



Department of Vermont Health Access

Therapeutic Class Review Tetracyclines

Overview/Summary

Tetracyclines have a broad spectrum of activity and are active against most *Rickettsia*, *Chlamydia*, *Mycoplasma* and many other gram-negative and -positive bacteria.¹ In general, the antimicrobial activity of the tetracyclines is essentially the same, although some differences in the relative degree of activity against certain pathogens do exist.² This class of antibiotics works by inhibiting protein synthesis in susceptible organisms by reversibly binding to 30S ribosomal units.^{1,2} Of note, at high concentrations, tetracyclines can also inhibit mammalian protein synthesis. Tetracyclines are typically bacteriostatic in action, but in high concentrations or against highly susceptible organisms they may be bactericidal. Tetracyclines are also effective in the treatment of severe acne. The exact mechanisms by which the tetracyclines reduce lesions of acne vulgaris are not fully understood, but the effect appears to result in part from the antibacterial activity of the agents. Following oral administration, tetracyclines inhibit growth of susceptible organisms on the surface of the skin and reduce the concentration of free fatty acids in sebum. However, other mechanisms also appear to be involved.¹

Of the available tetracyclines (demeclocycline, doxycycline, minocycline, tetracycline), doxycycline and minocycline are the most frequently prescribed. Furthermore, doxycycline is one of the most active agents and is used most often clinically due to several advantages it possesses over the others available within the class. Specifically, doxycycline can be administered twice daily, achieves reasonable concentrations even if administered with food and is less likely to cause photosensitivity; a concern associated with this class of antibiotics. In addition, doxycycline may be an alternative for use in children because it binds calcium to a lesser extent than tetracycline, reducing the risk for tooth discoloration and bony growth retardation; which are other concerns associated with the tetracyclines.²

Included in this review are the oral tetracycline agents. Of note, Periostat[®] (doxycycline hyclate immediate-release) is only Food and Drug Administration (FDA) approved for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.³ In addition, Solodyn[®] (minocycline extended-release) also has only one FDA approved indication; treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age or older.⁴ All other available tetracyclines are FDA approved for a wide variety of bacterial infections which are outlined in Table 3.⁵⁻¹⁷ There are several different formulations of both doxycycline and minocycline currently available. Specifically, doxycycline is available as a capsule, delayed-release tablet, suspension, syrup and tablet. Minocycline is available as a capsule, extended-release tablet and tablet. In general, no significant clinical differences have been found among the various formulations, and all agents in the class are available generically in at least one dosage form and/or strength.³⁻¹⁷

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Demeclocycline*	Tetracycline	✓
Doxycycline (Adoxa ^{®*} , Adoxa Kit [®] , Adoxa Pak ^{®*} , Doryx [®] , Morgidox ^{®*} , Morgidox Kit [®] , Periostat ^{®*} , Vibramycin ^{®*})	Tetracycline	✓
Minocycline (Dynacin ^{®*} , Solodyn ^{®*})	Tetracycline	✓
Tetracycline*	Tetracycline	✓

*Generic available in at least one dosage form or strength.

The tetracyclines have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration approved indications for the tetracyclines that are noted in Table 3. The tetracyclines may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known; once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Tetracyclines³⁻¹⁷

Bacteria	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Gram-Positive Aerobes				
<i>Alpha-hemolytic streptococci</i>		✓ *		✓
<i>Bacillus anthracis</i>	✓	✓ †	✓	
<i>Enterococcus</i> spp.		✓ *		✓
<i>Listeria monocytogenes</i>	✓	✓ †	✓	
<i>Staphylococcus aureus</i>	✓	✓ †	✓	
<i>Streptococcus faecalis</i>		✓		
<i>Streptococcus pneumoniae</i>	✓	✓ *	✓	✓
<i>Streptococcus pyogenes</i>		✓ *		✓
Gram-Negative Aerobes				
<i>Acinetobacter</i> spp.	✓	✓	✓	✓
<i>Bacteroides</i> spp.		✓ *		✓
<i>Bartonella bacilliformis</i>	✓	✓	✓	✓
<i>Brucella</i> spp.	✓	✓	✓	✓
<i>Calymmatobacterium granulomatis</i>	✓	✓	✓	
<i>Campylobacter fetus</i>	✓	✓ †	✓	
<i>Enterobacter aerogenes</i>	✓	✓	✓	✓
<i>Enterobacter</i> spp.				
<i>Escherichia coli</i>	✓	✓	✓	✓
<i>Francisella tularensis</i>	✓	✓	✓	✓
<i>Haemophilus ducreyi</i>	✓	✓	✓	✓
<i>Haemophilus influenzae</i>	✓	✓	✓	✓
<i>Haemophilus parainfluenzae</i>				
<i>Klebsiella</i> spp.	✓	✓	✓	✓
<i>Neisseria gonorrhoeae</i>	✓	✓	✓	✓
<i>Neisseria meningitidis</i>			✓	
<i>Shigella</i> spp.	✓	✓	✓ ‡	✓
<i>Vibrio cholera</i>	✓	✓	✓	✓
<i>Yersinia pestis</i>	✓	✓	✓	✓
Other Microorganisms				
<i>Actinomyces israelii</i>	✓	✓ †		✓
<i>Actinomyces</i> spp.		✓ *	✓	
<i>Bacillus anthracis</i>		✓ *		✓
<i>Balantidium coli</i>		✓ *		✓
<i>Borrelia recurrentis</i>	✓	✓	✓	✓
<i>Chlamydia psittaci</i>	✓	✓	✓	✓
<i>Chlamydia trachomatis</i>	✓	✓	✓	✓
<i>Clostridium</i> spp.	✓	✓	✓	✓
<i>Entamoeba</i> spp.	✓	✓ *	✓	✓
<i>Fusobacterium fusiforme</i>	✓	✓	✓	✓
<i>Mycobacterium marinum</i>			✓	

Bacteria	Demeclocycline	Doxycycline	Minocycline	Tetracycline
<i>Mycoplasma pneumoniae</i>	✓	✓	✓	
<i>Plasmodium falciparum</i>		✓ *		
<i>Propionibacterium acnes</i>	✓	✓ *	✓	✓
<i>Rickettsiae</i>	✓	✓	✓	
<i>Treponema pallidum</i>	✓	✓	✓	✓
<i>Treponema pertenuis</i>		✓	✓	✓
<i>Ureaplasma urealyticum</i>	✓	✓ *	✓	✓

*Doxycycline hyclate.

†Doxycycline monohydrate.

‡Minocycline capsules.

Indications

Table 3. Food and Drug Administration Approved Indications³⁻¹⁷

Indication	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Alternative Treatment for Selected Infections When Penicillin is Contraindicated				
Gonococcal infections, uncomplicated	✓	✓ *	✓ *	
Listeriosis	✓		✓ *	
Syphilis	✓	✓	✓ *	✓
Vincent's infection	✓	✓	✓ *	✓
Yaws	✓	✓	✓ *	✓
Central Nervous System				
Treatment of asymptomatic meningococcal carriers			✓ *	
Dermatological				
Severe acne	✓ †	✓ †	✓ ‡	✓ †
Skin and soft tissue infections	✓		✓ *	✓
Gastrointestinal				
Acute intestinal amebiasis	✓	✓	✓ *	✓
Cholera	✓	✓	✓ *	✓
Genitourinary conditions				
Chancroid	✓	✓	✓ *	✓
Urinary tract infections	✓	✓	✓ *	✓
Ophthalmic Infections				
Conjunctivitis (inclusion)	✓	✓	✓ *	✓
Trachoma	✓	✓	✓ *	✓
Respiratory Infections				
Anthrax	✓ §	✓	✓ *§	✓ §
Psittacosis	✓	✓	✓ *	✓
Respiratory tract infection	✓	✓	✓ *	✓
Rickettsial Infections				
Disease caused by rickettsiae	✓	✓	✓ *	✓
Q fever	✓	✓	✓ *	✓
Rickettsialpox	✓	✓	✓ *	✓
Rocky Mountain spotted fever	✓	✓	✓ *	✓
Typhus	✓	✓	✓ *	✓
Sexually Transmitted Infections				
Endocervical infections			✓ *	✓
Granuloma inguinale	✓	✓	✓ *	✓
Lymphogranuloma venereum	✓	✓	✓ *	✓
Nongonococcal urethritis	✓	✓	✓ *	

Indication	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Rectal infections			✓ *	✓
Urethritis, uncomplicated	✓ §		✓ *§	✓
Miscellaneous				
Malaria prophylaxis		✓		
Periodontitis		✓		
Plague	✓	✓	✓ *	✓
Relapsing fever	✓	✓	✓ *	✓
Tularemia	✓	✓	✓ *	✓

*Immediate-release only.

†May be useful as adjunctive therapy.

‡Solodyn® (minocycline extended-release tablets) are indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age or older. Minocycline immediate-release may be useful as adjunctive therapy.

§ When penicillin is contraindicated.

|| Periostat® (doxycycline hyclate immediate-release tablets) indicated as adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Pharmacokinetics

Table 4. Pharmacokinetics¹⁸

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Demeclocycline	Not reported	34 to 56	None	10 to 15
Doxycycline	Good (% not reported)	35 to 45	None	15 to 24
Minocycline	90	10 to 13	None	11.0 to 22.1
Tetracycline	Not reported	60	None	8 to 10

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the tetracyclines in their respective Food and Drug Administration (FDA) approved indications are outlined in Table 5.¹⁹⁻⁴³ Of note, clinically relevant trials evaluating tetracycline as combination therapy for the eradication of *Helicobacter pylori* infections have also been included. Despite being noted as an off-label use, treatment guidelines recognize tetracycline as part of the recommended first line combination therapies.^{44,45} Results from the two trials were consistent. In both, tetracycline was administered as part of a quadruple drug combination regimen and compared to a standard, triple drug combination regimen. In both trials, the quadruple drug combination regimen demonstrated significantly better eradication rates of *H pylori* ($P < 0.05$ and $P < 0.001$).^{30,31}

As mentioned earlier, the tetracyclines are approved for the treatment of moderate to severe acne. Several clinical trials have been conducted; however, they are of relatively poor quality and have small patient populations. However, in line with treatment guidelines, the oral tetracyclines demonstrate efficacy in reducing baseline comedone, inflammatory and noninflammatory lesion counts, and in some trials, in improving clinician global assessment of the condition.^{19,21-29,46,47} In general, head-to-head trials do not consistently demonstrate "superiority" of one tetracycline over another.²⁵⁻²⁹ Results of a Cochrane Review could not reliably determine the relative efficacy of minocycline to other acne treatments due to the poor methodological quality of the trials included and the lack of consistent outcomes measured; however, results demonstrated that minocycline is likely to be an effective treatment for moderate acne vulgaris.²⁸

The remaining clinical trials consistently demonstrated the effectiveness of the tetracyclines in the treatment of their FDA approved indications, with no significant differences observed among the available agents in class.³²⁻⁴³

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acne Vulgaris				
Toossi et al ¹⁹ Doxycycline 20 mg BID vs doxycycline 100 mg/day	DB, PRO, RCT Patients with moderate facial acne	N=100 3 months	Primary: Efficacy Secondary: Safety	Primary: With both treatments, the mean inflammatory lesion count reduced significantly at each visit when compared to baseline (<i>P</i> values not reported). The improvements were evident after one month of treatment. Secondary: Doxycycline 40 mg/day was well tolerated. A total of seven adverse events occurred; one and six with doxycycline 40 and 100 mg/day (<i>P</i> values not reported).
Goulden et al ²⁰ Minocycline modified release 100 mg/day vs minocycline modified release 100 and 200 mg/day on alternate days vs minocycline modified release 200 mg/day	RCT Patients with acne vulgaris	N=700 10.5 months (mean duration; range, 2 weeks to 4 years)	Primary: Safety Secondary: Not reported	Primary: Side effects were recorded in 13.6% of patients and included vestibular disturbance, candida infection, gastrointestinal disturbance, cutaneous symptoms (pigmentation, pruritis, photosensitive rash and urticaria) and benign intracranial hypertension. Side effects occurred in 8.4, 6.9 and 10.9% of patients receiving minocycline 100 mg/day, 100 and 200 mg/day on alternate days and 200 mg/day. The increase in side effects with increasing dose was not significant (<i>P</i> >0.05). Pigmentation was the only side effect found to be significantly increased with minocycline 200 mg/day (4.0%) compared to the lower doses (100 mg/day, 0.4%; 100 and 200 mg/day on alternate days, 1.1%; <i>P</i> <0.01). No differences between the doses were found in any hematological and biochemical profiles. Secondary: Not reported
Plewig et al ²¹ Doxycycline 200 mg/day for 4 weeks vs	PC, RCT, XO Patients ≥14 years of age with predominantly inflammatory acne	N=62 12 weeks	Primary: Inflammatory count response (excellent, >75.0% reduction; good, 50.0 to 74.9% reduction; fair, 25.0	Primary: Thirty three and 22% of patients showed good or excellent response with doxycycline and placebo (<i>P</i> value not reported). Open and closed comedones showed a poor response with both treatments (76 vs 76%). A good or excellent improvement in papules was achieved in 43 and 20% of patients receiving doxycycline and placebo. A good or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo for 4 weeks			<p>to 49.9% reduction; poor, no change to 24.9% reduction; worsening, an increase in lesions), response by particular lesion type (open comedo, closed comedo, papule, pustule, cyst)</p> <p>Secondary: Not reported</p>	<p>excellent improvement in pustules was achieved in 39 and 24% of patients receiving doxycycline and placebo. A good or excellent improvement in cysts was achieved in 25 and 17% of patients receiving doxycycline and placebo (<i>P</i> values not reported).</p> <p>Doxycycline reduced the number of inflammatory lesions (Phase 1; <i>P</i><0.001 and Phase 2; <i>P</i><0.05) whereas placebo led to either a worsening or had no effect (<i>P</i>>0.05 for both Phases).</p> <p>Secondary: Not reported</p>
<p>Skidemore et al²²</p> <p>Doxycycline 20 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Adults with moderate facial acne</p>	<p>N=51</p> <p>6 months</p>	<p>Primary: Change from baseline in number of inflammatory, noninflammatory and total lesions</p> <p>Secondary: Global assessment of clinical improvement</p>	<p>Primary: After six months, doxycycline had a significantly greater percent reduction in the number of comedones (54 vs 11%; <i>P</i><0.01), inflammatory and noninflammatory lesions combined (52 vs 18%; <i>P</i><0.01) and total inflammatory lesions (50 vs 30%; <i>P</i>=0.04) compared to placebo.</p> <p>Secondary: Doxycycline achieved a significantly greater improvement compared to placebo in clinician's global assessment (<i>P</i>=0.03), but not in patient's global assessment (<i>P</i> value not reported).</p>
<p>Parish et al (abstract)²³</p> <p>Doxycycline 20 mg BID</p> <p>vs</p> <p>placebo</p> <p>All patients received</p>	<p>PC, RCT</p> <p>Patients ≥14 years of age with acne vulgaris</p>	<p>N=14</p> <p>16 weeks</p>	<p>Primary: Efficacy</p> <p>Secondary: Not reported</p>	<p>Primary: During the first eight weeks of treatment, 11 patients had a 50% reduction in lesions, which qualified them to enter the second eight week phase of the trial. During this time, six patients receiving doxycycline maintained their improvement while those randomized to placebo did not.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>doxycycline for the first 8 weeks of treatment.</p> <p>Based on response to treatment, patients were then randomized to either doxycycline or placebo for another 8 weeks.</p>				
<p>Fleischer et al (abstract)²⁴</p> <p>Minocycline ER 1 mg/kg/day</p> <p>vs</p> <p>placebo</p>	<p>2 DB, MC, PC, PRO, RCTs</p> <p>Patients with moderate to severe acne</p>	<p>N=1,038</p> <p>12 weeks</p>	<p>Primary: Efficacy, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Independently, each trial demonstrated that minocycline significantly reduced the number of inflammatory lesions and significantly improved EGSA scores ($P < 0.001$ for both). Pooled analysis demonstrated similar benefits (P values not reported).</p> <p>The proportion of patients reporting acute vestibular adverse events was comparable between treatments (approximately 10% for both treatments). Individual and pooled analyses were similar (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Laux B (abstract)²⁵</p> <p>Doxycycline 50 mg once daily</p> <p>vs</p> <p>minocycline 50 mg BID</p>	<p>RCT</p> <p>Patients with acne vulgaris</p>	<p>N=50</p> <p>12 weeks</p>	<p>Primary: Efficacy</p> <p>Secondary: Not reported</p>	<p>Primary: Cure or improvement of acne was found in 78 and 82% of patients receiving doxycycline and minocycline (P value not reported). The rate of unsatisfactory therapeutic results was 22 and 18% (P value not reported). The authors note that no differences between the two treatments were found.</p> <p>Secondary: Not reported</p>
<p>Hubbell et al²⁶</p> <p>Minocycline 50 mg BID</p>	<p>DB, RCT</p> <p>Patients ≥ 14 years of age with Pillsbury</p>	<p>N=49</p> <p>6 months</p>	<p>Primary: Proportion of patients who converted to grade</p>	<p>Primary: There were no significant differences between the two treatments with regard to the proportion of patients who achieved grade 1 acne, who had a least two consecutive visits at which they had grade 1 acne or who reached</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tetracycline 250 mg BID	grade 2 (comedones and small, superficial pustules and inflammation at the follicular orifices of the face) or 3 (comedones, small pustules and deeper inflammatory lesions not confined to single follicles) acne		1 acne, mean times required to attain conversion to grade 1 Secondary: Safety	and maintained grade 1 acne status through the duration of the trial (<i>P</i> values not reported). However, the proportions were higher with minocycline for each of these three grade 1 level groups (<i>P</i> values not reported). After six weeks, minocycline exhibited a faster rate of conversion to grade 1 acne (52 vs 26%, respectively; <i>P</i> =0.083). After nine weeks and at subsequent visits, the conversion rates were equal (<i>P</i> values not reported). Secondary: Nine and eight patients receiving minocycline and tetracycline reported side effects; all of mild or moderate severity except for hives, headache, dizziness and nausea which were all reported as severe. No notable abnormalities were observed in the results of any of the laboratory values either before or after six months of treatment with either agent (<i>P</i> values reported).
Cullen et al (abstract) ²⁷ Minocycline 50 mg BID vs tetracycline 250 mg BID	DB, RCT Patients with acne vulgaris	N=not reported Duration not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Minocycline was as effective as tetracycline for the treatment of acne vulgaris. Minocycline produced no vestibular side effects, and like tetracycline, did not produce the phototoxicity associated with demeclocycline or the life threatening colitis associated with clindamycin. Patients did not develop a resistance to either treatment.
Garner et al ²⁸ Minocycline vs active control (cyproterone acetate/ ethinyloestradiol*, doxycycline,	SR (26 RCTs) Patients with inflammatory acne vulgaris	N=not reported Duration varied	Primary: Lesion counts, acne grades/severity scores, doctors' and patients' global assessments, adverse reactions, drop-out rates	Primary: <i>Minocycline vs placebo (one trial)</i> Minocycline significantly reduced a summed weighted acne lesion score, while placebo did not (<i>P</i> <0.05). No measures of dispersion were presented, and no statistical comparison was performed between the two treatments. <i>Minocycline vs oxytetracycline or tetracycline (seven trials)</i> Five trials found no difference between the two treatments and two found minocycline to be "superior". In one, minocycline was significantly "superior" to tetracycline in terms of the reduction in inflamed lesion count at 12 weeks

