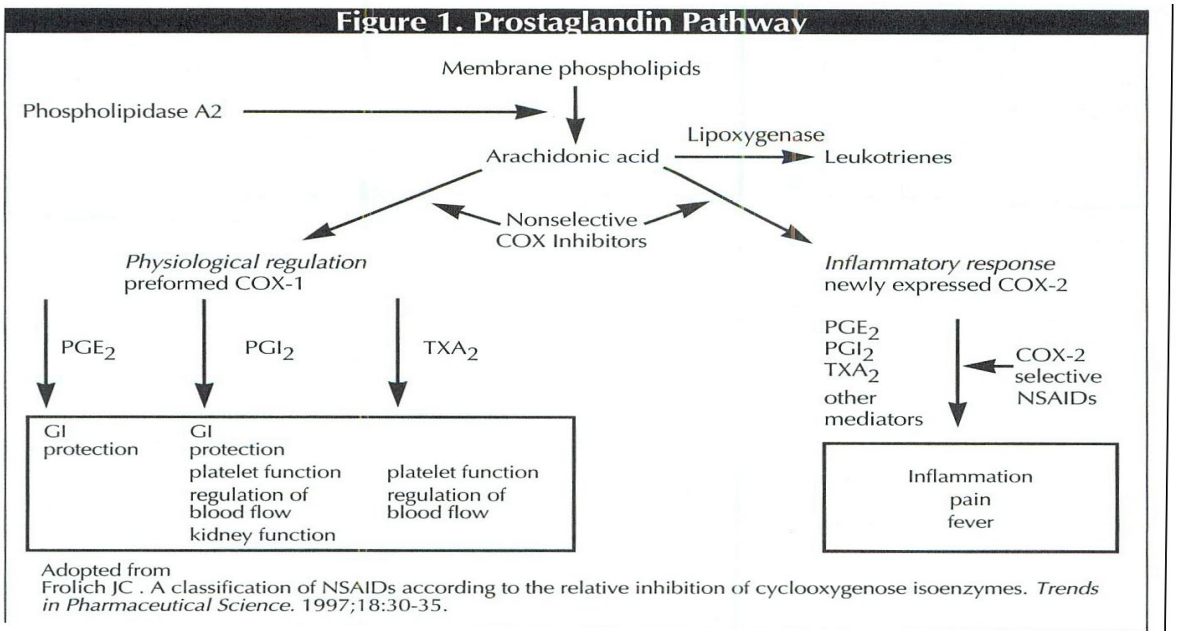
PRODUCT	***DOSAGE***	***ACUTE***	***CHRONIC***
Regular Strength APAP	325mg	12/day	8/day
Extra Strength APAP	500mg	8/day	5/day
Extended Relief APAP	650mg	6/day	4/day

Toxicity risk is increased by:

- *Fasting (depleted glutathione) and/or dehydration during acetaminophen therapy*
- *Greater than two alcoholic drinks per day*

TOXICITY: ORAL: Ingestions of 200 mg/kg or 10 g, whichever is less, are considered potentially toxic. IV: A 10 fold overdose caused hepatotoxicity in a chronically malnourished child. THERAPEUTIC DOSE: ADULT: Oral: 650 to 1000 mg every 4 hours up to 4 g/day. IV: (50 kg or greater): 650 to 1000 mg every 4 to 6 hours, up to 4 g/day; (less than 50 kg): 12.5 mg/kg to 15 mg/kg every 4 to 6 hours, up to 3750 mg/day (75 mg/kg/day). PEDIATRIC: Oral: 10 to 15 mg/kg every 4 hours up to 60 mg/kg/day. IV: 12.5 mg/kg to 15 mg/kg every 4 to 6 hours, up to 75 mg/kg/day.

IV. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (Non-acetylated)



A. NSAIDS COMMONLY USED FOR ACUTE PAIN AND INFLAMMATION

NSAID	*ROLE in Therapy **	*Tp (hr)*	*t 1/2 (hr)*	*ANALGESIC Onset (hr)*	*Duration (hr)*	*USUAL ADULT DOSE (mg)*	*MAX. DAILY DOSE (mg)*
PROPRIONIC ACIDS							
ibuprofen (Motrin,G,otc)	P	1-2	1.8-2.	.5	4-6	400-600 q4-6h	3200/1200
naproxen(Naprosyn,G)	P,I	2-4	12-15	1	up to 7	500 stat, then 250 q6-8h	1500
naproxen Na (Anaprox,DS,G)	P,I	1-2	12-13	1	up to 7	550 stat, then 275 q6-8h	1650
naproxen Na (Aleve – OTC,G)	P,I	1-2	12-13	1	up to 7	440 stat, then 220 q 8-12h	660
ACETIC ACIDS							
diclofenac K(Cataflam)	P,I	1-2	1-2	.5	4-6	100 stat, then 50 q6-8h	200
diclofenac Na (Voltaren,G)	P,I	2-3	1-2	1	4-6	50 q6h	200
etodolac (Lodine,G)	P	1-2	7.3	.5	4-12	200-400 q6-8h	1200
ketorolac (Toradol oral,G)	P	.5-1	3.8-6	.5	6-8	20 stat, then 10 q4-6h	40
nabumetone (Relafen,G)	P,I	2-4	24	4 2	up to 12	750-1000mg q 12h	2000
ENOLIC ACIDS							
Meloxicam (Mobic,G)	P	5	20-26	4	up to 24	5-15mg once daily	15
Piroxicam (Feldene,G)	P	5	50	4	up to 48	10-20mg once daily	20
SALICYLATE							
diflunisal (Dolobid,G)	P,I	2-3	8-12	1	8-12	1000 stat, then 500 q8h	1500
COX-2 SELECTIVE							
Celecoxib (Celebrex)	I	3	11	2	up to 24h	100-200mg 1d-bid	400

***P=pain relief, I=inflammation reduction**

B. CLINICAL APPLICATIONS:

1. NSAIDS VS OPIOIDS

ADVANTAGES OF PRESCRIBING NSAIDS	*DISADVANTAGES OF NSAIDS*
no sedation, constipation or respiratory depression	GI irritation is common
reduced swelling and trismus	no adult liquid preps are available
no central nausea and vomiting side effects	patient expectations are not fufilled
no potential for abuse or habituation	no activity limitations or sedation
	possible increased risk of blood clots

2. GENERAL PRESCRIBING GUIDELINES

a) NSAIDS can be mixed with narcotics +/or acetaminophen for additional effects, not synergistic
b) *AVOID* NSAID + NSAID combinations:
- take medication history, including OTC agents
- no therapeutic advantage, deleterious effects on GI tract, platelets

c) NSAID failure - try switching chemical classes
-acetic acid derivatives are structurally different so switching may improve response
-pre procedural dosing of ibuprofen 400mg or naproxen sodium 275mg reduces postop pain

3. PATIENT-SPECIFIC FACTORS

AERD (Samter's Triad)	Asthma, chronic urticaria, nasal polyps = sensitivity triad.
ASTHMA	Avoid NSAIDS if one triggers asthma, avoid COX-2s
ELDERLY	Choose NSAID with short t ½ to avoid accumulation
GASTRITIS, ALCOHOLISM	Use cytoprotective agent prophylaxis, COX-2s are better
LIVER DISEASE	Avoid diclofenac and piroxicam (Feldene)
HIATAL HERNIA	AVOID ASPIRIN, caution with any NSAID, COX-2s are better
PEPTIC ULCER HX	Caution with any agent, may need prophylaxis, COX-2s are better
POST-OP PAIN	Ketorolac very effective if substance abuse history
RENAL DISEASE	Caution, diflunisal may be best NSAID, COX-2s NO BETTER
MAJOR SURGERY	D/C ASA 1 week prior, D/C other NSAIDS 24 hours prior,Celebrex DOESN'T increase bleeding risk and don't have to be D/C'd.
CLOPIDOGREL THERAPY	CONSIDER AVOIDING NSAID THERAPY INCLUDING CELECOXIB
ANTICOAGULANT THERAPY	AVOID NSAID THERAPY. COX-2's increase bleeding due to a drug intx.