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lymecycline*, isotretinoin, oxytetracycline, tetracycline, topical clindamycin, topical erythromycin/zinc, topical fusidic acid* or placebo			Secondary: Not reported	<p>(results only presented in graphical form and did not include any measures of dispersion or state the method used to calculate <i>P</i> values). Visual inspection of the graphical data does not support the conclusion that minocycline is “superior”. The second trial was also flawed and the outcome measure used was the number of patients improving by at least two grades at each assessment point (weeks 12 and 20), with no indication of what grade they improved from or to. Another trial recorded a significantly difference in favor of minocycline in the acne lesion score at six weeks suggesting a faster onset of improvement with minocycline.</p> <p><i>Minocycline vs lymecycline (two trials)</i> In one trial, the primary endpoint was declared in advance as the percent reduction in inflamed lesion count at week 12. No difference was found between the two treatments for this or any other outcome measured. The results of the second trial were similar.</p> <p><i>Minocycline vs doxycycline (five trials)</i> All trials showed no overall difference between the two treatments and no evidence of an earlier onset of improvement with minocycline. Pooling of the data was impossible because of variability between the trials in both the dosage used and the methodological design.</p> <p><i>Minocycline vs isotretinoin in nodular acne (two trials)</i> In one trial, patients receiving minocycline also received topical azelaic acid, and very high percentage reductions in all types of lesion count were reported for both treatments. A significant difference in favor of isotretinoin was observed against non-inflamed lesions as well as papules and pustules after 24 weeks of treatment. Changes in nodule count were similar between the two treatments. The speed of onset of improvement with minocycline plus azelaic acid was rapid and equivalent to isotretinoin after one month of treatment. The second trial demonstrated that isotretinoin was significantly superior to minocycline with respect to reductions in the number and diameter of nodular lesions.</p> <p><i>Minocycline vs cyproterone acetate/ethinylloestradiol (one trial)</i> No overall difference between the two treatments was noted.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p><i>Minocycline vs topical acne treatments (five trials)</i> In one trial there was a trend for “superiority” of topical clindamycin although this did not reach significance due to the large range of lesion counts included and the small number of patients. Two other trials comparing minocycline and topical clindamycin demonstrated identical results for both minocycline and clindamycin. Another trial demonstrated that at the end of treatment, the overall reduction in the inflamed lesion count was significantly “superior” with minocycline compared to topical fusidic acid ($P=0.04$). Another trial demonstrated that topical erythromycin/zinc acetate was significantly better than minocycline against both inflamed and non-inflamed lesions after 12 weeks; however, no difference between the treatments was noted in terms of acne grade at any time point or in patients’ self-assessment using a visual analog scale.</p> <p><i>Adverse events</i> Pooled estimates of the incidence of side effects are likely to be erroneous due to differences in the way the data were collected and interpreted. Overall, 11.1% (137/1,230) of patients receiving minocycline experienced an adverse event that was attributed to therapy. In 36 instances these adverse events resulted in discontinuation of therapy. Fifty two patients had gastrointestinal disturbances and there were five reported cases of vaginal candidiasis. Twenty two patients reported vertigo or dizziness, either alone or associated with other symptoms, and there were three incidences of abnormal pigmentation. One patient reported joint pain and four reported photosensitization. Forty one had symptoms suggesting an acute hypersensitivity reaction.</p> <p>Secondary: Not reported</p>
Leyden et al ²⁹ Tetracycline 1,000 mg/day for 6 weeks vs	RCT, XO Patients with moderately severe inflammatory acne vulgaris	N=15 15 weeks	Primary: Complete count of all inflammatory lesions, quantitative measurement of P	Primary: The mean inflammatory lesion count was significantly reduced with tetracycline after three ($P<0.05$) and six weeks ($P<0.01$), with the count being no different from baseline three weeks after discontinuation of treatment (P value not significant). Similar results were seen with minocycline (three and six weeks; $P<0.001$); however, the mean count was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>minocycline 200 mg/day for 6 weeks</p>			<p><i>acnes</i> on the forehead and cheek, analysis of skin-surface lipid levels, safety</p> <p>Secondary: Not reported</p>	<p>still significantly different from baseline three weeks after discontinuation of treatment ($P<0.05$).</p> <p>Minocycline produced a significantly greater reduction in the <i>P acnes</i> count ($P<0.05$) that persisted even up to three weeks after discontinuation of treatment ($P<0.01$). In contrast, the <i>P acnes</i> count returned to baseline within three weeks after discontinuing tetracycline.</p> <p>Tetracycline produced a significant reduction in free fatty acid levels on both the forehead and cheek after three weeks ($P<0.001$ for both) and was further reduced after six ($P<0.001$ for both), but three weeks after discontinuation the values returned to pretreatment levels. Minocycline also produced a significant reduction of free fatty acid levels after three and six weeks ($P<0.001$ for all); however, after three weeks of no treatment, the levels were still significantly reduced ($P<0.001$ for both).</p> <p>Both treatments were associated with mild transient gastrointestinal tract irritation. No signs or symptoms of vertigo, dizziness or light-headedness developed with either treatment. No signs or symptoms of vaginitis developed in women.</p> <p>Secondary: Not reported</p>
<i>Helicobacter pylori</i> eradication				
<p>Zheng et al³⁰</p> <p>Amoxicillin 1,000 mg, clarithromycin 500 mg and pantoprazole 40 mg BID for 7 days (PAC group)</p> <p>vs</p> <p>metronidazole 400 mg TID, tetracycline</p>	<p>OL, PG, RCT</p> <p>Patients 18 to 70 years of age with <i>H pylori</i> positive non-ulcer dyspepsia in China</p>	<p>N=170</p> <p>5 weeks</p>	<p>Primary: Eradication rates</p> <p>Secondary: Not reported</p>	<p>Primary: Eradication rates were significantly higher with PBMT compared to PAC ($P<0.05$).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>750 mg BID, bismuth 220 mg BID and pantoprazole 40 mg BID (PBMT group)</p> <p>Malfertheiner et al³¹</p> <p>Amoxicillin 1,000 mg, clarithromycin 500 mg and omeprazole 20 mg BID for 7 days (standard regimen)</p> <p>vs</p> <p>bismuth 140 mg, metronidazole 125 mg, tetracycline 125 mg taken as 3 capsules TID with omeprazole 20 mg BID for 10 days (quadruple therapy regimen)</p>	<p>NI, OL, RCT</p> <p>Patients ≥18 years of age with confirmed <i>H pylori</i> and upper gastrointestinal symptoms</p>	<p>N=440</p> <p>10 weeks</p>	<p>Primary: <i>H pylori</i> eradication</p> <p>Secondary: Comparison of eradication as a function of antibiotic resistance and disease or disorder, adverse events, compliance</p>	<p>Primary: Eradication rates were 93% with quadruple therapy and 70% with the standard regimen for the per-protocol population ($P<0.0001$). Treatment with quadruple therapy met the criteria for noninferiority.</p> <p>The ITT population was used for superiority testing and showed that quadruple therapy was significantly better than standard therapy in eradicating <i>H pylori</i> ($P<0.0001$).</p> <p>Secondary: Baseline metronidazole sensitivity was similar between quadruple and standard therapy ($P=0.695$) and did not affect the efficacy of quadruple therapy in the per-protocol population ($P=0.283$).</p> <p>Baseline clarithromycin sensitivity was similar between quadruple and standard therapy ($P=0.464$) and this did affect the efficacy of standard therapy in the per-protocol population ($P<0.0001$).</p> <p>Simultaneous metronidazole and clarithromycin resistance reduced efficacy only with standard therapy ($P=0.001$).</p> <p>In patients with non-ulcer dyspepsia, quadruple therapy had higher eradication rates compared to standard therapy ($P<0.0001$).</p> <p>No significant difference was observed in patients with peptic ulcer disease ($P=0.340$) but this should be interpreted cautiously due to the overall low number of patients in this subgroup.</p> <p>The incidence of adverse events was similar between the two treatments.</p> <p>Compliance exceeded 95% with both treatments.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lyme Disease				
Wormser et al ³² Doxycycline for 10 days vs doxycycline for 10 days plus a single IV dose of ceftriaxone vs doxycycline for 20 days	DB, RCT Patients with early Lyme disease	N=180 30 months	Primary: Complete response rate (resolution of erythema migraines and symptoms, return to pre-Lyme disease health) Secondary: Adverse events	Primary: No differences in clinical response were found at 20 days and 30 months between the three treatments ($P>0.2$ for both). Secondary: Combination therapy had a significantly higher incidence of diarrhea than 10 and 20 days of doxycycline ($P<0.001$). Patients receiving combination therapy were more likely to experience an adverse drug event than patients receiving doxycycline (10 days; $P=0.055$ and 20 days; $P=0.035$).
Luger et al ³³ Cefuroxime 500 mg BID vs doxycycline 100 mg TID	MC, RCT, SB Patients ≥ 12 years of age weighing ≥ 45 kg with early Lyme disease	N=232 12 months post-treatment	Primary: Clinical response at one month post-treatment, clinical signs and symptoms Secondary: Adverse effects	Primary: Satisfactory clinical response was observed in 90% of patients receiving cefuroxime and 95% receiving doxycycline at one month post-treatment (difference, -5%; 95% CI, -12 to 3). No differences were observed between treatments in the number and severity of signs and symptoms (P values not reported). Of patients with satisfactory clinical response at one month post-treatment, 95 and 100% of patients receiving cefuroxime and doxycycline had a satisfactory clinical outcomes 12 months post-treatment (difference, -5%; 95% CI, -10 to 4). Secondary: Significantly more patients receiving doxycycline reported one or more adverse events ($P=0.041$). Adverse effects related to the skin were significantly more common with doxycycline compared to cefuroxime ($P=0.009$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Significantly more patients receiving cefuroxime reported diarrhea compared to doxycycline ($P=0.03$).				
Periodontitis				
<p>Preshaw et al³⁴</p> <p>Doxycycline 20 mg BID</p> <p>vs</p> <p>placebo</p> <p>All patients were treated with scaling and roots planing.</p>	<p>DB, MC, RCT</p> <p>Patients with moderate to severe chronic periodontitis</p>	<p>N=209</p> <p>9 months</p>	<p>Primary: Changes from baseline in clinical attachment loss and probing depth, total number of sites with attachment gains, probing depth reductions of at least two or three millimeters from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: Improvements in clinical attachment loss and probing depth were greater with doxycycline, achieving significance in all baseline disease categories at nine months ($P<0.05$).</p> <p>At nine months, 42.3% of sites with doxycycline demonstrated clinical attachment loss gain of at least two millimeters compared to 32.0% of sites with placebo ($P<0.01$). Clinical attachment loss gain of at least three millimeters was seen in 15.4% of sites with doxycycline compared to 10.6% of sites with placebo ($P<0.05$). When considering the same thresholds of change in probing depth, 42.9% of sites with doxycycline compared to 31.1% of sites with placebo demonstrated probing depth reduction of at least two millimeters ($P<0.01$) and 15.4% of sites with doxycycline compared to 9.1% of sites with placebo demonstrated probing depth reduction of at least three millimeters ($P<0.01$).</p> <p>Secondary: Not reported</p>
<p>Tuter et al (abstract)³⁵</p> <p>Doxycycline for 6 weeks</p> <p>vs</p> <p>placebo</p> <p>Patients receiving doxycycline and placebo also received 2 regimens of scaling and root</p>	<p>RCT</p> <p>Patients with chronic periodontitis or healthy individuals</p>	<p>N=58</p> <p>6 weeks</p>	<p>Primary: Plaque index, gingival index, probing depth, gingival crevicular fluid volumes, gingival crevicular fluid matrix metalloproteinase levels, hsCRP</p> <p>Secondary: Not reported</p>	<p>Primary: Significant differences in plaque index, gingival index, probing depth, gingival crevicular fluid volumes, gingival crevicular fluid matrix metalloproteinase levels and hsCRP between pre- and post-treatment were noted with both treatments. Between treatments there were significant decreases in probing depth, gingival index and gingival crevicular fluid levels of matrix metalloproteinase 8 favoring doxycycline ($P<0.05$).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
planing.				
Respiratory Tract Infections				
<p>Daniels et al³⁶</p> <p>Doxycycline 200 mg/day for 7 days</p> <p>vs</p> <p>placebo</p> <p>All patients received systemic corticosteroids.</p>	<p>DB, PC, RCT</p> <p>Hospitalized patients ≥45 years of age with an acute exacerbation of COPD</p>	<p>N=223 (265 exacerbations)</p> <p>30 days</p>	<p>Primary: Clinical response on day 30</p> <p>Secondary: Clinical response on day 10, clinical cure on days 10 and 30, antibiotic treatment for lack of efficacy, lung function, time to treatment failure, CRP, symptoms, microbiological response</p>	<p>Primary: At 30 days, clinical success was observed in 61 (n=78) and 53% (n=72) of patients receiving doxycycline and placebo (OR, 1.3; 95% CI, 0.8 to 2.0; <i>P</i>=0.32).</p> <p>Secondary: At 10 days, doxycycline showed “superiority” over placebo in terms of clinical success (OR, 1.9; 95% CI, 1.1 to 3.2; <i>P</i>=0.03).</p> <p>At 10 days, clinical cure was observed in 67 (n=86) and 51% (n=69) of patients receiving doxycycline and placebo (OR, 1.9; 95% CI, 1.2 to 3.2; <i>P</i>=0.01). At 30 days, the corresponding proportions were 51 (n=65) and 41% (n=56) (OR, 1.4; 95% CI, 0.9 to 2.3; <i>P</i>=0.15).</p> <p>Time to treatment failure was not significantly longer with doxycycline compared to placebo (<i>P</i>=0.19). Thirty seven (n=46) and 46% (n=62) of patients had treatment failure.</p> <p>OL antibiotic treatment for lack of efficacy was applied in 15 (n=19) and 28% (n=38) of patients receiving doxycycline and placebo by 10 days (OR, 0.5; 95% CI, 0.03 to 0.9; <i>P</i>=0.01). At 30 days, the corresponding proportions were 33 (n=42) and 45% (n=61) (OR, 0.7; 95% CI, 0.1 to 1.1; <i>P</i>=0.13).</p> <p>Paired lung function data were available for 85% (n=224) of patients on days 1 and 10 and in 71% (n=189) of patients on days 1 and 30. The mean increase in FEV₁ on day 10 was 0.16±0.26 L with doxycycline and 0.11±0.26 L with placebo (mean difference, 0.05 L; 95% CI, -0.02 to 0.12; <i>P</i>=0.016). On day 30, the mean increase was 0.15±0.33 and 0.08±0.25 L with doxycycline and placebo (mean difference, 0.07 L; 95% CI, -0.03 to 0.13; <i>P</i>=0.22).</p> <p>The mean change in CRP at 10 days, was -56.4±65.5 and -38.9±72.7 mg/L with doxycycline and placebo (<i>P</i>=0.07). This trend was no longer present at 30 days.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>The mean change in total symptom scores on day 10 was -10.1 ± 9.0 and -6.2 ± 8.6 with doxycycline and placebo (mean difference, -2.3; 95% CI, -3.9 to -0.8; $P=0.003$). The corresponding changes at day 30 were -9.4 ± 9.7 and -8.3 ± 8.6 (mean difference, -1.0; 95% CI, -3.7 to 1.8; $P=0.50$). Separate mean symptom scores of cough and sputum purulence were significantly more reduced with doxycycline at 10 days, but not at 30 days (P value not reported).</p> <p>Two hundred and fourteen potential bacterial pathogens were isolated in 158 exacerbations. Bacteriological success was accomplished in 67 (52/78) and 34% (25/73) of patients receiving doxycycline and placebo (OR, 3.8; 95% CI, 1.9 to 7.5; $P<0.001$). The most predominant bacteria were <i>H influenzae</i> (41%), <i>S pneumoniae</i> (24%) and <i>M catarrhalis</i> (22%).</p>
<p>Maesen et al³⁷</p> <p>Doxycycline 100 mg BID for 7 days</p> <p>vs</p> <p>minocycline 100 mg BID for 7 days</p>	<p>DB, RCT</p> <p>Patients admitted to the hospital because of purulent exacerbations of chronic respiratory disease</p>	<p>N=41</p> <p>15 days</p>	<p>Primary: Bacteriological and clinical assessment</p> <p>Secondary: Not reported</p>	<p>Primary: Bacteriological and clinical assessment before and immediately after treatment showed no differences between doxycycline and minocycline, nor did further evaluation after seven days follow up (P values not reported).</p> <p>Secondary: Not reported</p>
Sexually Transmitted Diseases				
<p>Kovacs et al³⁸</p> <p>Minocycline 100 mg BID for 1 day, followed by 100 mg/day for 9 days</p> <p>vs</p> <p>doxycycline 100 mg BID for 1 day, followed by 100</p>	<p>PRO, RCT, SB</p> <p>Patients with <i>C trachomatis</i> infection of the cervix</p>	<p>N=103</p> <p>12 weeks</p>	<p>Primary: Efficacy (resolution of signs and symptoms of infections and eradication of organism)</p> <p>Secondary: Adverse events</p>	<p>Primary: Minocycline and doxycycline demonstrated equal effectiveness in the eradication of mycoplasmas in over 80% of patients. Minocycline appeared to have a slight advantage with respect to the resolution of the gynecological symptoms that were associated with the <i>Chlamydial</i> infection (83.3 vs 81.2%; P value not reported).</p> <p>A 10 day course of either treatment resulted in a negative result of a <i>Chlamydial</i> culture for all patients at the follow up assessment, which occurred between 11 days to 12 weeks after treatment.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for 9 days				A total of 19 patients reported adverse events; 11 and eight patients receiving minocycline and doxycycline. The adverse events were generally mild, the most frequent event being gastric upset, which was seen with both treatments and giddiness/dizziness with minocycline (<i>P</i> value not reported).
Romanowski et al ³⁹ Minocycline 100 mg BID for 7 days vs doxycycline 100 mg BID for 7 days	DB, RCT Patients with nongonococcal urethritis, mucopurulent cervicitis or whose sexual partner had either condition or a positive culture for <i>Chlamydia</i> treatments	N=253 7 weeks	Primary: Clinical cure (symptoms subsiding or resolving by day 14) Secondary: Adverse effects	Primary: The proportion of patients with urethritis or cervicitis did not differ by treatments at any follow up visit (men, 88 vs 82%; women, 91 vs 90%; combined, 89 vs 85%; <i>P</i> >0.08). Unprotected sexual contact did not affect clinical or microbiological cure rates. Secondary: Adverse effects occurred more frequently with doxycycline (men, 43 vs 26%; <i>P</i> =0.05; women, 62 vs 35%; <i>P</i> =0.009). Although the proportion with dizziness did not differ between the two treatments (<i>P</i> =0.1), dizziness was reported more often by women (11 vs 3%; <i>P</i> value not reported).
Martin et al ⁴⁰ Azithromycin 1 g as a single dose vs doxycycline 100 mg BID for 7 days	OL, RCT Patients 16 to 50 years of age with presumptive <i>Chlamydia</i> urethral or endocervical infections	N=457 35 days	Primary: Clinical response, bacteriologic cure (negative culture for <i>C trachomatis</i> at follow up) Secondary: Not reported	Primary: At the last follow up visit, 97% of males and 98% of females receiving azithromycin had clinically responded to treatment and 91% of males and 95% of females receiving doxycycline had responded. No differences between treatments were identified (<i>P</i> values not reported). There were no differences in bacteriologic cure rates between treatments at any time (<i>P</i> values not reported). Secondary: Not reported
Lauharanta et al ⁴¹ Azithromycin 1 g as a single dose vs doxycycline 100 mg BID daily for 7 days	OL, PRO, RCT Patients 18 to 60 years of age with signs and symptoms of nongonococcal urethritis	N=120 35 days	Primary: Clinical response, eradication rate Secondary: Not reported	Primary: There was no difference in clinical response or eradication rates between treatments at any time, except at visit three (35 days), when there was a significantly higher cure rate with azithromycin compared to doxycycline in <i>Chlamydia</i> negative patients (79 and 35% respectively, <i>P</i> =0.017). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lister et al ⁴² Azithromycin 1 g as a single dose vs doxycycline 100 mg BID for 7 days	OL Men 19 to 57 years of age with symptoms and/or signs of nongonococcal urethritis and ≥5 polymorphonuclear leucocytes	N=143 21 days	Primary: Clinical cure, microbiological cure (eradication of <i>C trachomatis</i> from the urethra) Secondary: Not reported	Primary: No differences were seen between treatments in any primary outcome measure (<i>P</i> values not reported). Secondary: Not reported
Urinary Tract Infection				
Rosenstock et al ⁴³ Tetracycline 2 g as a single dose vs tetracycline 500 mg QID for 10 days vs amoxicillin 3 g as a single dose	RCT Women with signs and symptoms compatible with lower UTIs	N=62 29 to 39 days	Primary: Efficacy (disappearance of symptoms and organism on culture and follow up visits) Secondary: Not reported	Primary: Single dose tetracycline cured 75% of women with documented UTIs compared to 94% with multi dose tetracycline and 54% with amoxicillin. Adding patients who were cured of the initial pathogen but acquired a second pathogen during the month of follow up, the cure rates were 88, 94 and 69%, respectively (<i>P</i> value not reported). Two grams of single dose tetracycline is as effective as other reported regimens regardless of the susceptibility of the initial pathogen and has minimal toxicity. Secondary: Not reported

*Not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IV=intravenous, QID=four times daily, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double-blind, ITT=intention-to-treat, MC=multicenter, NI=noninferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group,

PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, EGSA=Evaluator's Global Severity Assessment, FEV₁=forced expiratory volume in one second, hsCRP=high sensitivity C-reactive protein, UTI=urinary tract infection

Special Populations**Table 6. Special Populations**^{3-17,48-51}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Demeclocycline	No dosage adjustment required in the elderly. Not recommended in children <8 years of age.	Avoid in renal dysfunction.	Avoid in hepatic dysfunction.	D	Yes (% not reported); use with caution.
Doxycycline	No dosage adjustment required in the elderly. Not recommended in children <8 years of age. Use of Periostat® in children is contraindicated.	No dosage adjustment required.	No dosage adjustment required.	D	Yes (% not reported); use with caution.
Minocycline	No dosage adjustment required in the elderly. Not recommended in children <8 years of age.	Use with caution. Renal dose adjustment required; for creatinine clearances <80 mL/minute, a maximum daily dose of 200 mg is recommended.	No dosage adjustment required.	D	Yes (% not reported); use with caution.
Tetracycline	No dosage adjustment required in the elderly. Not recommended in children <8 years of age.	Renal dose adjustment required; for creatinine clearances 50 to 80 mL/minute, administration every eight to 12 hours is recommended; for creatinine clearances 10 to 50 mL/minute, administration	No dosage adjustment required; use with caution.	D	Not reported; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		every 12 to 24 hours is recommended and for creatinine clearances <10 mL/minute, administration every 24 hours is recommended.			

Adverse Drug Events

Table 7. Adverse Drug Events (%)³⁻¹⁷

Adverse Event(s)	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Cardiovascular				
Myocarditis	-	-	✓	-
Pericarditis	✓	✓	✓	✓
Vasculitis	-	-	✓	-
Central Nervous System				
Bulging fontanels (infants)	✓	✓	✓	-
Dizziness	✓	-	✓	-
Fatigue	-	-	✓	-
Fever	-	-	✓	-
Headache	-	-	✓	-
Hypoesthesia	-	-	✓	-
Intracranial pressure increased	-	-	-	✓
Intracranial hypertension	-	✓	-	-
Malaise	-	-	✓	-
Mood changes	-	-	✓	-
Paresthesia	-	-	✓	✓
Pseudotumor cerebri	✓	-	✓	✓
Sedation	-	-	✓	-
Seizure	-	-	✓	-
Somnolence	-	-	✓	-
Vertigo	-	-	✓	-
Dermatological				
Alopecia	-	-	✓	-
Angioneurotic edema	✓	✓	-	-
Erythema multiforme	✓	-	✓	-
Erythema nodosum	-	-	✓	-
Erythematous rash	✓	-	✓	-
Exfoliative dermatitis	-	✓	✓	✓
Maculopapular rash	✓	-	✓	-
Photosensitivity	✓	✓	✓	✓
Pruritis	-	-	✓	✓
Rash	-	✓	-	-
Skin hyperpigmentation	-	✓	-	-
Stevens-Johnson syndrome	✓	-	✓	-
Toxic epidermal necrolysis	-	-	✓	-
Urticaria	✓	✓	✓	-

Adverse Event(s)	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Endocrine and Metabolic				
Diabetes insipidus syndrome	-	-	-	✓
Hepatic cholestasis	-	-	✓	-
Hepatic failure	-	-	✓	-
Hepatitis	✓	-	✓	-
Hepatotoxicity	✓	-	-	✓
Hyperbilirubinemia	-	-	✓	-
Jaundice	-	-	✓	-
Liver failure	✓	-	-	-
Nephrogenic diabetes insipidus	✓	-	-	-
Thyroid dysfunction	-	-	✓	-
Gastrointestinal				
Abdominal cramps	-	-	-	✓
Anogenital inflammatory lesions	-	✓	-	-
Anorexia	✓	✓	✓	✓
Diarrhea	✓	✓	✓	✓
Dyspepsia	-	-	✓	-
Dysphagia	✓	✓	✓	-
Enterocolitis	✓	✓	✓	-
Esophageal ulcerations	✓	✓	✓	-
Esophagitis	-	✓	✓	✓
Glossitis	✓	✓	✓	-
Nausea	✓	-	✓	✓
Oral pigmentation	-	✓	-	-
Pancreatitis	✓	-	✓	✓
Pseudo-membranous colitis	-	-	✓	-
Stomatitis	-	-	✓	-
Tooth discoloration	✓	✓	✓	-
Vomiting	✓	-	✓	✓
Xerostomia	-	-	✓	-
Genitourinary				
Balanitis	✓	-	✓	-
Porphyria	-	-	✓	-
Hematologic				
Agranulocytosis	-	-	✓	-
Eosinophilia	✓	✓	✓	-
Hemolytic anemia	✓	✓	✓	-
Leukopenia	-	-	✓	-
Neutropenia	✓	✓	✓	-
Pancytopenia	-	-	✓	-
Thrombocytopenia	✓	✓	✓	-
Thrombophlebitis	-	-	-	✓
Musculoskeletal				
Arthralgia	-	-	✓	-
Arthritis	-	-	✓	-
Joint stiffness	-	-	✓	-
Joint swelling	-	-	✓	-
Myalgia	-	-	✓	-
Polyarthralgia	✓	-	-	-
Renal				
Acute renal failure	✓	-	✓	✓

Adverse Event(s)	Demeclocycline	Doxycycline	Minocycline	Tetracycline
Azotemia	-	-	-	✓
Blood urea nitrogen increased	-	✓	-	-
Interstitial nephritis	-	-	✓	-
Renal damage	-	-	-	✓
Respiratory				
Bronchospasm	-	-	✓	-
Cough	-	-	✓	-
Dyspnea	-	-	✓	-
Pneumonitis	-	-	✓	-
Pulmonary infiltrates	✓	-	✓	-
Other				
Anaphylaxis	✓	✓	✓	✓
Candidal superinfection	-	-	-	✓
Hypersensitivity reaction	-	-	✓	✓
Superinfection	-	-	-	✓
Tinnitus	✓	-	-	-
Visual disturbances	✓	-	-	-

✓ Percent not specified.