C. INDIVIDUAL AGENTS

1. IBUPROFEN (Motrin, g)

- Many dosage forms: 100mg caplet, 50 & 100mg chewable tablets, 100mg/5ml susp, gel caps
- still the best first line agent due to good safety profile and reliable efficacy in acute pain (Oxford League)
- 800mg q 6 hours can be given initially, no anti-inflammatory value in doses above 3200mg/day

2. NAPROXEN SODIUM (Anaprox, Anaprox DS, G)

-May give lowest risk of blood clots so safest for atherosclerosis or peripheral artery disease
-Longer half-life than ibuprofen so may accumulate in elderly but works for about 8 hours

3. *KETOROLAC (Toradol, g, Sprix Nasal Spray)*

MANUFACTURER PRESCRIBING GUIDELINES LIMIT USE OF ORAL TABLETS

- Prescribing guidelines serve to limit tablet prescribing in response to serious adverse events
- Manufacturer bears less responsibility for adverse outcomes if practitioner uses medication outside of labeling
- Emphasizes the importance of proper patient selection criteria for all NSAIDS

V. TRAMADOL (Ultram, G, Ultracet - Ortho/McNeil, RYBIX ODT - Victory)

A. MECHANISM OF ACTION:

- unique complimentary dual mechanisms
- tramadol is a weak opioid receptor binder as well as an inhibitor of serotonin and norepinephrine reuptake
- no inhibition of prostaglandin synthesis
- **controlled substance Schedule IV as of 8/18/14/ FDA pregnancy category C**

B. *THERAPEUTIC USE: 100MG =ASA/codeine 650/60 for acute pain.*
COMBINATION: Ultracet = 37.5mg tramadol/325mg acetaminophen, Ultram ER

C. ADVERSE REACTIONS:

Dizziness	26%	Nausea 24%
Constipation	24%	Headache 18%
Sedation	16%	

D. DRUG INTERACTIONS

carbamazepine $\rightarrow\rightarrow$ reduced tramadol effectiveness
MAOI $\rightarrow\rightarrow$ possible sympathomimetic potentiation (AVOID TRAMADOL)
CYP206 inhibitor $\rightarrow\rightarrow$ increased tramadol levels – caution with Prozac, Paxil, Zoloft SSRIs
CNS depressants $\rightarrow\rightarrow$ increased tramadol sedation

E. DOSAGE & ADMINISTRATION

- 50-100mg q 4-6 hours prn pain to maximum of 400mg/day (max dose for pts > 75 years is 300mg/day)
- 100mg initially is more effective for severe pain
- Tramadol 50mg ODT (Rybix) gives faster onset and comes in a 50mg tablet with no generic

F. *PATIENT SELECTION CRITERIA*

- Patients on NSAIDs, Warfarin, Pradaxa. Eliquis, Xarelto, Savaysa or oral hypoglycemics
- Patients with history of histamine release with opiates or on hemodialysis
- Diagnosis of neuropathic pain or history of gastrointestinal ulceration
- **Patients with an opiate dependence hx. Should <u>not</u> take tramadol – Controlled Substance Schedule IV**
- **Patients with severe allergic rx to CODEINE OR OTHER OPIATES should NOT take tramadol**

VI. Corticosteroids for Dental Pain and Inflammation Management

Glucocorticoid	Approximate equivalent dose (mg)	Relative anti-inflammatory (glucocorticoid) potency	Relative mineralocorticoid potency	Half-life	
				Plasma (min)	Biologic (hrs)
Short-acting					
Cortisone	25	0.8	2	30	8-12
Hydrocortisone	20	1	2	80-118	8-12
Intermediate-acting					
Prednisone	5	4	1	60	18-36
Prednisolone	5	4	1	115-212	18-36
Triamcinolone	4	5	0	200+	18-36
Methylprednisolone	4	5	0	78-188	18-36
Long-acting					
Dexamethasone	0.75	20-30	0	110-210	36-54
Betamethasone	0.6-0.75	20-30	0	300+	36-54

- 25 high quality studies in post extraction patients show effectiveness for pain, trismus and swelling thereby reducing need or demand for opiates
- 15 high quality studies in patients post RCT show effectiveness in reducing pain, swelling and inflammation thereby reducing need for opiates
- Opioid-sparing analgesia is what we are striving for in dentistry
- Contra-indications:
  - Uncontrolled diabetics and/or Type I Diabetics
  - Severe psychiatric conditions (Schizophrenia, Bipolar Disorder, Suicidal Ideation, etc.)
  - Angle-closure glaucoma
  - Pediatric or pregnant patients

VII. OPIOID ANALGESICS AND THEIR CHARACTERISTICS

A. OPIOIDS COMMONLY USED ORALLY FOR MILD TO MODERATE PAIN

OPIOID AVAILABLE	MME ORAL POTENCY	PEAK (HR)	DURATION (HR)	COMMENTS	PRECAUTIONS
Codeine (avoid in pts. On $2D_6$ inhibitors* - Prozac, Paxil, Cymbalta)	0.15	1.5-2	4-6	2D6 polymorphism may cause toxicity-not for pediatric patients	Impaired ventilation, asthma, high intracranial pressure,avoid in children
Hydrocodone (Norco,Lortab,G)	1.0	2	4-6	not useful after 10mg q 3 hr	Schedule II but less euphoria and more adverse effects than Oxy
Morphine (immediate release dosage form)	1.0	1.5-2	4-5	Recommended by AAP for mod-severe peds pain	Not dependent on Phase I metabolism
Hydromorphone (Dilaudid,G)	4.0	1-1.5	4-5	Potent oral morphine,high abuse potential	Not dependent on Phase I metabolism
Meperidine (Demerol,G)	0.1	1-1.5	4-5	Biotransformed to normeperidine, a toxic metabolite, max dose 200mg/24 hours orally	Normeperidine can accumulate with repeated dosing – causing seizures, avoid in pts. on MAOIs
Oxycodone (plain, Percocet,G)	1.5	1	3-4	not useful after 10mg q 3 hr	always a C II substance as it causes euphoria
Tramadol (avoid in pts. On 2D6 inhibitors*)	0.1	1	3-4	2D6 polymorphism may cause toxicity-not for peds	Schedule IV CS, AVOID in children

***Amiodarone, Cimetidine, Desipramine, Duloxetine,Fluoxetine, Paroxetine, Propafenone, Quinidine, Ritonavir**

B. CLINICAL USE OF NARCOTIC ANALGESICS

1. POTENCY ESCALATION

STEP 1. Maximize non opioids

STEP 2. Add Opioids for "rescue"

STEP 3. Increase Opioid potency if needed

Rx: Hydrocodone 5mg w/APAP 325mg (Lorcet,G)
Disp: #8 (5mg of Hydrocodone = 50mg of Tramadol)
Sig: 1 tab q 6 hrs prn pain. Maximum 4tabs/24 hours

Rx: Oxycodone 5mg w/APAP 325mg (Percocet, G)
Disp: #6 (5mg of Oxy = 7.5mg of Hydrocodone)
Sig: 1 tab q 6 hrs prn pain. Maximum 4tabs/24 hours

PATIENT CAUTIONS/INSTRUCTIONS

STEP 1. Combine NSAID&APAP for **SYNERGISM**

STEP 2. Add opioids for additional pain relief or rest

STEP 3. Increase potency only if uncomfortable at rest
- if vestibular or GI problems, try 1/2 dose with 1/2 dosing interval

to provide ADDITIVE pain relief but NOT for anxiety
- consider APAP content of RX when prescribing

-hydrocodone/APAP is Schedule II as of 10/6/14

-oxycodone/APAP has always been Schedule II

NOTE: Percocet now comes in FOUR combinations (2.5/325, 5/325, 7.5/325, 10/325)

C. FIXED OPIOID COMBINATIONS WITH IBUPROFEN – useful for APAP allergic patients

1. **OXYCODONE 5MG/IBUPROFEN 400MG (COMBUNOX)**
2. **HYDROCODONE 2,5, 5.0,7.5mg or 10mg/IBUPROFEN 200mg (VICOPROFEN,g)**

D. ALLERGY VS PSEUDO-ALLERGY

True allergies involve an immune response while other reactions can fall into either side effects or pseudoallergy, which is generally the result of histamine release but no actual immune response. Below are some groups of symptoms followed with points to take into consideration when a patient exhibits one or more of the symptoms.
If the following symptoms occur with respect to opioid administration, they are likely related to a pseudoallergy rather than a true IgE mediated drug allergy:

- ✓ Generalized flushing, itching, sweating
- ✓ Mild hypotension accompanied by nausea and/or vomiting
- ✓ Itching, flushing, or hives at injection/application site

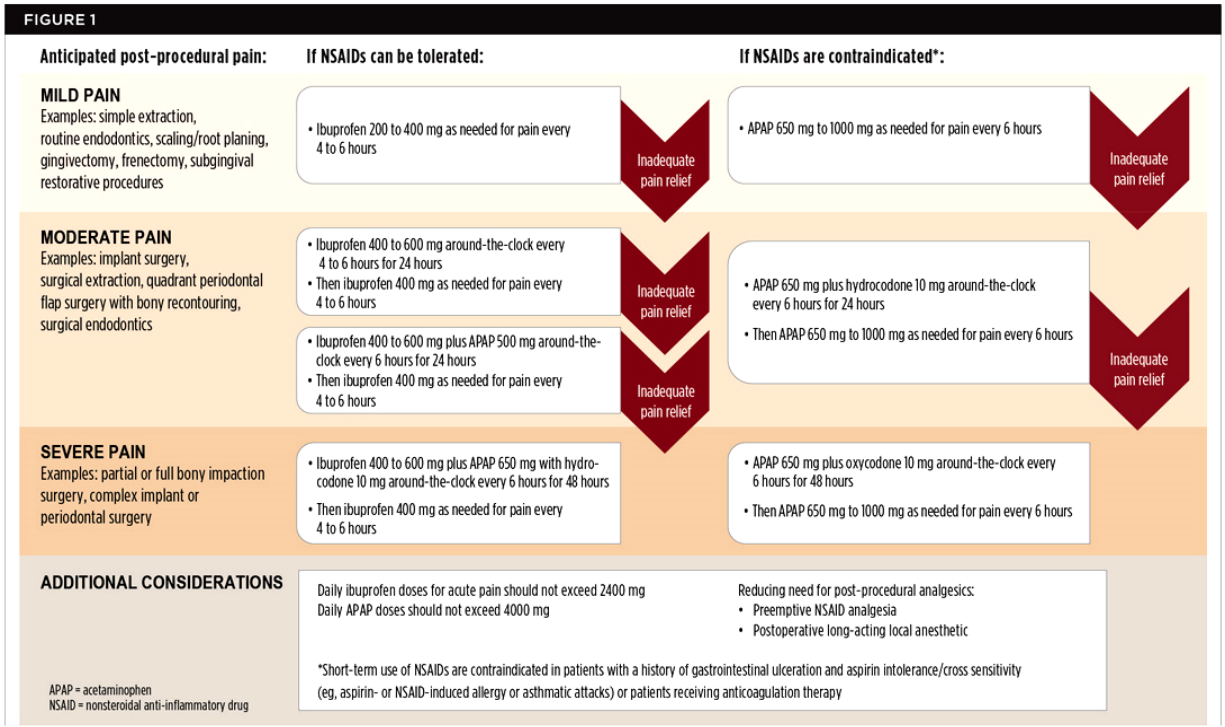
Pseudoallergy reactions can be managed and/or minimized using the following strategies:

- Try nonopioid analgesic if mild pain (acetaminophen & NSAID given at the same time)
- Avoid codeine, morphine & meperidine as these are most likely to trigger pseudoallergy.
- Use a more potent opioid (drugs listed below from least to most potent):
- Meperidine < codeine < morphine < hydrocodone < oxycodone < hydromorphone < fentanyl
- If effective against pain and symptoms are mild, consider administering opioid with an antihistamine such as diphenhydramine 25mg preferably in liquid form 30min prior to opioid dose.
- Consider reduction in opioid dose with more frequent administration if tolerated.

E.Prescribing Analgesics for Postoperative Dental Pain Compendium of Continuing Education in Dentistry

Mana Saraghi, DMD; Elliot V. Hersh, DMD, MS, PhD; Victor M. Badner, DMD, MPH; and Nadia Laniado, DDS, MPH

FIGURE 1



Managing Postoperative Pain in Pediatric Dentistry

Decisions in Dentistry, November 2018; 4(11):32, 35-37.

TABLE 1. Common Medications Used in Children for Mild-to-Severe Postoperative Pain

Analgesic	Pediatric Oral Dosage Children < 12 years (Daily Maximum)	Indication(s)	Caution(s)
Mild-to-Moderate Pain (Examples: Dental procedures, such as restorations, stainless steel crowns, and extractions.)			
Ibuprofen	4–10 mg/kg q6–8h; maximum single dose is 400 mg (40 mg/kg/day)	First-line choice for pain caused by routine dental procedures	Asthmatics, gastric irritant, renal toxicity, liver dysfunction, bleeding (may impair clotting)
Acetaminophen	10–15 mg/kg q4–6h (90 mg/kg/day; not more than five doses/day)	Used for individuals who cannot use an nonsteroidal anti-inflammatory drugs (pregnancy and asthmatics)	Hepatotoxicity
Naproxen Sodium	5–6 mg/kg q12h (1000 mg/day)	While not a typical first-line agent, the longer duration of action may make compliance easier for some patients	Same cautions as those for ibuprofen; over-the-counter instructions will say the medication is for children ≥ 12 years
Moderate-to-Severe Pain (Example: Full-mouth rehabilitation performed under general anesthesia.)			
Ibuprofen and Acetaminophen Combination	**Ibuprofen:** 4–10 mg/kg q6h **Acetaminophen:** 10–15 mg/kg q6h	Alternate each medication every three hours and administer for the first 36–48 hours after surgery	The same cautions listed above for ibuprofen and acetaminophen
Acetaminophen With Oxycodone	0.05–0.1mg/kg/dose of oxycodone Typically, only two to four doses are prescribed for breakthrough pain; maximum doses are limited by daily maximums of acetaminophen	Prescribed for break-through pain; the decision to use this medication may be made in consultation with the patient's primary care physician	In general, opioids are not recommended for children under 12 years of age

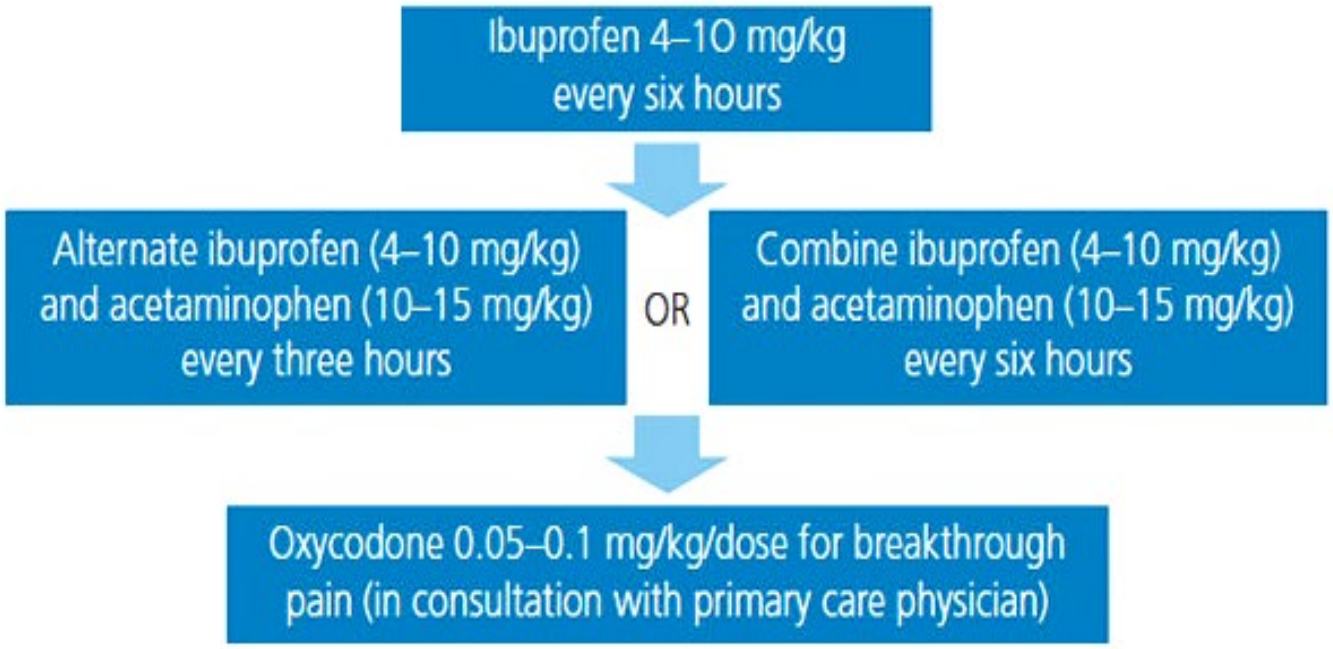


FIGURE 1. Analgesics should be administered around the clock for the first 36–48 hours.