-Event not reported.

Contraindications/Precautions

The tetracyclines are contraindicated in patients hypersensitive to tetracyclines or any component of the various formulations.⁴⁸⁻⁵¹ In addition, demeclocycline is contraindicated with concurrent use of methoxyflurane.⁴⁸

The tetracyclines may cause tissue hyperpigmentation, enamel hypoplasia or permanent tooth discoloration. Use of tetracyclines should be avoided during tooth development (children less than eight years of age) unless other drugs are not likely to be effective or are contraindicated. The tetracyclines should also not be used during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.⁴⁸⁻⁵¹

The tetracyclines may cause photosensitivity. Therapy should be discontinued if skin erythema occurs. Patients receiving tetracyclines should use skin protection and avoid prolonged exposure to sunlight. Patients should also not use tanning equipment.⁴⁸⁻⁵¹

The tetracyclines may be associated with increases in blood urea nitrogen secondary to antianabolic effects of the agents; therefore, caution should be used with renal dysfunction.⁴⁸⁻⁵¹

Pseudotumor cerebi has been rarely reported with use of tetracyclines. Once therapy is discontinued, the condition usually resolves.⁴⁸⁻⁵¹

Prolonged use of tetracyclines may result in fungal or bacterial superinfection, including *Clostridium difficile*-associated diarrhea and pseudomembranous colitis. *C. difficile*-associated diarrhea has been observed greater than two months post-antibiotic treatment.⁴⁸⁻⁵¹

Outdated demeclocycline and tetracycline may cause nephropathy.^{48,51} In addition, autoimmune syndromes, including lupus-like, hepatitis and vasculitis, have been reported with doxycycline and minocycline. Treatment should be discontinued if symptoms occur.^{49,50}

Lightheadedness and vertigo may occur with minocycline. In addition, rash, along with eosinophilia, fever and organ failure may occur with minocycline. Onset of symptoms may be delayed up to several weeks and reports have been fatal in up to 10% of cases. Minocycline should be discontinued immediately if Drug Reaction with Eosinophilia and Systemic Symptoms syndrome is suspected.⁵⁰

Drug Interactions**Table 8. Drug Interactions**⁴⁴

Drug	Interaction	Mechanism
Tetracyclines (all)	Aluminum salts	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response.
Tetracyclines (all)	Anticoagulants	Pharmacologic action of warfarin may be increased.
Tetracyclines (all)	Bismuth salts	Coadministration of bismuth salts in liquid formulation may decrease the serum levels of tetracyclines, possibly reducing the anti-infective response.
Tetracyclines (all)	Calcium salts	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response.
Tetracyclines (all)	Digoxin	Serum levels of digoxin may be increased, possibly resulting in digoxin toxicity.
Tetracyclines (all)	Iron salts	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response. Absorption of iron salts may also be decreased.
Tetracyclines (all)	Magnesium salts	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response.
Tetracyclines (all)	Methoxyflurane	Enhanced renal toxicity may occur.
Tetracyclines (all)	Penicillins	Pharmacologic and therapeutic action of penicillins may be decreased.
Tetracyclines (all)	Retinoids	Risk of pseudotumor cerebri (benign intracranial hypertension) may be increased.
Tetracyclines (all)	Urinary alkalinizers	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response.
Tetracyclines (all)	Zinc salts	Serum levels of tetracyclines may be decreased, possibly reducing the anti-infective response.

Dosage and Administration**Table 9. Dosing and Administration**³⁻¹⁷

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Demeclocycline	Alternative treatment for <u>gonococcal infections (uncomplicated); listeriosis; syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, granuloma inguinale, lymphogranuloma venereum, nongonococcal urethritis, urethritis, (uncomplicated)[†], plague, relapsing fever, tularemia:</u>	Alternative treatment for <u>gonococcal infections (uncomplicated); listeriosis; syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, granuloma inguinale, lymphogranuloma venereum, nongonococcal</u>	Tablet: 150 mg 300 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>Tablet: 150 mg QID or 300 mg BID; gonorrhea patients sensitive to penicillin may be treated with an initial dose of 600 mg followed by 300 mg BID for four days to a total of 3 g</p>	<p><u>urethritis, urethritis (uncomplicated)[†], plague, relapsing fever, tularemia in children >8 years of age:</u> Tablet: 7 to 13 mg/kg/day, depending upon the severity of the disease, divided into two to four doses; maximum, 600 mg/day; gonorrhea patients sensitive to penicillin may be treated with an initial dose of 600 mg followed by 300 mg BID for four days to a total of 3 g</p>	
<p>Doxycycline</p>	<p><u>Alternative treatment for gonococcal infections (uncomplicated)[†]; syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax, psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, granuloma inguinale, lymphogranuloma venereum, nongonococcal urethritis, malaria prophylaxis, plague, relapsing fever, tularemia:</u> Capsule (hyclate, monohydrate), delayed-release tablet, suspension, syrup, tablet (hyclate, monohydrate): initial, 200 mg; maintenance, 100 mg/day; more severe infections, 100 mg BID</p> <p><u>Adjunct to scaling and root planing attachment level gain and to reduce pocket depth in patients with adult periodontitis:</u> Tablet (hyclate, Periostat[®]): 20 mg BID for nine months</p>	<p><u>Alternative treatment for gonococcal infections (uncomplicated)[†]; syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax, psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, granuloma inguinale, lymphogranuloma venereum, nongonococcal urethritis, malaria prophylaxis, plague, relapsing fever, tularemia in children >8 years of age and <100 lbs:</u> Capsule (hyclate, monohydrate), delayed-release tablet, suspension, syrup, tablet (hyclate, monohydrate): initial, 2 mg/lb divided into two doses; maintenance, 1 mg/lb given as a single daily dose or divided into two doses; more severe infections, up to 2 mg/lb may be used</p> <p><u>Adjunct to scaling and root planing attachment level gain and to reduce pocket</u></p>	<p>Capsule (hyclate): 50 mg 100 mg (Morgidox[®], Vibramycin[®])</p> <p>Capsule (monohydrate): 50 mg 75 mg 100 mg 150 mg (Adoxa[®])</p> <p>Delayed-release tablet (hyclate, Doryx[®]): 75 mg 100 mg 150 mg</p> <p>Oral suspension (monohydrate, Vibramycin[®]): 25 mg/5 mL</p> <p>Oral syrup (calcium, Vibramycin[®]): 50 mg/5 mL</p> <p>Tablet (hyclate): 20 mg (Periostat[®]) 100 mg</p> <p>Tablet (monohydrate, Adoxa[®], Adoxa Pak[®]):</p>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		depth in patients with adult periodontitis: Use of Periostat [®] is contraindicated.	50 mg 75 mg 100 mg 150 mg
Minocycline	<p><u>Alternative treatment for gonococcal infections (uncomplicated); listeriosis; syphilis; Vincent's infection and yaws when penicillin is contraindicated, treatment of asymptomatic meningococcal carriers, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, endocervical infections, granuloma inguinale, lymphogranuloma venereum, nongonococcal urethritis, rectal infections urethritis (uncomplicated)[†], plague, relapsing fever, tularemia:</u> Capsule, tablet: initial, 200 mg or two or four 50 mg units; maintenance, 100 mg BID or 50 mg QID</p> <p><u>Treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris:</u> Extended-release tablet: 1 mg/kg once daily</p>	<p><u>Alternative treatment for gonococcal infections (uncomplicated); listeriosis; syphilis; Vincent's infection and yaws when penicillin is contraindicated, treatment of asymptomatic meningococcal carriers, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera, chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, endocervical infections, granuloma inguinale, lymphogranuloma venereum, nongonococcal urethritis, rectal infections urethritis (uncomplicated)[†], plague, relapsing fever, tularemia for children >8 years of age:</u> Capsule, tablet: initial, 4 mg/kg; maintenance, 2 mg/kg/day BID; maximum, not to exceed the usual adult dose</p> <p><u>Treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in children <12 years of age:</u> Safety and efficacy have not been established.</p>	<p>Capsule: 50 mg 75 mg 100 mg</p> <p>Extended-release tablet (Solodyn[®]): 45 mg 55 mg 65 mg 80 mg 90 mg 105 mg 115 mg 135 mg</p> <p>Tablet (Dynacin[®]): 50 mg 75 mg 100 mg</p>
Tetracycline	<p><u>Alternative treatment for syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera, chancroid, urinary tract</u></p>	<p><u>Alternative treatment for syphilis; Vincent's infection and yaws when penicillin is contraindicated, severe acne*, skin and soft tissue infections, acute intestinal amebiasis, cholera,</u></p>	<p>Capsule: 250 mg 500 mg</p>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, endocervical infections, granuloma inguinale, lymphogranuloma venereum, rectal infections, urethritis (uncomplicated), plaque, relapsing fever, tularemia: Capsule: 500 mg BID or 250 mg QID</p>	<p>chancroid, urinary tract infections, conjunctivitis (inclusion), trachoma, anthrax[†], psittacosis, respiratory tract infection, disease caused by rickettsiae, Q fever, rickettsialpox, Rocky Mountain spotted fever, typhus, endocervical infections, granuloma inguinale, lymphogranuloma venereum, rectal infections, urethritis (uncomplicated), plaque, relapsing fever, tularemia in children >8 years of age: Capsule: 25 to 50 mg/kg/day divided into four doses</p>	

BID=twice-daily, QID=four times daily

*May be useful as adjunctive therapy.

[†]When penicillin is contraindicated.

[‡]Immediate-release only.

Clinical Guidelines

The clinical guidelines contained in Table 10 are summarized globally and are not limited to the role of the sulfonamides. However, the summary of the chronic obstructive pulmonary disease (COPD) guideline focuses only on the treatment of exacerbations which have a bacterial component. The global treatment strategy for COPD is not discussed in this summary. In addition, the summary of the opportunistic infections in patients infected with human immunodeficiency virus guidelines focuses only on the treatment of malaria, *Mycobacterium avium* complex, *Pneumocystis pneumonia* and *Toxoplasmosis* encephalitis.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation
<p>Infectious Diseases Society of America/ American Thoracic Society: Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)⁵²</p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> • Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. <p><u>Empiric therapy - outpatient treatment</u></p> <ul style="list-style-type: none"> • For previously healthy patients with no risk factors for drug resistant <i>Streptococcus pneumoniae</i> infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant <i>S pneumoniae</i>, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used

Clinical Guideline	Recommendation
	<p>for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate.</p> <p><u>Empiric therapy - inpatient, non-intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. • Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. • A respiratory fluoroquinolone should be used for penicillin allergic patients. <p><u>Empiric therapy - inpatient, intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. • For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. • For <i>Pseudomonas</i> infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. • The antipneumococcal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone. • For penicillin-allergic patients, substitute aztreonam for the above β-lactam for <i>Pseudomonas</i> infection. <p><u>Pathogen-directed therapy</u></p> <ul style="list-style-type: none"> • <i>S pneumonia</i> (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. • <i>S pneumonia</i> (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). • <i>Haemophilus influenza</i> (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>H influenza</i> (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>Mycoplasma pneumonia/Chlamydia pneumonia</i>- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. • <i>Legionella</i> species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. • <i>Chlamydia psittaci</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Coxiella burnetii</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Francisella tularensis</i>- doxycycline preferred; alternative agents include gentamicin or streptomycin. • <i>Yersinia pestis</i>- streptomycin, gentamicin recommended; alternative

Clinical Guideline	Recommendation
	<p>agents include doxycycline or fluoroquinolone.</p> <ul style="list-style-type: none"> • <i>Bacillus anthracis</i> (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam if susceptible. • <i>Enterobacteriaceae</i>- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone. • <i>Pseudomonas aeruginosa</i>- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. • <i>Burkholderia pseudomallei</i>- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). • <i>Acinetobacter</i> species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin. • <i>Staphylococcus aureus</i> (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. • <i>S aureus</i> (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. • <i>Bordetella pertussis</i>- macrolide preferred; alternative agent is SMX/TMP. • Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem. • Influenza virus- oseltamivir or zanamivir preferred. • <i>Mycobacterium tuberculosis</i>- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. • <i>Coccidioides</i> species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. • <i>Histoplasmosis</i>- itraconazole preferred; alternative agent is amphotericin B. • <i>Blastomycosis</i>- itraconazole preferred; alternative agent is amphotericin B. • Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting <i>S pneumonia</i> and <i>S aureus</i>.
<p>American College of Chest Physicians: Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)⁵³</p>	<ul style="list-style-type: none"> • The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate. • Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision. • The use of a macrolide, doxycycline, or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients. • Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients. • A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for

Clinical Guideline	Recommendation
	<p>treatment with a β-lactam/macrolide combination or an antipneumococcal fluoroquinolone.</p> <ul style="list-style-type: none"> • Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.
<p>Infectious Diseases Society of America/ American Thoracic Society: Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)⁵⁴</p>	<ul style="list-style-type: none"> • Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received. • Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with β-lactam to treat <i>P aeruginosa</i> pneumonia. • De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response. • For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended. • The following initial empiric therapy is recommended for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem. • The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.
<p>Infectious Diseases Society of America: Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)⁵⁵</p>	<p><u>General observations</u></p> <ul style="list-style-type: none"> • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant <i>S aureus</i> (MRSA) strains. • In patients with severe infection or infection that has progressed while on empirical antibiotic treatment, selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis. • In the case of <i>S aureus</i>, the clinician should assume the organism is resistant due to the high prevalence of community-associated MRSA strains. Agents effective against MRSA should be used in patients who have severe infections requiring hospitalization or those who have not responded to attempts to eradicate the infection (vancomycin, linezolid, daptomycin). Step-down treatment to other agents may be possible based on susceptibility tests.

Clinical Guideline	Recommendation
	<ul style="list-style-type: none"> • An increase in the macrolide resistance of <i>Streptococcus pyogenes</i> has been noted, while 99.5% of strains remain susceptible to clindamycin and 100% to penicillin. • Osteomyelitis typically requires treatment for four to six weeks. <p><u>Animal bites</u></p> <ul style="list-style-type: none"> • The decision to administer oral or intravenous antibiotic therapy is determined by the depth and severity of the wound and the time elapsed since the bite. • Appropriate first-line therapy includes oral amoxicillin/clavulanate, doxycycline, or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, SMX/TMP, and cefuroxime. The patient may also require an additional agent that is active against anaerobes, such as metronidazole or clindamycin. • Intravenous options include ampicillin/sulbactam, piperacillin/tazobactam, second generation cephalosporins, and carbapenems. Second- and third-generation cephalosporins may be used but require the addition of an antianaerobic agent. <p><u>Animal contact</u></p> <ul style="list-style-type: none"> • Though no randomized controlled trials exist for treatment of cutaneous anthrax, most data indicate that penicillin is effective. Less evidence supports the use of tetracyclines, chloramphenicol and erythromycin. • Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred. • Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin. • Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are effective alternatives. • Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin. • Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents. • Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents. • Streptomycin is considered the drug of choice for tularemia. Acutely ill patients should receive streptomycin or gentamicin. Mild to moderate disease may be treated with oral tetracycline or doxycycline. <p><u>Cellulitis</u></p> <ul style="list-style-type: none"> • Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin. • For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin. • In patients with severe penicillin allergy, clindamycin or vancomycin is indicated. • To reduce the risk of recurrence, it is important to keep the affected area well-hydrated and to reduce edema with elevation or compression stockings. Prophylactic treatment with monthly intramuscular

Clinical Guideline	Recommendation
	<p>benzathine penicillin, oral erythromycin, or penicillin V is also an option.</p> <p><u>Erysipelas</u></p> <ul style="list-style-type: none"> • Oral or intravenous penicillin is the first-line treatment depending on severity. • In the presence or suspicion of staphylococcal infection, a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin is indicated. <p><u>Human bites</u></p> <ul style="list-style-type: none"> • Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems. • Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy. <p><u>Impetigo</u></p> <ul style="list-style-type: none"> • Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents. • Erythromycin is indicated in the presence of pyoderma, but use is limited by erythromycin-resistant strains of <i>S aureus</i> and <i>S pyogenes</i>. • Topical therapy with mupirocin is equivalent to oral systemic antibiotics. <p><u>Necrotizing infections</u></p> <ul style="list-style-type: none"> • Antimicrobial therapy (coverage against aerobes and anaerobes) should be directed at the specific pathogen and appropriate doses should be used until operative procedures are no longer needed. • The combination of ampicillin/sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • Clindamycin and penicillin should be used in necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci. The efficacy of intravenous gamma globulin in these cases is still under investigation. • <i>Streptococcus</i> infection should be treated with high-dose penicillin or ampicillin plus clindamycin. • <i>S aureus</i> infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin/dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. • In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin. <p><u>Soft-tissue infections caused by community-acquired MRSA</u></p> <ul style="list-style-type: none"> • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin. <p><u>Surgical site infections</u></p> <ul style="list-style-type: none"> • Surgical site infections often resolve without the use of antibiotics.

Clinical Guideline	Recommendation
	<ul style="list-style-type: none"> • In patients with a temperature >38.5°C, pulse rate >100 beats/minute or erythema diameter >5 cm from incision with induration or necrosis, a short course of antibiotics is recommended. • For wounds of the perineum or operation on the gastrointestinal tract or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended. • For clean wounds on the trunk, head, neck or extremities, ceftazidime, oxacillin or clindamycin are recommended. <p><u>Immunocompromised patients</u></p> <ul style="list-style-type: none"> • In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever. • For gram-negative infections, monotherapy with carbapenems, cephalosporins with antipseudomonal activity, and piperacillin/tazobactam, are all appropriate. Recommended combination therapy regimens are (1) an aminoglycoside plus either an antipseudomonal penicillin or an extended-spectrum cephalosporin, or (2) an extended-spectrum penicillin plus ciprofloxacin. Adjunct treatment with granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor is recommended. • For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin. • For <i>Nocardia</i> infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate. • Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate. • Amphotericin B and its lipid formulations have been the gold standard to treatment for yeast and fungal infections in neutropenic patients. Caspofungin and voriconazole appear to be as effective as amphotericin B and with less serious acute toxicity but are more expensive. • Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide. • Cutaneous <i>Nocardia</i> infections should be treated with SMX/TMP, the treatment of choice. Other sulfa antibiotics and imipenem are also effective. • Initial therapy for Cryptococcal cellulitis is fluconazole, which is also used to complete therapy after patients have shown an initial response to amphotericin B and 5-flucytosine induction therapy. • Amphotericin B is recommended in patients with cellular immune deficiency and disseminated histoplasmosis. Itraconazole may replace amphotericin B after one to two weeks to complete at least six to 12 months of treatment. • Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus. • Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective. • Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.

Clinical Guideline	Recommendation
<p>Centers for Disease Control and Prevention: Traveler's Diarrhea (2011)⁵⁶</p>	<ul style="list-style-type: none"> At this time, prophylactic antibiotics should not be recommended for most travelers. Use should be weighed against the results of using prompt, early self treatment with antibiotics when traveler's diarrhea occurs, which can limit the duration of illness to six to 24 hours in most cases. Prophylactic antibiotics may be considered for short term travelers who are high risk hosts (e.g., immunocompromised patients) or who are taking critical trips during which even a short bout of diarrhea could affect the trip. Both as empiric therapy or for treatment of a specific bacterial pathogen, fluoroquinolones are recommended first line. Azithromycin is an alternative in areas of fluoroquinolone resistance. Rifaximin is approved for the treatment of noninvasive strains of <i>E. coli</i>.
<p>Infectious Diseases Society of America: The Practice of Travel Medicine: Guidelines by the Infectious Diseases of Society of America (2006)⁵⁷</p>	<p><u>Traveler's diarrhea</u></p> <ul style="list-style-type: none"> Bismuth subsalicylate, norfloxacin, ciprofloxacin and rifaximin are recommended for prophylaxis. Drugs that are no longer recommended for prophylaxis or treatment because of drug resistance world-wide include the sulfonamides, neomycin, ampicillin, doxycycline, tetracyclines, TMP and SMX/TMP. Fluoroquinolones remain the recommended first line therapy, with azithromycin and rifaximin recommended as alternatives. Azithromycin is an alternative treatment in all destinations, particularly for treatment in areas of fluoroquinolone resistance. Rifaximin is an alternative to fluoroquinolones in the treatment of persons with afebrile, nondysenteric traveler's diarrhea. Rifaximin is not approved for the treatment of persons with diarrhea associated with fever or passage of bloody stools or when <i>Shigella</i>, <i>Salmonella</i> or <i>Campylobacter</i> species are suspected pathogens. Three days of treatment with any antibiotic is recommended. If after 24 hours after the first dose, patients are still not well, they are advised to complete the three day course. If patients feel better after 24 hours they can stop treatment.
<p>Centers for Disease Control and Prevention: Sexually Transmitted Diseases Treatment Guidelines (2010)⁵⁸</p>	<p><u>Chancroid</u></p> <ul style="list-style-type: none"> Azithromycin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies. <p><u>Genital herpes simplex virus</u></p> <ul style="list-style-type: none"> First episodes should be treated with acyclovir, famciclovir, or valcyclovir. Acyclovir, famciclovir or valcyclovir may be used as suppressive therapy, though famciclovir may be somewhat less effective for suppression of viral shedding. Ease of administration and cost are important considerations for prolonged treatment. Episodic treatment requires initiation of therapy within one day of lesion onset or during the prodrome that precedes outbreak. Intravenous acyclovir is recommended for severe disease. <p><u>Granuloma inguinale</u></p> <ul style="list-style-type: none"> Doxycycline is recommended. Alternative agents include azithromycin, ciprofloxacin, erythromycin or SMX/TMP.

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	<ul style="list-style-type: none"> • The addition of an aminoglycoside may be considered if improvement is not evident within the first few days of therapy. <p><u>Lymphogranuloma venereum</u></p> <ul style="list-style-type: none"> • Doxycycline is recommended. • An alternative agent is erythromycin. • Clinical data are lacking, though azithromycin is probably effective. • Fluoroquinolone treatment may also be effective, though extended treatment intervals are likely required. • Pregnant and lactating women should be treated with erythromycin. Azithromycin may be an alternative but clinical data are lacking. <p><u>Syphilis</u></p> <ul style="list-style-type: none"> • Penicillin G is the preferred drug for all stages of syphilis. Alternative agents include doxycycline and tetracycline. Limited studies suggest that ceftriaxone is effective. • Azithromycin may be effective in early syphilis but should only be used when treatment with penicillin G or doxycycline is not feasible. It should not be used in pregnant women and men who have sex with men. • Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized. • Benzathine penicillin G is recommended for primary and secondary syphilis. • Infants ≥ 1 month of age with primary or secondary syphilis should be treated with benzathine penicillin G. • Early latent syphilis should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. • Late latent syphilis or latent syphilis of unknown duration should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. Alternative agents include doxycycline or tetracycline. • Patients with tertiary syphilis with no evidence of neurosyphilis should be treated with benzathine penicillin G. • Patients with neurosyphilis should be treated with aqueous crystalline penicillin G. An alternative regimen in patients in whom compliance can be assured is procaine penicillin plus probenecid. • Congenital syphilis: <ul style="list-style-type: none"> ○ Proven or highly probably disease with abnormal physical exam, serum quantitative serologic titer fourfold higher than the mother's titer or positive darkfield test of body fluids should be treated with aqueous crystalline penicillin G or procaine penicillin G. ○ Normal physical exam and serum quantitative tier same or less than fourfold the maternal tier and the mother was not treated, inadequately treated or has no documentation of treatment or the mother was treated with erythromycin or other non-penicillin regimen or the mother received <4 weeks of treatment before delivery should be treated with aqueous crystalline penicillin G, procaine penicillin G, or benzathine penicillin G. ○ Normal physical exam with serum quantitative titer the same or less than fourfold the maternal titer and the mother was treated during pregnancy, treatment was appropriate and administered for >4 weeks before delivery and the mother has no evidence

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	<p>of reinfection or relapse should be treated with benzathine penicillin G.</p> <ul style="list-style-type: none"> • Infants ≥ 1 month of age identified as having reactive serologic tests for syphilis should be treated with aqueous crystalline penicillin G. • If the child has no clinical manifestations of the disease and the cerebrospinal fluid examination is normal, penicillin G at up to three weekly doses can be considered. • Any child suspected of having congenital syphilis with neurologic involvement should be treated with aqueous crystalline penicillin G. • Infants and children requiring treatment for syphilis who have a history of penicillin allergy or develop an allergic reaction should be desensitized. <p><u>Urethritis</u></p> <ul style="list-style-type: none"> • Azithromycin or doxycycline is recommended. Alternative regimens include erythromycin, levofloxacin or ofloxacin. • In the case of recurrent or persistent urethritis, if the patient was compliant with the initial regimen and re-exposure can be excluded, metronidazole or tinidazole plus azithromycin is recommended. <p><u>Cervicitis</u></p> <ul style="list-style-type: none"> • Azithromycin or doxycycline is recommended. <p><u>Chlamydia</u></p> <ul style="list-style-type: none"> • Azithromycin or doxycycline is recommended. • Alternative agents include erythromycin, levofloxacin or ofloxacin. • Azithromycin or amoxicillin is recommended in pregnant patients. An alternative agent is erythromycin. • Infants with ophthalmia neonatorum should be treated with oral erythromycin. • Infants with pneumonia caused by <i>Chlamydia trachomatis</i> should be treated with oral erythromycin. • Children with chlamydial infection should be treated with oral erythromycin (patients weighing <45 kg), azithromycin (patients weighing ≥ 45 kg and <8 years), or azithromycin or doxycycline (patients ≥ 8 years of age). <p><u>Gonococcal infections</u></p> <ul style="list-style-type: none"> • Patients infected with <i>Neisseria gonorrhoeae</i> are frequently coinfecting with <i>C trachomatis</i> and should be treated for both infections. • Ceftriaxone is recommended. If ceftriaxone is not an option, other regimens include cefixime or single dose injectable cephalosporin regimens plus azithromycin or doxycycline. • Gonococcal infections of the pharynx should be treated with ceftriaxone plus azithromycin or doxycycline. • Gonococcal conjunctivitis should be treated with ceftriaxone. • Disseminated gonococcal infection should be treated with ceftriaxone. Alternative agents include cefotaxime or ceftizoxime. • Gonococcal meningitis and endocarditis should be treated with ceftriaxone. • Ophthalmia neonatorum should be treated with ceftriaxone. • Gonococcal scalp abscesses should be treated with ceftriaxone or

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	<p>cefotaxime.</p> <ul style="list-style-type: none"> • Infants born to mothers with untreated gonorrhea should be treated with ceftriaxone. • Children weighing >45 kg should be treated with a regimen recommended for adults. • Children weighing ≤45 kg should be treated with ceftriaxone at an appropriate dose. • Ceftriaxone is recommended in children with bacteremia or arthritis. • Erythromycin ophthalmic ointment is recommended as prophylaxis against ophthalmia neonatorum at birth. If erythromycin is not available, infants at risk can be administered ceftriaxone. <p><u>Bacterial vaginosis</u></p> <ul style="list-style-type: none"> • Metronidazole orally or topically or topical clindamycin are recommended. • Alternative agents include oral tinidazole or oral or intravaginal clindamycin. • Intravaginal metronidazole is an option in patients who are unable to tolerate oral metronidazole. • Treatment of all pregnant women with symptoms is recommended. Oral metronidazole or clindamycin is recommended. <p><u>Trichomoniasis</u></p> <ul style="list-style-type: none"> • Oral metronidazole or tinidazole is recommended. <p><u>Vulvovaginal candidiasis</u></p> <ul style="list-style-type: none"> • Over-the-counter butoconazole, clotrimazole, miconazole or tioconazole are recommended. • Prescription agents include butoconazole, nystatin, terconazole or oral fluconazole. • Oral fluconazole weekly for six months is the recommended treatment for recurrent infection. • Severe vulvovaginal candidiasis should be treated with seven to 14 days of topical therapy or fluconazole in two consecutive doses (second dose 72 hours after initial dose). • Only topical therapies are recommended in pregnancy. <p><u>Pelvic inflammatory disease</u></p> <ul style="list-style-type: none"> • Mild to moderate pelvic inflammatory disease should be treated with parenteral or oral therapies. • Recommended parenteral regimen A: cefotetan or cefoxitin plus doxycycline (oral or intravenous). • Recommended parenteral regimen B: clindamycin plus gentamicin. • Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or intravenous). • Outpatient oral therapy may be considered in patients with mild to moderate disease. Recommended regimens include ceftriaxone plus doxycycline with or without metronidazole, cefoxitin and probenecid plus doxycycline with or without metronidazole, or another parenteral 3rd generation cephalosporin plus doxycycline with or without metronidazole. • If parenteral cephalosporin therapy is not feasible, fluoroquinolones