PEDIATRIC ANALGESIC DOSAGES FOR DENTAL PAIN

	ONSET (min)	PEAK (hrs)	DURATION (hrs)	PEDIATRIC DOSE (mg/day)	AVAILABLE PEDIATRIC PREPARATIONS
Non-Opioids					
Acetaminophen (Tylenol, Tempra, Panadol,	20-30	0.5-2	3-7	10mg/kg q 4-6 hrs (max 65mg/kg/day)	Oral Solution: 48-325mg/5ml Chewable tabs: 80 + 160mg Rectal supp: 120,125,325,650mg
Ibuprofen (Advil, Children's Motrin, Medipren, Nuprin, g)	20-30 30 30-45 30-45 18	1-2	4-6	5-10mg/kg q4-6 hrs (max 40mg/kg/day)	Oral Susp: 100mg/5ml Chew tabs: 50, 100mg Caplet:100 ,200mg Tablets: 200,400,600,800mg Liquigels: Advil minis 200mg
Naproxen (Naprosyn, g)	60	1-2	4-7	10mg/kg/day (max 1500mg/day)	Oral Susp: 125mg/5ml Tablets: 250,375,500mg
Naproxen Na (Anaprox, DS, g)	60	1-2	4-7	11mg/kg/day (max 1650mg/day)	Tablets: 220,275, 500mg Caplets: 220mg
Opioids					
Codeine (sulfate or phosphate) (**ultra-fast metabolizers can Suffer toxic effects)-BLACK BOX WARNING in children under the age of 12years. DON'T USE.**	15-30	0.5-1	3-6	0.5mg/kg q4 hr (max120mg/day)	Codeine/APAP elixir: 12mg/120mg per 5ml susp: 12mg/120mg/5ml
Hydocodone (Hydrocet, Lorcet, Vicodin, Zydone, g) **FDA issued Drug Safety Communication 1/11/18 stating that no one under age 18 years should receive codeine, hydrocodone or tramadol for cough/cold. DON'T USE.**	30-60	1-2	4-6	0.1-0.2mg/kg q4-6h (max= 90mg/day)	Lortab Elixir: 2.5 HC + 167 APAP/5ml Tabs: 5/325 (Lorcet,g) 2.5/325 (Lortab) 7.5/325 (Lortab 7.5)
Hydromorphone (Dilaudid,g) **(Not dependent on CYP450 for Activation/metabolism)**	20-30	1	4-5	0.03-0.1mg/kg every 4-6h	Oral Solution: 1mg/ml Tabs: 2mg,4mg,8mg
Morphine (immediate release) **Not dependent on CYP450 for Activation/metabolism**	15-20	1.5-2	4-5	0.2-0.5mg/kg Every 4-6h	Oral Solution:2,4,20mg/ml Tabs:15mg, 30mg Rectal Supp: 5,10,20,30
Oxycodone (immediate release) **(Depends on CYP450 3A4 for metabolism)**	15-30	1-2	4-6	0.05-0.15mg/kg Every 4-6h	Oral Solution: 1 & 20mg/ml Tabs: 5,7.5,10,20,30mg Rectal Supp: 10 & 20mg

Drugs (2021) 81:1627–1643
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REVIEW ARTICLE

Pharmacological Management of Acute Endodontic Pain

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(a)

Pain Intensity	Low	Moderate	Severe
Drugs Prescribed 1-2 days prior to treatment visit and 2-3 days Post-treatment	EXAMPLE A		
	Ibuprofen (200 to 400 mg) 4x day	Ibuprofen (600 mg) + Acetaminophen (500 mg) Both 4x day	Ibuprofen (600 mg) + Acetaminophen (500mg)/ Tramadol (50-100mg) Both 4x day
Drugs Prescribed 1-2 days prior to treatment visit and 2-3 days Post-treatment	EXAMPLE B		
	Naproxen (220 mg) 2x day + Acetaminophen (325mg) 4x day	Naproxen (440mg) 2x day + Acetaminophen (500 mg) 4x day + Acetaminophen (500mg) 4x day	Naproxen (440mg) 2x day + Acetaminophen (500mg)/ Tramadol (50-100mg) Both 4 x day + Acetaminophen (500mg) + Tramadol (50mg a 100mg) All 4 x day

(b)

Pain Intensity	Low	Moderate	Severe
Drugs Prescribed 1-2 days prior to treatment visit and 2-3 days post-Post-treatment	Acetaminophen (325mg) 4x day	Acetaminophen (500mg) 4x day	Acetaminophen (500mg) + Tramadol (50mg a 100mg) All 4 x day

Fig. 3 **a** Flexible prescription plan that could be implemented for patients with no contraindication for NSAIDS including two examples or alternative prescriptions for patients presenting with mild, moderate or severe pain. The plan can be initiated pre-operatively and extend to a minimal of 2–3 days post-treatment. Patient must be instructed to take the medications "by the clock as prescribed" (not "as needed"). **b** Flexible prescription plan that could be implemented for patients with contraindication for NSAIDS but without restrictions related to the use of Acetaminophen. The plan can be initiated pre-operatively and extend to a minimal of 2-3 days post-treatment. Patient must be instructed to take the medications "by the clock as prescribed" (not "as needed")

Drug Interactions Important in Clinical Dentistry

DENTAL DRUG	INTERACTING DRUG	RESULT/MANAGEMENT
ANTIBIOTICS		
Penicillins		
All Penicillins	Bacteriostatic antibiotics (clindamycin, erythromycin, tetracyclines)	Static agent may impair action of penicillins. Consult with other prescriber for modification.
Rare decrease in OC effectiveness with >48 hours of antibiotic therapy. Recommend additional barrier contraception for the remainder of the Pill package.	Methotrexate (Rheumatrex, g)	High dose penicillins may decease MTX secretion. Monitor MTX.
	Oral contraceptives	Rare decrease in estrogen effect. Use barrier contraception for duration of pill cycle.
	Probenecid (Benemid, g)	Tubular secretion of penicillins may be decreased. Usually not problematic.
Ampicillin	Allopurinol (Zyloprim, g)	Doubling in rate of ampicillin rash with concurrent administration (14-22%)
	Atenolol (Tenormin, g)	Atenolol bioavailability may be reduced.
Cephalosporins		
All Agents	Anticoagulants (Coumadin, g)	Risk of bleeding disorders might be increased in anticoagulated patients. Use cautiously.
	Bacteriostatic antibiotics (clindamycin, erythromycin, tetracyclines)	Static agent may impair action of cephalosporins. Consult with other practitioner for modification.
	Probenecid (Benemid, g)	Tubular secretion of penicillins may be decreased. Usually not problematic.
Cefdinir (Omnicef) Cefpodoxime (Vantin) Cefuroxime (Ceftin)	**Increased gastric Ph.** **(Antacids, Axid, Pepcid, Prilosec, Tagamet, Zantac)**	**Reduced absorption of the cephalosporins. AVOID CONCURRENT USE.**
Lincomycins		
Clindamycin (Cleocin, g)	Erythromycin (all macrolides)	Possibility of antagonism. AVOID CONCURRENT USE.
	Kaolin-Pectin	Delay in clindamycin absorption with concurrent use.
	Succinylcholine (Anectine)	Possibility of prolonged respiratory depression. Monitor patient.
Macrolides/Azalides	Alfentanil	Alfentanil actions increased. Use caution.
Azithromycin (Zithromax,Zpak,g) –only agent that does not inhibit CYP450 3A4 but DOES prolong QT interval so only QT prolongation interactions apply to Azithromycin	Anticoagulants (Coumadin, g)	Risk of bleeding disorders is increased in anticoagulated patients. Monitor pt.
	Benzodiazepines (alprazolam, diazepam, triazolam)	Increased benzodiazepine levels resulting in CNS depression. Avoid combination in elderly.
dirithromycin (Dynabac) clarithromycin (Biaxin, Biaxin XL, g) erythromycin (base, EC, EES, PCE)		
	Bromocriptine (Parlodel)	Increase in bromocriptine toxic effects. Consult MD.
	CCBs (diltiazem (Cardizem,g) and verapamil (Isoptin, Calan, Verelan,g)	**QT interval prolongation, sudden death, AVOID CONCURRENT USE**
	Carbamazepine (Tegretol, g)	Increased carbamazepine levels. Avoid concurrent use. Azithromycin is okay.
	Clindamycin	Possible antagonism. AVOID COMBINATION.
	Cyclosporine (Sandimmune, Neoral)	Increased cyclosporine renal toxicity. Consult MD.
	Digoxin	Increased digoxin levels in 10% of patients. May use cautiously.
	Disopyramide (Norpace, g)	Increased disopyramide levels may cause arrhythmias. Use cautiously.