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	<p>with or without metronidazole may be considered if the community prevalence and individual risk for gonorrhea are low.</p> <p><u>Epididymitis</u></p> <ul style="list-style-type: none"> • Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by enteric organisms, levofloxacin or ofloxacin are recommended. <p><u>Human papillomavirus</u></p> <ul style="list-style-type: none"> • External genital warts: <ul style="list-style-type: none"> ○ Podofilox 0.5% solution or gel, imiquimod 5% cream or sinecatechins 15% ointment are recommended as patient-applied treatments. ○ Cryotherapy with liquid nitrogen or cryoprobe, podophyllin resin, trichloroacetic acid or bichloroacetic acid or surgical removal are recommended as provider-administered treatments. ○ Alternative regimens include intralesional interferon, photodynamic therapy and topical cidofovir. • Cervical warts: <ul style="list-style-type: none"> ○ Biopsy evaluation is recommended to exclude high-grade squamous intraepithelial lesions • Vaginal warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen or trichloroacetic acid or bichloroacetic acid are recommended. • Urethral meatus warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen or podophyllin in compound tincture of benzoin is recommended. • Anal warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen, trichloroacetic acid or bichloroacetic acid or surgical removal is recommended. <p><u>Proctitis</u></p> <ul style="list-style-type: none"> • Ceftriaxone plus doxycycline is recommended. <p><u>Pediculosis pubis</u></p> <ul style="list-style-type: none"> • Permethrin or pyrethrins are recommended. • Alternative agents include malathion or ivermectin. <p><u>Scabies</u></p> <ul style="list-style-type: none"> • Permethrin or ivermectin are recommended. • Lindane is an alternative agent, not recommended as first-line. <p><u>Prophylaxis after sexual assault</u></p> <ul style="list-style-type: none"> • Hepatitis B vaccination. • Empirical regimen for Chlamydia, gonorrhea and trichomonas. • Emergency contraception. • Ceftriaxone or cefixime plus metronidazole plus azithromycin or doxycycline is the recommended regimen.
<p>Infectious Diseases Society of America: The Clinical Assessment,</p>	<p><u>Early Lyme disease</u></p> <ul style="list-style-type: none"> • Doxycycline, amoxicillin or cefuroxime for 10 to 21 days are the preferred treatment options for adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in

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<p>Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America (2006)^{58*}</p>	<p>the absence of specific neurologic manifestations or advanced atrioventricular heart block.</p> <ul style="list-style-type: none"> • Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. • Macrolides should be reserved for patients who are intolerant to doxycycline, amoxicillin or cefuroxime. • First generation cephalosporins are ineffective and should not be used. • When erythema migrans cannot be differentiated from bacterial cellulitis, it is reasonable to treat with cefuroxime or amoxicillin/clavulanate. • Ceftriaxone is effective but is not “superior” to oral agents and is more likely to cause serious adverse events. • Doxycycline should be avoided in pregnant patients. <p><u>Lyme meningitis and other manifestations of early neurologic Lyme disease</u></p> <ul style="list-style-type: none"> • Ceftriaxone is recommended. • Alternatives include parenteral cefotaxime or penicillin G. • Oral doxycycline may be used in patients intolerant to β-lactams. • Ceftriaxone is recommended in children. An alternative agent is cefotaxime or penicillin G. • Children eight years of age and older may be treated with oral doxycycline. • Antibiotics may not hasten the resolution of seventh cranial nerve palsy associated with Lyme disease but are recommended to prevent further sequelae. <p><u>Lyme carditis</u></p> <ul style="list-style-type: none"> • Patients with atrioventricular heart block and/or myopericarditis may be treated with oral or parenteral antibiotic therapy. • Ceftriaxone is recommended as initial management for hospitalized patients. <p><u>Borrelial lymphocytoma</u></p> <ul style="list-style-type: none"> • Recommended regimens are the same as for erythema migrans. <p><u>Late Lyme disease with Lyme arthritis</u></p> <ul style="list-style-type: none"> • Doxycycline, amoxicillin or cefuroxime are recommended in patients without neurological manifestations. • Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. • Adult patients with Lyme arthritis and evidence of neurological manifestations should be treated with parenteral ceftriaxone. Cefotaxime or penicillin G are acceptable alternatives. • Patient with persistent joint swelling may be treated with a second four-week course of oral antibiotics or a two to four week course of ceftriaxone. <p><u>Late neurological Lyme disease</u></p> <ul style="list-style-type: none"> • Parenteral ceftriaxone is recommended for adults and children. • Cefotaxime or penicillin G are alternatives.

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	<p><u>Acrodermatitis chronic atrophicans</u></p> <ul style="list-style-type: none"> Recommended regimens are the same as for erythema migrans. <p><u>Long-term treatment</u></p> <ul style="list-style-type: none"> Antibiotic therapy is not recommended for patients with long-term (≥6 months) subjective symptoms. <p><u>Human granulocytic anaplasmosis</u></p> <ul style="list-style-type: none"> Doxycycline is recommended. Children <8 years of age without concomitant Lyme disease may be treated with an abbreviated course of doxycycline. If the child has concomitant Lyme disease, amoxicillin or cefuroxime are recommended after the course of doxycycline. In patients not suited for treatment with doxycycline, rifampin is recommended. Patients with concomitant Lyme disease should also be treated with amoxicillin or cefuroxime. <p><u>Babesiosis</u></p> <ul style="list-style-type: none"> Atovaquone plus azithromycin or clarithromycin plus quinine is recommended. Clarithromycin plus quinine is recommended in patients with severe disease.
<p>Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2010)⁶⁰</p>	<p><u>Management of exacerbations of Chronic Obstructive Pulmonary Disease (COPD) with a bacterial component</u></p> <ul style="list-style-type: none"> Predominant bacteria include <i>H influenzae</i>, <i>S pneumoniae</i> and <i>M catarrhalis</i>. Patients with severe COPD requiring mechanical ventilation may be more frequently infected with <i>P aeruginosa</i>. Patients with mild exacerbations and no risk for poor outcome may be treated with oral penicillin, ampicillin, amoxicillin, tetracycline or SMX/TMP. Alternative agents include amoxicillin/clavulanate, a macrolide, a second or third generation cephalosporin or a ketolide. Patients with moderate exacerbations and risk factors for poor outcomes should be treated with amoxicillin/clavulanate. Alternative agents are fluoroquinolones. Parenteral options include β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones. Patients with severe exacerbations with risk factors for <i>P aeruginosa</i> should be treated with high dose oral or parenteral fluoroquinolones or parenteral β-lactam with <i>P aeruginosa</i> activity.
<p>Infectious Diseases Society of America: Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant <i>Staphylococcus Aureus</i> Infections in Adults and Children (2011)⁶¹</p>	<p><u>Empiric therapy for community-associated MRSA in skin and soft-tissue infections</u></p> <ul style="list-style-type: none"> For outpatients oral antibiotic options include: clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline) and linezolid. If additional coverage for β-hemolytic streptococci and community acquired-MRSA is desired, options include: clindamycin alone, SMX/TMP or tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. For hospitalized patients with complicated skin and soft-tissue infections, therapy for MRSA in addition to broad-spectrum antibiotics should be considered depending on culture data. Options include: intravenous vancomycin, intravenous or oral linezolid, intravenous daptomycin, intravenous telavancin and intravenous or oral

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	<p>clindamycin.</p> <ul style="list-style-type: none"> In hospitalized children with complicated skin and soft-tissue infections that are stable without ongoing bacteremia or intravascular infection, intravenous clindamycin (if resistance rate is low) with transition to oral therapy is recommended. Oral or intravenous linezolid is an alternative therapy. <p><u>Therapy for MRSA bacteremia and infective endocarditis</u></p> <ul style="list-style-type: none"> For adults with bacteremia and infective endocarditis with native valve, vancomycin or daptomycin is recommended. For patients with infective endocarditis and prosthetic valve, vancomycin plus rifampin and gentamicin is recommended. For children with bacteremia and infective endocarditis, vancomycin is recommended. Limited data shows daptomycin as a treatment option. <p><u>Therapy for MRSA pneumonia</u></p> <ul style="list-style-type: none"> For health-care associated or community acquired pneumonia, intravenous vancomycin or oral or intravenous linezolid or oral or intravenous clindamycin, if the strain is susceptible is recommended. For children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Linezolid is an alternative. <p><u>Therapy for bone and joint infections</u></p> <ul style="list-style-type: none"> For osteomyelitis and septic arthritis, antibiotic options include intravenous vancomycin, intravenous daptomycin, intravenous or oral SMX/TMP with rifampin, intravenous or oral linezolid and intravenous or oral clindamycin. In patients with concurrent bacteremia, rifampin can be added to the previous agents after clearance of bacteremia. For early-onset or acute hematogenous prosthetic joint infections involving a stable implant with short duration of symptoms and debridement, initiate therapy with parental therapy (see above) plus rifampin for two weeks followed by rifampin plus a fluoroquinolone, SMX/TMP, a tetracycline or clindamycin for three or six months. For early-onset spinal implant infections or implants in an actively infected site, initial parental therapy plus rifampin followed by prolonged oral therapy is recommended. For children with acute hematogenous MRSA osteomyelitis and septic arthritis, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Alternative agents include daptomycin or linezolid. <p><u>Therapy for MRSA infections of the central nervous system</u></p> <ul style="list-style-type: none"> For meningitis, brain abscess, subdural empyema and spinal epidural abscess, intravenous vancomycin is recommended. Rifampin may be added to the regimen. Alternative agents include linezolid or SMX/TMP. For children, intravenous vancomycin is recommended. <p><u>Therapy for persistent bacteremia and vancomycin treatment failures</u></p>

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	<ul style="list-style-type: none"> The following treatment regimens should be considered: high-dose daptomycin, if isolate is susceptible, in combination with another agent (e.g., gentamicin, rifampin, linezolid or a β-lactam antibiotic). If reduced susceptibility to vancomycin and daptomycin is present, treatment options include: quinupristin/dalfopristin, SMX/TMP, linezolid, telavancin. <p><u>Therapy of MRSA infections in neonates</u></p> <ul style="list-style-type: none"> For localized neonatal pustulosis in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in a full-term infant, intravenous vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded. For neonatal MRSA sepsis, intravenous vancomycin is recommended. Clindamycin and linezolid are alternatives for non-endovascular infections.
<p>Treatment Guidelines from the Medical Letter: Drugs for Parasitic Infections (2010)⁶²</p>	<p><u>Amebiasis (<i>Entamoeba histolytica</i>)</u></p> <ul style="list-style-type: none"> Asymptomatic: <ul style="list-style-type: none"> Drug of choice: iodoquinol 650 mg three times daily for 20 days. Alternatives: paromomycin 25 to 35 mg/kg/day in three daily doses for seven days or diloxanide furoate 500 mg three times daily for 10 days. Mild to moderate intestinal disease: <ul style="list-style-type: none"> Drug of choice: metronidazole 500 to 750 mg three times daily for seven to 10 days. Alternatives: tinidazole 2 g once daily for three days followed by iodoquinol 650 mg three times daily for 20 days, or paromomycin 25 to 35 mg/kg/day in three doses daily for three days. Severe intestinal and extraintestinal disease: <ul style="list-style-type: none"> Drug of choice: metronidazole 750 mg three times daily for seven to 10 days. Alternatives: tinidazole 2 g once daily for five days followed by iodoquinol 650 mg three times daily for 20 days or paromomycin 25 to 35 mg/kg/day in three daily doses for seven days. <p><u>Amebic meningoencephalitis (primary and granulomatous <i>Naegleria fowleri</i>)</u></p> <ul style="list-style-type: none"> Drug of choice: amphotericin B 1.5 mg/kg/day intravenous in two daily doses for three days, then 1 mg/kg/day for six days plus 1.5 mg/day intrathecally for two days, then 1 mg/day every other day for eight days. <p><u>Ancylostoma caninum (<i>Eosinophilic enterocolitis</i>)</u></p> <ul style="list-style-type: none"> Drug of choice: albendazole 400 mg for one dose. Alternatives: mebendazole 100 mg twice daily for three days or Endoscopic removal. <p><u>Ascariasis (<i>Ascaris lumbricoides</i>, roundworm)</u></p> <ul style="list-style-type: none"> Drug of choice: albendazole 400 mg for one dose. Alternatives: mebendazole 100 mg twice daily for three days or ivermectin 150 to 200 μg/kg for one dose.

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	<p><u>Babesiosis</u></p> <ul style="list-style-type: none"> • Drug of choice: atovaquone 750 mg twice daily for seven to 10 days plus azithromycin 500 to 1,000 mg on day one, then 250 to 1,000 mg on days two through 10. • Alternatives: clindamycin 300 to 600 mg intravenous four times daily or 600 mg three times daily for seven to 10 days plus quinine 650 mg three times daily for seven to 10 days. <p><u>Balantidiasis (<i>Balantidium coli</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: tetracycline 500 mg four times daily for 10 days. • Alternatives: metronidazole 500 to 750 mg three times daily for five days or iodoquinol 650 mg three times daily for 20 days. <p><u>Capillariasis (<i>Capillaria philippinensis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: mebendazole 200 mg twice daily for 20 days. • Alternative: albendazole 400 mg daily for 10 days. <p><u>Cryptosporidiosis (<i>Cryptosporidium</i>)</u></p> <ul style="list-style-type: none"> • Non-HIV infected patients: <ul style="list-style-type: none"> ○ Drug of choice: nitazoxanide 500 mg twice daily for three days. • HIV infected: <ul style="list-style-type: none"> ○ No drug has proven efficacy against cryptosporidiosis in advanced acquired immunodeficiency syndrome. <p><u>Cutaneous Larva Migrans (creeping eruption, dog and cat hookworm)</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg daily for three days. • Alternative: ivermectin 200 µg/kg daily for one to two days. <p><u>Cyclosporiasis (<i>Cyclospora cayetanensis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: SMX/TMP 800/160 mg twice daily for seven to 10 days. • Alternative: ciprofloxacin 500 mg twice daily for seven days. <p><u>Cystoisosporiasis (<i>Cystoisospora belli</i>, formerly known as <i>Isospora</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: SMX/TMP 800/160 mg twice daily for 10 days. <p><u><i>Dientamoeba fragilis</i></u></p> <ul style="list-style-type: none"> • Drug of choice: iodoquinol 650 mg three times daily for 20 days. • Alternative: paromomycin 25 to 35 mg/kg/day in three doses daily for seven days, or metronidazole 500 to 750 mg three times daily for 10 days. <p><u><i>Enterobius vermicularis</i> (pinworm infection)</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg for one dose; repeat in two weeks. • Alternative: mebendazole 100 mg for one dose; repeat in two weeks, or pyrantel pamoate 11 mg/kg base once (maximum, 1 g); repeat in two weeks. <p><u>Filariasis (<i>Wuchereria bancrofti</i>, <i>Brugia malayi</i>, <i>Brugia timori</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: diethylcarbamazine 6 mg/kg/day in three daily doses for 12 days. • Alternative: diethylcarbamazine 9 mg/kg/day in three daily doses for 12 days.

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	<p><u>Mansonella perstans</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg twice daily for 10 days. • Alternative: mebendazole 100 mg twice daily for 30 days. <p><u>Mansonella streptocerca</u></p> <ul style="list-style-type: none"> • Drug of choice: diethylcarbamazine 6 mg/kg/day in three daily doses for 12 days. • Alternative: ivermectin 150 µg/kg for one dose. <p><u>Tropical pulmonary eosinophilia</u></p> <ul style="list-style-type: none"> • Drug of choice: diethylcarbamazine 6 mg/kg/day in three daily doses for 12 to 21 days. <p><u>Onchocerca volvulus (River blindness)</u></p> <ul style="list-style-type: none"> • Drug of choice: ivermectin 150 µg/kg for one dose, repeated 150 µg/kg once every six to 12 months until asymptomatic. <p><u>Fluke (hermaphroditic, infection)</u></p> <ul style="list-style-type: none"> • <u>Clonorchis sinensis</u> (Chinese liver fluke): <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 75 mg/kg/day in three daily doses for two days. ○ Alternative: albendazole 10 mg/kg/day for seven days. • <u>Fasciola hepatica</u> (sheep liver fluke): <ul style="list-style-type: none"> ○ Drug of choice: triclabendazole 10 mg/kg for one or two doses. ○ Alternative: bithionol 30 to 50 mg/kg on alternate days for 10 to 15 doses or nitazoxanide 500 mg twice daily for seven days. • <u>Fasciolopsis buski</u>, <u>Heterophyes heterophyes</u>, <u>Metagonimus yokogawai</u> (intestinal flukes): <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 75 mg/kg/day in three daily doses for one day. • <u>Metorchis conjunctus</u> (North American liver fluke): <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 75 mg/kg/day in three daily doses for one day. • <u>Nanophyetus salmincola</u>: <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 60 mg/kg/day in three daily doses for one day. • <u>Opisthorchis viverrini</u> (Southeast Asian liver fluke): <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 75 mg/kg/day in three daily doses for two days. • <u>Paragonimiasis</u> (<i>P westermani</i>, <i>P miyazaki</i>, <i>P skrjabini</i>, <i>P hueitungensis</i>, <i>P heterotrema</i>, <i>P utcerobilaterus</i>, <i>P Africanus</i>, <i>P Mexicanus</i>, <i>P Kellicott</i>) (lung fluke): <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 75 mg/kg/day in three daily doses for two days. ○ Alternative: triclabendazole 10 mg/kg for one or two doses or bithionol 30 to 50 mg/kg on alternating days for 10 to 15 doses. <p><u>Giardiasis (<i>Giardia duodenalis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: metronidazole 250 mg three times daily for five to seven days or tinidazole 2 g for one dose, or nitazoxanide 500 mg twice daily for three days. • Alternative: paromomycin 25 to 35 mg/kg/day in three daily doses for

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	<p>five to 10 days or furazolidone 100 mg four times daily for seven to 10 days, or quinacrine 100 mg three times daily for five days.</p> <p><u>Gnathostomiasis (<i>Gnathostoma spinigerum</i>)</u></p> <ul style="list-style-type: none"> • Treatment of choice: albendazole 400 mg twice daily for 21 days, or ivermectin 200 µg/kg/day for two days. <p><u>Gongyloemiasis (<i>Gongylonema species</i>)</u></p> <ul style="list-style-type: none"> • Treatment of choice: albendazole 400 mg daily for three days . <p><u>Hookworm infection (<i>Ancylostoma duodenale, Necator americanus</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg for one dose or mebendazole 100 mg twice daily for three days or 500 mg for one dose. • Alternative: pyrantel pamoate 11 mg/kg (maximum, 1 g) daily for three days. <p><u>Leishmaniasis</u></p> <ul style="list-style-type: none"> • Visceral: <ul style="list-style-type: none"> ○ Drug of choice: liposomal amphotericin B 3 mg/kg/day intravenous on days one to five and 14 and 21, or sodium stibogluconate 20 mg/kg/day intravenous or intramuscular for 28 days or meglumine 20 mg/kg/day intravenous or intramuscular for 28 days, or miltefosine 2.5 mg/kg/day (maximum, 150 mg/day) for 28 days. ○ Alternatives: amphotericin B 1 mg/kg intravenous daily for 15 to 20 days or every second day for up to eight weeks, or paromomycin 15 mg/kg/day intramuscular for 21 days. • <i>Cutaneous</i>: <ul style="list-style-type: none"> ○ Drugs of choice: sodium stibogluconate 20 mg/kg/day intravenous or intramuscular for 20 days or meglumine antimonate 20 mg/kg/day intravenous or intramuscular for 20 days or miltefosine 2.5 mg/kg/day (maximum, 150 mg/d) for 28 days. ○ Alternative: paromomycin topically twice daily for 10 days or pentamidine 2 to 3 mg/kg intravenous or intramuscular every second day for four to seven doses. • Mucosal: <ul style="list-style-type: none"> ○ Drug of choice: sodium stibogluconate 20 mg/kg/day intravenous or intramuscular for 28 days or meglumine 20 mg/kg/d intravenous or intramuscular for 28 days or amphotericin B 0.5 to 1 mg/kg intravenous daily or every second day for up to eight weeks, or miltefosine 2.5 mg/kg/day (maximum, 150 mg/d) for 28 days. <p><u>Lice infestation (<i>Pediculus humanus, P. capitis, Phthirus pubis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: pyrethrins with piperonyl butoxide topically twice, at least seven days apart, or permethrin 1% topically twice, at least seven days apart or benzyl alcohol 5% topically twice, at least seven days apart, or malathion 0.5% topically twice, at least seven days apart. • Alternative: ivermectin 200 or 400 µg/kg once. <p><u>Malaria, treatment of</u></p> <ul style="list-style-type: none"> • Uncomplicated or mild infection (<i>P. falciparum</i> or unidentified species

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	<p>acquired in areas of chloroquine-resistant <i>P falciparum</i>):</p> <ul style="list-style-type: none"> ○ Drug of choice: atovaquone/proguanil, four adult tabs once daily for three days or two adult tabs twice daily for three days, or artemether/lumefantrine six doses over three days (four tablets per dose at same intervals zero, eight, 24, 36, 48 and 60 hours), or quinine sulfate 650 mg three times daily for three or seven days plus doxycycline 100 mg twice daily for seven days, or tetracycline 250 mg four times daily for seven days, or clindamycin 20 mg/kg/day in three daily doses for seven days. ○ Alternative: mefloquine 750 mg followed 12 hours later by 500 mg or artesunate 4 mg/kg/day for three days. <ul style="list-style-type: none"> ● <i>P vivax</i> acquired in areas of chloroquine-resistant <i>P vivax</i>: <ul style="list-style-type: none"> ○ Drug of choice: artemether/lumefantrine six doses over three days (four tablets per dose at same intervals zero, eight, 24, 36, 48 and 60 hours), or atovaquone/proguanil, four adult tabs once daily for three days or two adult tabs twice daily for three days, or quinine sulfate 650 mg three times daily for three or seven days plus doxycycline 100 mg twice daily for seven days all plus primaquine phosphate 30 mg base/day for 14 days. ○ Alternative: mefloquine 750 mg once followed 12 hours later by 500 mg or chloroquine 25 mg base/kg in three daily doses over 48 hrs plus doxycycline 100 mg twice daily for seven days all plus primaquine phosphate 30 mg base/day for 14 days. <p><u>Malaria, prevention of</u></p> <ul style="list-style-type: none"> ● All Plasmodium species in chloroquine-resistant areas: <ul style="list-style-type: none"> ○ Drug of choice: atovaquone/proguanil one adult tab daily, or doxycycline 100 mg daily, or mefloquine 250 mg once weekly. ○ Alternative: primaquine phosphate 30 mg base once daily. ● All Plasmodium species in chloroquine-sensitive areas: <ul style="list-style-type: none"> ○ Drug of choice: chloroquine phosphate 500 mg (300 mg base) once weekly. <p><u>Malaria, prevention of relapses due to <i>P vivax</i> and <i>P ovale</i></u></p> <ul style="list-style-type: none"> ● Drug of choice: primaquine phosphate 30 mg base daily for 14 days. <p><u>Malaria, self-presumptive treatment</u></p> <ul style="list-style-type: none"> ● Drug of Choice: atovaquone/proguanil four adult tabs once daily or two adult tabs twice daily for three days, or artemether/lumefantrine six doses over three days (four tablets per dose at same intervals zero, eight, 24, 36, 48 and 60 hours), or quinine sulfate 650 mg three times daily for three to seven days plus doxycycline 100 mg twice daily for seven days or artesunate 4 mg/kg/day daily for three days. <p><u>Microsporidiosis</u></p> <ul style="list-style-type: none"> ● Ocular (<i>Encephalitozoon hellem</i>, <i>E cuniculi</i>, <i>Vittaforma [Nosema] corneae</i>): <ul style="list-style-type: none"> ○ Drug of choice: fumagillin (dose not specified) plus albendazole 400 mg twice daily. ● Intestinal (<i>E bienewsi</i>): <ul style="list-style-type: none"> ○ Drug of choice: fumagillin 120 mg three times daily for 14 days. ● Intestinal (<i>E intestinalis</i>): <ul style="list-style-type: none"> ○ Drug of choice: albendazole 400 mg twice daily for 21 days.

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	<ul style="list-style-type: none"> • Disseminated (<i>E hellem</i>, <i>E cuniculi</i>, <i>E intestinalis</i>, <i>Pleistophora species</i>, <i>Trachipleistophora species</i>, <i>Anncaliia [Brachiola] vesicularum</i>): <ul style="list-style-type: none"> ○ Drug of choice: albendazole 400 mg twice daily. <p><u>Moniliformis infection</u></p> <ul style="list-style-type: none"> • Drug of choice: pyrantel pamoate 11 mg/kg for one dose, repeat in two weeks. <p><u><i>Pneumocystis jirovecii</i> (formerly <i>carinii</i>) pneumonia</u></p> <ul style="list-style-type: none"> • Moderate to severe disease: <ul style="list-style-type: none"> ○ Drug of choice: TMP 15 to 20 mg/kg/day with SMX 75 to 100 mg/kg/day oral or intravenous in three or four daily doses (change to oral after clinical improvement) for 21 days. ○ Alternative: pentamidine 3 to 4 mg/kg intravenous daily for 21 days, or primaquine phosphate 30 mg base daily for 21 days plus clindamycin 600 to 900 mg intravenous three to four times daily for 21 days, or 300 to 450 mg three to four times daily for 21 days. • Mild to moderate disease: <ul style="list-style-type: none"> ○ Drug of Choice: SMX/TMP two double strength (800/160 mg) tablets three times daily for 21 days. ○ Alternative: dapsone 100 mg daily for 21 days plus TMP 15 mg/kg/day in three daily doses for 21 days, or primaquine 30 mg base daily for 21 days plus clindamycin 300 to 450 mg three to four times daily for 21 days, or atovaquone 750 mg twice daily for 21 days. • Primary and secondary prophylaxis: <ul style="list-style-type: none"> ○ Drug of Choice: SMX/TMP one single (400/80 mg) or double strength tablet daily, or one double strength tablet three times per week. ○ Alternative: dapsone 50 mg twice daily or 100 mg daily, or dapson 200 mg weekly plus pyrimethamine 50 mg daily or 75 mg weekly, or atovaquone 1500 mg/day in one or two doses, pentamidine 300 mg aerosol inhaled monthly via Respirgard II nebulizer. <p><u>Scabies (<i>Sarcoptes scabiei</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: permethrin 5% topically twice, at least seven days apart. • Alternative: ivermectin 200 µg/kg for two doses at least seven days apart, or crotamiton 10% topically overnight on days one, two, three and eight. <p><u>Schistosomiasis (Bilharziasis)</u></p> <ul style="list-style-type: none"> • <i>S haematobium</i>: <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 40 mg/kg/day in one or two doses for one day. • <i>S intercalatum</i>: <ul style="list-style-type: none"> ○ Drug of Choice: praziquantel 40 mg/kg/day in one or two doses for one day. • <i>S japonicum</i>: <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 60 mg/kg/day in one or two doses for one day.

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	<ul style="list-style-type: none"> • <i>S mansoni</i>: <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 40 mg/kg/day in one or two doses for one day. ○ Alternative: oxamniquine 15 mg/kg for one dose. • <i>S mekongi</i>: <ul style="list-style-type: none"> ○ Drug of choice: praziquantel 60 mg/kg/day in two or three doses for one day. <p><u>Strongyloidiasis (<i>Strongyloides stercoralis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: ivermectin 200 µg/kg/day for two days. • Alternative: albendazole 400 mg twice daily for seven days. <p><u>Tapeworm infection</u></p> <ul style="list-style-type: none"> • Adult (intestinal stage): <ul style="list-style-type: none"> ○ <i>Diphyllobothrium latum</i> (fish), <i>Taenia saginata</i> (beef), <i>Taenia solium</i> (pork) and <i>Dipylidium caninum</i> (dog): <ul style="list-style-type: none"> ▪ Drug of choice: praziquantel 5 to 10 mg/kg for one dose. ▪ Alternative: niclosamide 2 g for one dose. ○ <i>Hymenolepis nana</i> (dwarf tapeworm): <ul style="list-style-type: none"> ▪ Drug of choice: praziquantel 25 mg/kg for one dose. ▪ Alternative: niclosamide 2 g daily for seven days. • Larval (tissue stage): <ul style="list-style-type: none"> ○ <i>Echinococcus granulosus</i> (hydatid cyst): <ul style="list-style-type: none"> ▪ Drug of choice: albendazole 400 mg twice daily for one to six months. • <i>Taenia solium</i> (Cysticercosis): <ul style="list-style-type: none"> ○ Treatment of choice: initial therapy should be focus on symptomatic treatment with anti-seizure medications. ○ Alternative: albendazole 400 mg twice daily for eight to 30 days; can be repeated as necessary, or praziquantel 100 mg/kg/day in three daily doses for one day, then 50 mg/kg/day in three daily doses for 29 days. <p><u>Toxoplasmosis (<i>Toxoplasma gondii</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: pyrimethamine 200 mg for one dose, then 50 to 75 mg/day for three to six weeks, plus sulfadiazine 1 to 1.5 g four times daily for three to six weeks, or clindamycin 1.8 to 2.4 g/day intravenous or orally in three or four doses, or atovaquone 1,500 mg twice daily. • Alternative: TMP 15 to 20 mg/kg/ SMX 75 to 100 mg/kg/day in three or four daily doses. <p><u>Trichinellosis (<i>Trichinella spiralis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: steroids for severe symptoms plus albendazole 400 mg twice daily for eight to 14 days. • Alternative: mebendazole 200 to 400 mg three times daily for three days, then 400 to 500 mg three times daily for 10 days. <p><u>Trichomoniasis (<i>Trichomonas vaginalis</i>)</u></p> <ul style="list-style-type: none"> • Drug of choice: Metronidazole 2 g for one dose, or tinidazole 2 g for one dose. <p><u>Trichostrongylus infection</u></p>