Macrolides(excluding azithromycin)	Ergotamine	Acute ergotamine toxicity. Use cautiously
	Methylprednisolone	Steroid clearance may be decreased. Caution.
	Penicillins	possible antagonism. Avoid static with cidal
	Pimozide (Orap)	Avoid all macrolides-risk of sudden death
	SSRIs (citalopram, escitalopram,fluoxetine, Sertraline, vilazodone)	AVOID CONCURRENT USE MACROLIDES DECREASE METABOLISM OF LISTED SSRIS.MONITOR..
	"**Statins" (except fluva-,pitava-prava)**	**Increased statin levels with possible muscle toxicity. AVOID CONCURRENT USE**
	Theophyllines	Increased theophylline levels (20-25%). Decreased erythromycin levels may also occur. AVOID CONCURRENT USE if possible. SBE prophylaxis should not cause problems.
	Tolterodine (Detrol)	Increased Detrol effects causing arrhythmias
Metronidazole (Flagyl, Flagyl ER, Prostat, g)	Anticoagulants (Coumadin)	Risk of bleeding disorders is increased in anticoagulated patients. Consult MD.
	Barbiturates	Decreased metro. Levels. Increase dose.
	Cholestyramine (Questran, g)	Reduced absorption of metronidazole
	Cimetidine (Tagamet, g)	Metronidazole levels may increase. Not sig.
	Disulfuram (Antabuse)	Concurrent use may result in acute psychosis or confusion.
	Ethanol (IV diazepam, IV TMP-SMZ)	**Risk of disulfuram-type reaction. AVOID CONCURRENT USE**.
	Lithium	Increased lithium levels with possible toxicity. Consult MD.
	Phenytoin (Dilantin)	Eff. of phenytoin may be incr. Monitor closely.
	Quinidine	Increased Quinidine levels. Monitor closely.
	Tacrolimus (Prograf)	Metronidazole doubles Prograf levels
Tetracyclines		
All Agents (doxycycline, minocycline, tetracycline)	Antacids containing Al, calcium, magnesium	Reduced serum concentrations of tets. Space administration by 1-2 hours.
	Bismuth (Pepto-Bismol)	Inhibition of tetracycline absorption. Avoid concomitant administration.
	Iron Salts	Decreased absorption of tets. Space use by 2-3h.Doxy always affected.
	Oral Contraceptives	Slightly increased risk of ovulation. Use additional method during cycle.
Doxycycline (Vibramycin, Periostat??)	Carbamazepine (Tegretol)	Metabolism of doxy increased. Monitor response to doxycycline.
	Methotrexate (highdose IV)	**AVOID DOXYCYCLINE WITH IV METHOTREXATE**
	Phenobarbital	Decreased serum levels and effect of doxy. Monitor clinical response.
	Phenytoin (Dilantin, g)	Phenytoin stimulates doxy metabolism. Increase doxy dose or use other tet.
Tetracycline (Sumycin, Panmycin)	Colestipol (Colestid)	Colestipol binds tet in intestine. Do not administer concomitantly.
	Food (Milk and Dairy)	Decreased absorption of tet. Space use by 2-3 hours.
	Zinc sulfate	Tetracycline absorption is decreased. Space use by 2-3 hours.
Quinolones: all prolong QT interval		
All Agents:	Antacids	Decreased quinolone absorption. AVOID
Ciprofloxacin (Cipro,g))	(iron, sucralfate, zinc)	CONCURRENT USE.
Levofloxacin (Levaquin)	Anticoagulants (Coumadin, g)	Increased risk of bleeding disorders. Monitor
Moxafloxacin (Avelox)		INR.
Ofloxacin (Floxin)	Antineoplastics	Quinolone serum levels may be decreased.
	Cimetidine (Tagamet, g)	Quinolone serum levels may be increased.
	Cyclosporine (Sandimmune, Neoral)	Cyclosporine renal toxicity may be enhanced.
	NSAIDs	Enhanced CNS stimulation
	Probenecid (Benemid, g)	Quinolone serum level may be increased50%.
	Theophylline	Increased theophylline toxicity possible with
Ciprofloxacin	Caffeine	Cipro and other. Consult MD Increased caffeine effects are possible.

ANTIFUNGALS	Anticoagulants (Coumadin)	Increased risk of bleeding disorders in anticoagulated patient. Consult MD.
Systemic Azole Agents (fluconazole, itraconazole, ketoconazole): all agents prolong QT interval		
	Benzodiazepines	Alprazolam, triazolam are contraindicated with itraconazole and ketoconazole. AVOID
	Cyclosporine (Sandimune, Neoral)	Increased cyclosporine levels. Can be used to the patients advantage.
	Rifampin	Decreased levels of the antifungal. AVOID CONCURRENT USE.
	"Statins" (except fluva-,pitava-prava.)	Increased levels and SE of statins.
	Tolterodine (Detrol, Detrol LA)	**Increased Detrol-causing arrhythmias.AVOID**
	Zolpidem (Ambien)	Increased Ambien effect. Caution.
fluconazole (Diflucan)	Cimetidine (Tagamet, g)	Reduced fluconazole levels. AVOID CONCURRENT USE.
	Citalopram (Celexa,g)	**QT interval prolongation.AVOID COMBO.**
	Hydrochlorothiazide	Increased fluconazole levels.
	Losartan (Cozaar, Hyzaar)	Increased Losartan hypotension effect
	Oral Contraceptives	**Decreased estrogen levels. AVOID CONCURRENT USE.**
	Phenytoin (Dilantin, g)	Increased phenytoin levels. Monitor carefully.
	Sulfonylureas	Increased hypoglycemic effect. Monitor blood glucose.
itraconazole (Sporonax)	Digoxin	Increased digoxin levels. AVOID COMBINATION.
	Increased gastric pH	Reduced itraconazole levels
	Isoniazid (INH)	Reduced itraconazole levels
	Losartan (Cozaar)	Increased Losartan hypotension effect
	Sulfonylureas	Increased hypoglycemic effects. Monitor blood glucose.
ketoconazole (Nizoral, g)	Corticosteroids	Possible increase in steroid levels.
	Increased gastric pH	Decreased ketoconazole levels. AVOID CONCURRENT USE.
	Isoniazid (INH)	Decreased ketoconazole levels
	Theophyllines	Decreased theophylline levels. Consult with MD.
NON-NARCOTIC ANALGESICS		
NSAIDS		
(including aspirin and COX-2s)	**Anticoagulants (apixaban, dabigatran,edoxaban,,rivaroxaban,warfarin)**	**Increase risk of bleeding disorders in anticoagulated patient. AVOID COMBO**
	Antihypertensives (all but CCBs)	Decreased antihypertensive effect. Monitor Blood Pressure.
	(ACEI,B-blockers, diuretics)	
	Cimetidine (Tagamet, g)	NSAID levels increased/decreased
	Cyclosporine (Neoral, Sandimmune)	Nephrotoxicity of both agents may be increased. Avoid if possible.
	Combo of ACEor ARB & Diuretic	**30% increase in risk of kidney injury-called the TRIPLE WHAMMY on the kidney!**
	Fluoroquinolones	Increased CNS stimulation
	Lithium	Increased lithium levels. Use sulindac
	Methotrexate (Rheumatrex, Mexate)	Toxicity of methotrexate may be increased. Monitor.
	Phenytoin (Dilantin, g)	Increased phenytoin levels
	Probenecid (Benemid, g)	Increased toxicity of NSAIDs possible.
	Salicylates	**Decreased NSAID levels with increased GI effects. AVOID CONCURRENT USE.**
	SSRIs	Possible increased risk of bleeding but not thought to be clinically significant
COX-2 SELECTIVE NSAID		
Celecoxib (Celebrex)	$2C_9$ inhibitors (fluconazole)	Increased celecoxib levels

Ibuprofen (Motrin, g)	Digoxin	Possible increase in digoxin levels.
Ketorolac (Toradol,g)	Salicylates	Increased Ketorolac free drug conc.
Sulindac	DMSO	Decreased sulindac effectiveness and severe peripheral neuropathy. Avoid concurrent use.
Sulindac	Lithium	Lithium levels remain constant or decrease.
Acetaminophen only	Barbiturates, Carbamazepine, Phenytoin, Rifampin, Sulfinpyrazone	The hepatotoxicity of APAP may be increased by high dose or long term administration of these drugs.
	Cholestyramine (Questran, g)	Decreased APAP absorption. Do not administer within 2 hours of each other.
	Ethanol	Increased hepatotoxicity of APAP with chronic ethanol ingestion.
Tramadol (Ultram, Ultracet, g)	**Any drug that enhances serotonin activity(SSRI antidepressants,"triptans" for acute migraine**	**Possible serotonin syndrome. AVOID CONCURRENT USE**.
	Carbamazepine (Tegretol,g)	Decreased tramadol levels
	MAOI's ()	MAOI toxicity enhanced
	Quinidine	Tramadol increased/metabolite decreased
	Ritonavir (Norvir)	Increased Tramadol effect. AVOID COMBO.
NARCOTIC ANALGESICS		
Opioid analgesics	Alcohol, CNS depressants, local anesthetics, antidepressants, antipsychotics, antihistamines, cimetidine	Increased CNS and respiratory depression may occur. Use cautiously.
	Antimuscarinics and antidiarrheals (e.g. atropine), antihypertensives (e.g. guanadrel)	Opioids increase the effects of these drugs. Use cautiously.
	Buprenorphine, nalbuphine, naltrexone	These drugs block the analgesic effects of opioids. Substitute with NSAIDs.
	Lybalvi (olanzepine/samidorphan)	**Samidorphan is an opioid antagonist so d/c 7 days prior to use of opioid analgesic**
Codeine (Hydrocodone lesser extent)	$2D_6$ Inhibitors, Amiodarone, Cimetidine, Desipramine, Fluoxetine, Paroxetine, Propafenone, Quinidine, Ritonavir	Inhibition of biotransformation of Codeine to active analgesic form. Use different narcotic on $2D_6$ Inhibitor patients.
Meperidine (Demerol, g)/Fentanyl/All Fentanyl derivatives	**MAOIs (Marplan, Nardil, Parnate, Furoxone) selegiline (Eldepryl)**	**Hypertension/hyperpyrexia or coma and hypotension.AVOID CONCURRENT USE if MAOI taken within 14 days**.
	Protease inhibitors	Increased CNS/resp. depression- AVOID
	Ritonavir (Norvir)	Large increase in meperidine. AVOID COMBO.
LOCAL ANESTHETICS	Alcohol,CNS depressants,opioids, antide-pressants,antipsychotics, antihistamines	Increased CNS and resp. depression may occur. Use caution.
	Antiarrhythmic drugs	Increased cardiac depression.
Amides (e.g. lidocaine)	Beta Blockers, cimetidine	Metabolism of lidocaine is reduced. Use caution
Esters (e.g. procaine)	Anticholinesterases (Neostigmine) Sulfonamides	Metabolism of esters reduced. Inhibit sulfonamide action.
VASOCONSTRICTORS (epinephrine,levo-nordefrin)	Inhalation anesthetics (halothane)	Increased chance of arrhythmia
	Tricyclic antidepressants-high dose (amitriptyline, desipramine, imipramine, nortriptyline, etc)	Increased sympathomimetic effects possible. Limit epi to 0.04mg with high dose TCA's.
	Beta-blockers (nonselective)	Hypertensive and/or cardiac rx possible.
	(e.g. propranolol, nadolol)	Limit epi to 0.04mg/2hr. visit.
	Phenothiazines (e.g. chlorpromazine)	Vasoconstrictor action inhibited,leading to possible hypotensive responses. Use cautiously.
	Monoamine Oxidase Inhibitors (MAOIs)	Slight possibility of hypertensive rx.
	Selegiline (Eldepryl,g)	Slight possibility of hypertensive rx.
	COMT Inhibitors (Comtan, Tasmar)	Slight possibility of hypertensive rx.

AGENTS FOR PARENTERAL ANESTHESIA		
Antihistamines		
diphenhydramine (Benadryl) hydroxyzine (Atarax, Vistaril) Promethazine (Phenergan)	Anticholinergics	Increased dry mouth, tachycardia, urinary retention. Monitor.
	CNS depressants (alcohol, narcotics)	Enhanced duration and intensity of sedation. Reduce dosages.
Barbiturates		
methohexital (Brevital,g)	CNS depressants (alcohol, narcotics)	Additive CNS and resp. depression
	Furosemide (Lasix, g)	Orthostatic hypotension
	Sulfisoxazole IV	Sulfa competes with barb. for binding sites. Smaller and more frequent barb. doses may have to be given.
Benzodiazepines		
diazepam (Valium,G)	CNS depressants (anticonvulsants, alcohol)	Oversedation so may use slower titration.
	Cimetidine,OCs,INH,Ketoconazole, Metoprolol, Omeprazole, Propoxyphene, Propranolol,Valproic Acid	Decreased clearance of diazepam. Can avoid with lorazepam.
	Digoxin	Increased digoxin levels.
midazolam (Versed,g)	Calcium Channel Blockers or CCBs (diltiazem-Cardizem, verapamil-Isoptin,Calan, Verelan)	CCBs inhibit Cyp3A4 which prolongs the actions of midazolam. Evaluate patient factors to determine clinical significance.
	CNS depressants (alcohol, barbs)	Increased risk of underventilation or apnea. May prolong the effect of midazolam.
	Erythromycin	Increased midazolam levels. Monitor.
	Narcotics (morphine, meperidine, fentanyl)	Increased hypnotic effect of midazolam. More hypotension with Versed and Demerol.
	Saquinavir (Fortovase)	Increased midazolam levels. AVOID COMBO.
	Thiopental	After premed with Versed, decrease dose of thiopental for induction by 15%
Narcotics		
fentanyl (Sublimaze,g)	Barbiturate anesthetics	Additive CNS and resp. depression.
	Chlorpromazine (Thorazine, g)	Increased toxicity of both agents.
	Cimetidine (Tagamet, g)	CNS toxicity case reports only. (confusion, apnea,
	Citalopram (Celexa,g)	Increased risk of serotonin syndrome
	Diazepam	With high dose fentanyl gives CV depression.
	Droperidol (Inapsine)	Hypotension < pulmonary arterial pressure.
	MAOIs and furazolidone (Furoxone)	**Risk of hypertensive crisis.AVOID COMBO**
	Nitrous Oxide	With high dose fentanyl may cause CV depress.
	Ritonavir (Norvir)	Increased fentanyl levels with Norvir
meperidine (Demerol, G)	Barbiturate anesthetics	Additive CNS and resp. depression
	Chlorpromazine (Thorazine, g)	Increased toxicity of both agents.
	Cimetidine (Tagamet, g)	CNS toxicity as with fentanyl.
	MAOIs and furazolidone (Furoxone)	**Meperidine has predictable and sometimes fatal reactions with use within 14 days. Typel :coma,resp dep,cyanosis,low BP Type2:seizures,hyperpyrexia,hypertension,tachy-cardia. AVOID CONCURRENT USE!!!!!**
	Phenytoin (Dilantin, g)	Decrease meperidine effects by increased hepatic metabolism
Miscellaneous		
etomidate (Amidate)	Verapamil	Possibility of prolonged anesthesia
ketamine (Ketalar,g)	Barbiturates	Prolonged recovery time.
	Thyroid Hormone	May produce hypertension/tachycardia
	Tubocurarine and nondepolarizing muscle relaxants	Ketamine may increase neuromuscular effects and result in prolonged resp. depression.
Propofol (Diprivan, G)	CNS depressants (sedative/hypnotic, inhalation anesthetics, narcotics)	Increase CNS depression of propofol. Premed with narcotics may lead to more pronounced decrease in systolic, diastolic, and mean arterial pressures and cardiac output.

QT Prolongation and Torsades de Pointes: Drugs and Sudden Death [20 CDN'2023]

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What is Torsades de Pointes (TdP)?

- TdP or "twisting of the points" refers to a polymorphic ventricular tachycardia.
- It is associated with a prolonged QT_c interval and bradycardia; patients may also report shortness of breath or syncope.
- TdP is thought to be caused by early after-depolarizations during prolonged repolarization.[1]
- It is often self-limiting but may be **potentially fatal**, sometimes leading to syncope and/or sudden death.
- TdP can be 1° (congenital) or 2° (acquired) due to metabolic disturbances, medical conditions, or (**most commonly**) drugs.[1]
- Some USA black box **FDA WARNINGS** due to QT prolongation: amiodarone, cisapride, droperidol, itraconazole & thioridazine.[13]
- Drug **FDA REMOVALS** due to QT prolongation: astemizole HISMANAL, grepafloxacin RAXAR & terfenadine SELDANE.[13]

Who is at risk?[1-6,14] - may use scoring system e.g. Pro-QTc score,[17] Tisdale Risk Score[18], 1-2-3-LQTS-Risk [19]

- The "**multiple hit**" theory suggests that a culmination of several factors is required to induce TdP.[2]
- Generally, these factors promote early after-depolarizations or prolongation of the action potential.[1]

Table 1: Risk Factors for QT interval Prolongation and TdP [1-6,14] greatest significance highlighted in yellow

Cardiac underlying conditions	Metabolic	Other
Bradycardia < 50 bpm	Altered nutritional status:	**Age** - ↑ risk with **↑ age**
Cardiomyopathy:	Alcoholism	Cerebrovascular disease
Heart failure	**Anorexia**, starvation	**Female sex** –sex hormones regulate channel expression
Left ventricular hypertrophy	Diabetes	**Herbs**: e.g. aloe, echinacea, gingko, ginseng, licorice, St Johns wort
Myocardial infarction	Electrolyte disturbances:	**Hypothyroidism**
Congenital long QT interval	**Hypokalemia**	Obesity Pacritinib, Vernakalant, Fexinidazole
(incidence ~ 1/2500)[8]	**Hypomagnesemia** e.g. PPI's	Pituitary insufficiency; Male hypogonadism
Hypertension	Hypocalcemia	Poisoning –arsenic, organophosphates, nerve gas
Ischemic heart disease	Hypoglycemia	**Renal** & Liver disease
	Hypothermia	**DRUGS (see Table 2), esp. at high-dose & if IV**

Which drugs are implicated?

- Many **drugs** from a variety of therapeutic classes have been associated with **QT interval prolongation** and/or TdP **(see table)**.
- All of these drugs have in common their ability to block the I(kr) potassium channel; this results in ↑ repolarization time & a prolonged QT interval (beginning of QRS complex to end of T wave) on ECG.[1] Inward Na^+ & Ca^{++} influx channels may be affected.[8]
- Prolongation of the QT interval is thought to be **dose-related** and can occur within therapeutic range for some agents (e.g. amiodarone) but only at supra-therapeutic concentrations for others (e.g. clarithromycin).
- Different drugs can be **additive**. (Besides QT/DI's effects, a metabolic effect may be important e.g. ↓K^+⇒ **diuretics, laxatives**).
- Watch for drug interactions increasing risk of QT prolongation - see column on Cytochrome P450 Inhibitors.

How to avoid trouble:[2,6] Beware of common warning symptoms: dizziness, palpitations & syncope.

- **Identify those at risk** (Table 1); be aware however, that individuals' vulnerability can vary greatly due to a complexity of genetic and environmental factors which are not completely understood. Check family hx for syncope!
- **For patients with major or multiple risk factors, obtain a baseline ECG** and determine the QTc interval [corrected for heart rate (caution: correction less accurate with very fast or slow heart rates) – equation described elsewhere[7]].
- Long QTc interval is > 470msec for postpubertal males & > 480msec for postpubertal females.

Short QTc ≤ 410 msec ..... VERY LOW RISK[2]

-may not require ECG monitoring after initiating a QT-prolonging agent. Start monitoring if additional risk factors develop or if a drug interaction is likely.

Intermediate QTc 411-449 msec ..... LOW to MODERATE RISK

- repeat ECG after initiating any QT-prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT-prolonging agent is added or if a drug interaction is likely.
- if QTc ≥ 450 msec, reduce dosages or avoid these agents and use alternatives.

Prolonged QTc ≥ 450 msec ..... MODERATE to HIGH RISK

- repeat ECG after initiating any QT-prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT-prolonging agent is added or if a drug interaction is likely
- if **QTc > 500 msec or > 60 msec over baseline avoid** these agents and use alternatives
- regular **monitoring of serum K+ and Mg++** also advised

Rule of thumb:[8]

A QTc change of < 10 msec is acceptable as long as there are no other significant risk factors.
If the QTc change is > 10 msec, reduce dosage or eliminate the drug(s), monitor more closely.

How to treat TdP:

Emergency:[9] *Do not use standard antiarrhythmics.*

- Give **magnesium** sulphate 2g IV over 2min. If ineffective, consider isoproterenol, dobutamine, or atropine IV.
- Consider potassium if serum K+ is low; bicarbonate for TCP (phencyclidine) or quinidine poisoning.
- Lidocaine & phenytoin have also been used; alternatives are cardiac pacing & isoproterenol.
- **Later:** Stop the offending agent. Maintain normal K^+, Mg^{++}, HCO_3^-. Keep out of trouble as above.

Table 2: Drugs which can prolong QT Interval [1,3,6,9,12,13,14] - see www.torsades.org / www.crediblemeds.org

Cardiovascular

Anti-arrhythmics
Amiodarone (low risk of TdP compared to other class III agents such as sotalol; however potential for DIs)
Bepridil
Bretylium
Diltiazem
Disopyramide
Dofetilide
Dronedarone
Flecainide
Hydroquinidine
Ibutilide
Mexiletine
Nifekalant
Procainamide
Propafenone
Quinidine less at ↑ dose
Sotalol 0.3% at 80mg/day, 3.8% at > 680mg/day
Vernakalant

Dobutamine
Dopamine
Isradipine
Nicardipine
Norepinephrine
Ranolazine

Caution: COMBINATIONS of PHENOTHIAZINES with TCAs, BETA BLOCKERS, & ANTICONVULSANTS since ↑ QT risk especially if ↑↑ risk factors present.

CNS / Psychotropic

ADHD agents
Amphetamine
Atomoxetine
Dextroamphetamine
Guanfacine
Lisdexamfetamine
Dex- & Methylphenidate
Serdexmethylphenidate

Antipsychotics
Amisulpride, Asenapine, **Aripiprazole,** Benperidol, **Brexpiprazole**
Butyrophenones
Haloperidol esp. if ↑ dose or IV
Chlorprothixene,Clotiapine
Clozapine, Flupentixol, Iloperidone, **Levosulpiride,** Lumateperone, Lurasidone
Paliperidone,
Phenothiazines
Chlorpromazine
Mesoridazine
Methotrimeprazine
Perphenazine
Thioridazine
Pimavanserin
Pimozide
Quetiapine
Risperidone
Sertindole, Sultopride
Tiapride
Ziprasidone, Zotepine
Zuclopenthixol

Anticonvulsants
Felbamate
Lithium

SSRIs
Citalopram >40mg/d; >20mg in elderly
Escitalopram if >20mg/day, or >10mg in elderly
Fluoxetine
Fluvoxamine
Paroxetine (esp. ↑ pimozide)
Sertraline-concentration dependent
Trazodone

Gepirone

SNRI
Des & -venlafaxine
Mirtazapine

TCAs
Amitriptyline
Amoxapine -seems ok
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protripyline -seems ok
Trimipramine
Moclobemide

Mianserin

Anti-Infective

Antibiotics
Cotrimoxazole
Fluoroquinolones
Ciprofloxacin mainly through DI on a ↑QT drug, but some direct QT effect
Gatifloxacin
Gemifloxacin
Garenoxacin
Levofloxacin
Moxifloxacin
Nemonoxacin
Norfloxacin
Ofloxacin
Sparfloxacin
Lefamulin
? Linezolid
Macrolides
Azithromycin
Clarithromycin
Erythromycin[11]
Roxithromycin
Telavancin
Telithromycin

Azole Antifungals
Fluconazole
Itraconazole
Levoketoconazole
Ketoconazole
Posaconazole
Voriconazole

Antimalarials
Artemether/lumefantrine
Chloroquine
Halofantrine
Hydroxychloroquine
Mefloquine
Piperaquine
Primaquine
Quinine
Pentamidine

Metronidazole

Top 3 suspected drugs:
1) **sotalol** 66% (58/88) 2) **digoxin** 11% (10/88)
3) **citalopram** 10% (9/88)
[**Swedish ADR Registry 2008**: n=61,788 ADRs, n=88 torsades (0.14%)][15]

Drugs removed from USA due to QT: astemizole, cisapride, grepafloxacin, levomethadyl, probucol, & terfenadine.

Miscellaneous

Abarelix, Abiraterone acetate , **Aclarubicin**, Alfuzosin, Alimemazine, Alpelisib, Amantidine, Amphotericin B, Amsacrine, Anagrelide, Apalutamide, Apomorpine, **Arsenic** trioxide, Asciminib, Atazanavir, Bedaquiline, Bendrofluazide, Betrixaban, Bicalutamide,Bosutinib, Brigatinib, Buprenorphine, Cabozantinib, Caffeine, Capecitabine, Carbetocin, **Ceritinib, Cesium chloride**, Chloral hydrate, Cilostazol, Cinacalcet, **Cisapride** (special access), Clofazimine, **Cocaine**, Cobimetinib, Crizotinib, Cyclosporine, Dasatinib, Degarelix, Delamanid, Dexmedetomidine, Dextromethorphan+ Quinidine, **Donepezil**, Efavirenz, Eliglustat, Encorafenib, Energy drinks, entrectinib, Enzalutamide, Eperisone, Epirubicin, Eribulin, Etrasimod, Ezogabine, Fenspiride, Fexinidazole, Fingolimod, Fluorouracil, Foscarnet, Galantamine, Ginseng, Gilteritinib , Glasdegib, Gilteritinib, Givinostat, Goserelin, Grapefruit juice ~ 1 liter, Histrelin, Hydrocodone ER, **Hydroxyzine**, Ibogaine, Imatinib, Indapamide, ?Inotuzumab ozogamicin, Isoflurane, **Ivabradine**, Ivosidenib, Kaletra, Ketanserin, Lacidipine, Lapatinib, Lenvatinib, Leuprolide, Levetiracetam, **Levmetamfetamine,** Levomethadone, Levomethadyl, Loperamide: abuse or DI's, Lopinavir/Ritonavir, Lofexidine, Macimorelin, **Meglumine antimoniate, Methadone,** Metolazone, Mididorine, Midostaurin, Mifepristone, Mirabegron, **Mobocertinib** , Motixafortide, Necitumumab, Nilotinib, Nusinersen, Octreotide, Oliceridine, Orphenadrine, Osilodrostat, Osimertinib, **Oxaliplatin**, Oxytocin, Oxycodone, Oxymetazoline, Ozanimod, Pacritinib, Panobinostat, **Papaverine IV**, Pasireotide, Pazopanib, Phenylephrine, Pilsicainide, Pitolisant, Ponesimod, Pretomanid, **Probucol**, **Propofol**, **Propoxyphene**, Pseudoephedrine, Pralsetinib, Prothipendyl, **Quizartinib**, Relugolix, Remdesivir, Remimazolam, Ribociclib, Rilpivirine ≥75mg/d, Ritodrine, Rivastigmine, Romidepsin, Rucaparib, **Saquinavir**, Selpercatinib, **Sevoflurane**, Sibutramine, Siponimod, Solifenacin, Sorafenib, Sunitinib, Tacrolimus, Tamoxifen, Tazemetostat, Tebentafusp, Telaprevir, **Terodiline**, Tizanidine, Tolterodine, Torsemide, **Tramadol**, **Triclabendazole, Trifluridine,** Triptans recently off QT list, Triptorelin, Valbenazine, **Vandetanib**, Vardenafil, **Vemurafenib**, Voclosporin & Xylometazoline.

Antiemetics
Dolasetron esp if IV
Domperidone esp if IV, >30mg orally/day or with ketoconazole/3A4 inhibitors
Droperidol more if ≥ 1.25mg
Granisetron, Metoclopramide
Ondansetron esp ≥ 32mg **IV**, avoid over 8mg if ≥75yr ; >16mg if <75yr
Palonosetron; Promethazine
Tropisetron

Appetite suppressant
Benzphetamine, **Diethylpropion**, Ephedrine, Fenfluramine, **Phendimetrazine**, Phentermine, Sibutramine

Antihistamines
Bilastine, Diphenhydramine Clemastine, Loratidine (but no reports), Rupatadine.
Withdrawn: Astemizole, Terfenadine

Bronchodilators
Epinephrine, Fenoterol, Indacaterol, Isoproterenol, Levalbuterol, Metaproterenol, **Olodaterol,** Salbutamol/Albuterol, Salmeterol, Terbutaline, **Vilanterol** minimal at 100mcg

Cytochrome P450 Inhibitors (DIs)

- Since many QT-prolonging agents are metabolized by the **cytochrome P450 system**, serious and sometimes lethal drug interactions can occur when combined with drugs which **inhibit** or compete for binding to these isoenzymes.
- **Some drugs** (eg. erythromycin & amiodarone) **prolong the QT Interval AND act as inhibitors to potentially increase levels or QT effects of concomitant medications.**

CYP3A4 Inhibitors
Amiodarone; Azole antifungals (e.g. Flu-, Itra-, & Keto-conazole); **Calcium channel blockers** (Diltiazem, Verapamil); Cimetidine; **Ciprofloxacin;** Grapefruit juice; **HIV protease inhibitors; Macrolides** (**Clarithromycin**, **Erythromycin**, Troleandomycin, NOT Azithromycin); Methadone; Telithromycin; **SSRIs** (Fluoxetine, Fluvoxamine, Norfluoxetine, Nefazodone, **Paroxetine**); Trazodone

CYP2D6 Inhibitors
Beta Blockers, Haloperidol, Phenothiazines, Quinidine, SSRIs (NOT citalopram), Terbinafine, TCAs

CYP1A2 Inhibitors (less significant)
Fluoroquinolones, Fluvoxamine, Grapefruit juice

Miscellaneous:
Piperacillin/tazobactam may ↓ K^+ ⇒ QT risk.
PPI's (eg. omeprazole) may ↓magnesium⇒ QT risk.

BOLD=major significance (well-documented) REGULAR=low-moderate significance (fewer case reports) *ITALIC=minor significance (theoretical, few if any case reports)*

(**Long QT syndrome**: a familial condition associated with recurrent syncope & sudden cardiac death resulting from ventricular arrhythmias; may be misdiagnosed as epilepsy. Triggers for arrhythmias: meds that prolong the QT interval or subtype specific factors such as swimming & other exercise (long QT1), auditory stimuli & emotional stress (long QT2), & rest or sleep (long QT3 ? mexiletine benefit). **β-blockers** (**nadolol**, propranolol) are usually effective; **implantable cardioverter defibrillators** reserved for people deemed at high risk or refractory to medical treatment. Thoracoscopic left cardiac sympathectomy an option - highly effective & useful if β-blockers not tolerated or an implantable cardioverter defibrillator is contraindicated.) [Abrams 2010]