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	<ul style="list-style-type: none"> • Drug of choice: pyrantel pamoate 11 mg/kg base once (maximum, 1 g). • Alternative: mebendazole 100 mg twice daily for three days, or albendazole 400 mg for one dose. <p><u>Trichuriasis (<i>Trichuris trichiura</i>, whipworm)</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg daily for three days. • Alternative: mebendazole 100 mg twice daily for three days, or ivermectin 200 µg/kg/day for three days. <p><u>Trypanosomiasis (<i>T cruzi</i> [American trypanosomiasis, Chagas' disease])</u></p> <ul style="list-style-type: none"> • Drug of choice: nifurtimox 8 to 10 mg/kg/day in three to four daily doses for 90 to 120 days, or benznidazole 5 to 7 mg/kg/day in two daily doses for 60 to 90 days <p><u><i>T brucei gambiense</i> (West African trypanosomiasis, sleeping sickness)</u></p> <ul style="list-style-type: none"> • Hemolympathic stage: <ul style="list-style-type: none"> ○ Drug of choice: pentamidine 4 mg/kg/day intramuscular for seven days. ○ Alternative: suramin 100 to 200 mg (test dose) intravenous, then 20 mg/kg on days one, three, seven, 14 and 21. • Late disease with central nervous system involvement: <ul style="list-style-type: none"> ○ Drug of choice: eflornithine 400 mg/kg/day intravenous in four daily doses for 14 days, or eflornithine 400 mg/kg intravenous in two daily doses for seven days plus nifurtimox 15 mg/kg/day in three daily doses for 10 days, or melarsoprol 2.2 mg/kg/day intravenous for 10 days. <p><u><i>T b rhodesiense</i> (East African trypanosomiasis, sleeping sickness)</u></p> <ul style="list-style-type: none"> • Hemolympathic stage: <ul style="list-style-type: none"> ○ Drug of choice: suramin 100 to 200 mg (test dose) intravenous, then 20 mg/kg intravenous on days one, three, seven, 14 and 21. • Late disease with central nervous system involvement: <ul style="list-style-type: none"> ○ Drug of choice: melarsoprol 2 to 3.6 mg/kg/day intravenous for three days, repeat after seven days with 3.6 mg/kg/day for three days. <p><u>Visceral larva migrans (Toxocariasis):</u></p> <ul style="list-style-type: none"> • Drug of choice: albendazole 400 mg twice daily for five days, or mebendazole 100 to 200 mg twice daily for five days.
<p>American College of Gastroenterology: Guideline on the Management of <i>Helicobacter pylori</i> Infection (2007)⁴⁵</p>	<ul style="list-style-type: none"> • Recommended primary therapies include a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole (clarithromycin-based triple therapy) or a proton pump inhibitor or a histamine₂ receptor antagonist, bismuth, metronidazole and tetracycline (bismuth quadruple therapy). • Sequential therapy consisting of a proton pump inhibitor and amoxicillin for five days followed by a proton pump inhibitor, clarithromycin and tinidazole for five days may be an alternative to clarithromycin-based triple therapy or bismuth quadruple therapy but requires validation in the United States before it becomes recommended as first-line therapy. • Bismuth quadruple therapy is favored in patients allergic to penicillin or those who have been previously treated with a macrolide. • Eradication rates are similar between clarithromycin- and bismuth-

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	<p>based therapies.</p> <ul style="list-style-type: none"> In patients who fail initial therapy, the prescriber should avoid using antibiotics employed in previous regimens. Bismuth-based quadruple therapy for seven to 14 days is accepted salvage therapy in patients with persistent infection. Levofloxacin-based triple therapy (proton pump inhibitor, amoxicillin and levofloxacin) is another option for salvage therapy but requires validation in the United States.
Centers for Disease Control and Prevention: Guidelines for the Treatment of Malaria in the United States (2010) ⁶³	<ul style="list-style-type: none"> Treatment should be initiated as soon as possible. Patients with severe <i>P falciparum</i> malaria or who cannot take oral medications should be given the treatment by continuous intravenous infusion. Most drugs used in treatment are active against the parasite forms in the blood and include chloroquine, atovaquone/proguanil, artemether/lumefantrine, mefloquine, quinine, quinidine, doxycycline, tetracycline, clindamycin and artesunate[†]. In addition, primaquine is active against the dominant parasite liver forms and prevents relapses.
Centers for Disease Control and Prevention: Guidelines for the Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-Infected Adults and Adolescents (2009) ⁶⁴	<p><i>Mycobacterium avium</i> Complex (MAC) disease</p> <p>Primary prophylaxis against disseminated MAC in adults and adolescents:</p> <ul style="list-style-type: none"> Initiate when CD4⁺ T lymphocyte count is <50 cells/μL. Clarithromycin and azithromycin are the preferred agents, and also protect against respiratory bacterial infections. Rifabutin is an alternative in patients who cannot tolerate clarithromycin or azithromycin. Primary prophylaxis may be discontinued when CD4⁺ count is >100 cells/μL for at least three months and re-instated when counts drop to below 50 cells/μL. <p>Treatment of disseminated MAC in adults and adolescents:</p> <ul style="list-style-type: none"> Initial treatment should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. Clarithromycin is the preferred first agent. Azithromycin may be used in patients when clarithromycin cannot be used due to drug interactions or intolerance. Ethambutol is the preferred second agent. Rifabutin may be added as a third drug. A third or fourth drug may be used in patients with advanced immunosuppression, high mycobacterial loads, or in the absence of effective antiretroviral therapy. If initial treatment fails, the patient should be treated with two medications not previously used including ethambutol, rifabutin, amikacin or a quinolone. Susceptibility testing should be performed before treatment. <p>Secondary prophylaxis:</p> <ul style="list-style-type: none"> Patients with disseminated MAC disease should receive life-long secondary prophylaxis unless immune reconstitution occurs as a result of antiretroviral therapy. Secondary prophylaxis may be discontinued in patients who have completed ≥12 months of therapy for MAC, remain asymptomatic with respect to MAC signs and symptoms and have a sustained increase (>6 months) in CD4⁺ counts to >100 cells/μL after antiretroviral therapy.

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	<ul style="list-style-type: none"> • Secondary prophylaxis should be reinstated if CD4⁺ counts drop to <100 cells/μL. <p>Pregnancy:</p> <ul style="list-style-type: none"> • Clarithromycin should not be used. • Azithromycin is the preferred drug for primary prophylaxis. • Azithromycin plus ethambutol is recommended as secondary prophylaxis. • Patients who have disseminated MAC disease and have not been treated previously with or are not receiving effective antiretroviral therapy should have it withheld until completion of the first two weeks of antimycobacterial therapy. <p><u>Pneumocystis pneumonia (PCP)</u></p> <ul style="list-style-type: none"> • SMX/TMP double strength is the recommended prophylactic agent. • If SMX/TMP cannot be tolerated, alternative prophylactic regimens include dapsone; dapsone plus pyrimethamine plus leucovorin; aerosolized pentamidine and atovaquone. • For patients seropositive for <i>Toxoplasma gondii</i> who cannot tolerate SMX/TMP, alternatives prophylactic regimens against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin or atovaquone plus leucovorin with or without pyrimethamine. • Pyrimethamine plus sulfadoxine* also has activity in preventing PCP but because SMX/TMP has “superior” efficacy, widespread availability and is low cost, pyrimethamine plus sulfadoxine should rarely be used in the United States. • Other prophylactic alternatives that cannot be recommended include aerosolized pentamidine, intermittently administered parental pentamidine and clindamycin plus primaquine. • SMX/TMP is the treatment of choice for PCP. Patients who have PCP despite SMX/TMP prophylaxis are usually effectively treated with standard doses of SMX/TMP. • Alternative treatments in mild to moderate disease include dapsone plus TMP, primaquine plus clindamycin or atovaquone suspension. • Alternative treatments for moderate to severe disease include clindamycin plus primaquine or intravenous pentamidine. • Aerosolized pentamidine is not recommended for the treatment of PCP. • Recommended duration of therapy for PCP is 21 days. • Patients who have a history of PCP should be administered prophylaxis for life with SMX/TMP unless immune reconstitution occurs as a result of antiretroviral therapy. • For patients who are intolerant of SMX/TMP, alternatives for lifelong prophylaxis include dapsone, dapsone plus pyrimethamine, atovaquone or aerosolized pentamidine. • SMX/TMP is the preferred initial therapy during pregnancy, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to SMX/TMP. • SMX/TMP is the recommended prophylactic agent in pregnant women, with dapsone as an alternative. <p><u>Toxoplasma gondii encephalitis</u></p> <ul style="list-style-type: none"> • SMX/TMP double strength is the recommended prophylactic agent.

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	<ul style="list-style-type: none"> • For patients who cannot tolerate SMX/TMP, alternative prophylactic regimens include dapsone plus pyrimethamine plus leucovorin. Atovaquone plus leucovorin with or without pyrimethamine can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin or clarithromycin cannot be recommended. • Aerosolized pentamidine is not recommended. • The recommended first line treatment for <i>toxoplasma gondii</i> encephalitis is pyrimethamine plus sulfadiazine plus leucovorin. The preferred alternative is pyrimethamine plus clindamycin plus leucovorin. • SMX/TMP may be considered an alternative option for treatment of <i>toxoplasma gondii</i> encephalitis. • The following regimens have been shown to be effective in the treatment of <i>toxoplasma gondii</i> encephalitis in at least two clinical trials: atovaquone plus either pyrimethamine plus leucovorin or sulfadiazine, or azithromycin plus pyrimethamine plus leucovorin. Atovaquone as a single agent may be used for patients intolerant of both pyrimethamine and sulfadiazine. • Active therapy should be continued for at least six weeks, if there is clinical and radiologic improvement. • Patients who have completed initial therapy for <i>toxoplasma gondii</i> encephalitis should be administered lifelong suppressive therapy unless immune reconstitution occurs as a consequence of antiretroviral therapy, in which case treatment should be discontinued. • Pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for <i>toxoplasma gondii</i> encephalitis. For those who cannot tolerate sulfonamides, pyrimethamine plus clindamycin is recommended. • For pregnant women, treatment should be the same as in nonpregnant adults. • SMX/TMP can be administered for primary prophylaxis against <i>toxoplasma gondii</i> encephalitis as described for PCP. Secondary prophylaxis should be provided using the same indications as for nonpregnant women.
<p>Centers for Disease Control and Prevention: Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children (2009)⁶⁵</p>	<p><u>MAC disease</u></p> <p>Primary prophylaxis against disseminated MAC in children ≥ 6 years of age:</p> <ul style="list-style-type: none"> • Initiate when CD4⁺ count is < 50 cells/mm³. • Clarithromycin and azithromycin are the preferred agents. <p>Primary prophylaxis against disseminated MAC in children two to five years of age:</p> <ul style="list-style-type: none"> • Initiate when CD4⁺ count is < 75 cells/mm³. • Clarithromycin and azithromycin are the preferred agents. <p>Primary prophylaxis against disseminated MAC in children one to two years of age:</p> <ul style="list-style-type: none"> • Initiate when CD4⁺ count is < 500 cells/mm³. • Clarithromycin and azithromycin are the preferred agents. <p>Primary prophylaxis against disseminated MAC in children < 12 months of age:</p> <ul style="list-style-type: none"> • Initiate when CD4⁺ count is < 750 cells/mm³.

Clinical Guideline	Recommendation
	<ul style="list-style-type: none"> • Clarithromycin and azithromycin are the preferred agents. <p>Discontinuing primary prophylaxis:</p> <ul style="list-style-type: none"> • Primary prophylaxis can be discontinued in HIV-infected children >2 years of age receiving stable highly active antiretroviral therapy for >6 months who are experiencing sustained (>3 months) CD4⁺ cell recovery well above the age-specific target for initiation of prophylaxis (>100 cells/mm³ for children >6 years of age and >200 cells/mm³ for children two to five years of age). • No specific recommendations exist for discontinuing MAC prophylaxis in HIV-infected children <2 years of age. <p>Treatment of disseminated MAC disease in children:</p> <ul style="list-style-type: none"> • Initial treatment should consist of at least two antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin or azithromycin plus ethambutol are recommended. • Clarithromycin may be used initially, reserving azithromycin for patients in whom drug interactions are a concern or who are intolerant to clarithromycin. • Rifabutin may be added to clarithromycin plus ethambutol combination. • If initial treatment fails, the patient should be treated with a new multidrug regimen not previously used. Options include rifabutin, amikacin and quinolones. <p>Secondary prophylaxis:</p> <ul style="list-style-type: none"> • Patients with disseminated MAC disease should receive life-long secondary prophylaxis. • Secondary prophylaxis may be discontinued in children >2 years of age who have completed >12 months of treatment for MAC, who remain asymptomatic for MAC, and who are receiving stable highly active antiretroviral therapy. Patients should have sustained (>6 months) CD4⁺ cell recovery well above the age specific target for initiation of primary prophylaxis (>100 cells/mm³ for children >6 years of age and >200 cells/mm³ for children two to six years of age). • Secondary prophylaxis should be reintroduced if the CD4⁺ count falls below the age-related threshold. <p><u>PCP</u></p> <ul style="list-style-type: none"> • SMX/TMP is the drug of choice for prophylaxis. • Alternative prophylactic regimens include atovaquone, dapsone or aerosolized pentamidine (in patients cannot take SMX/TMP, atovaquone or dapsone). Azithromycin has been used to supplement atovaquone for greater broad spectrum prophylaxis. • Pyrimethamine plus sulfadoxine* has not been evaluated adequately among human immunodeficiency virus (HIV) infected children. • SMX/TMP is the recommended treatment for PCP. • Intravenous pentamidine is recommended for patients who cannot tolerate SMX/TMP or who demonstrate clinical treatment failure after five to seven days of SMX/TMP therapy. • Atovaquone plus dapsone plus TMP or clindamycin plus primaquine are possible alternatives in adults and the guideline states these therapies have limited data in children. • None of the drugs administered to treat and prevent PCP completely

Clinical Guideline	Recommendation
	<p>eliminates <i>Pneumocystis</i>, and prophylaxis is effective only while the selected drug is administered. Patients who have experienced an episode of PCP should have prophylaxis administered continuously after completion of treatment.</p> <p><u>Malaria</u></p> <ul style="list-style-type: none"> • SMX/TMP is not recommended for prophylaxis of malaria as the agent will likely not provide adequate protection. • Uncomplicated chloroquine-sensitive <i>Plasmodium falciparum</i> malaria should be treated with chloroquine. Uncomplicated chloroquine-resistant malaria should be treated with atovaquone/proguanil, quinine plus clindamycin or doxycycline or with mefloquine. • The treatment of choice for non-<i>P falciparum</i> malaria is chloroquine. Chloroquine-resistant disease should be treated with quinine plus clindamycin or doxycycline, atovaquone/proguanil or with mefloquine. <p><u>Toxoplasma gondii encephalitis</u></p> <ul style="list-style-type: none"> • SMX/TMP is the recommended drug of choice for prophylaxis. • Alternative prophylactic regimens include dapsone plus pyrimethamine or atovaquone with or without pyrimethamine. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin or clarithromycin cannot be recommended due to lack of data. • Aerosolized pentamidine is not recommended. • The preferred treatment for congenital toxoplasmosis is pyrimethamine plus sulfadiazine, with supplementary leucovorin. • The recommended duration of treatment of congenital toxoplasmosis for infants without HIV infection is 12 months. • HIV infected children with central nervous system, ocular or systemic toxoplasmosis should be treated with pyrimethamine plus leucovorin plus sulfadiazine. • Acute treatment should be continued for six weeks, but longer courses may be required. • The primary alternative to sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin. Use of azithromycin, instead of clindamycin, has not been evaluated in children. • Corticosteroids are recommended for children with central nervous system disease when cerebrospinal fluid protein is highly elevated or with focal lesions with substantial mass effects. • Anticonvulsants should be administered to children with <i>toxoplasma gondii</i> encephalitis who have a history of seizures but should not be administered prophylactically to children without a history of seizures. If administered, anticonvulsants should be continued at least through acute therapy. • Patients who have completed initial therapy for acquired <i>toxoplasma gondii</i> encephalitis should be administered lifelong suppressive therapy unless immune reconstitution occurs with antiretroviral therapy. <ul style="list-style-type: none"> • Pyrimethamine plus sulfadiazine plus leucovorin is highly effective for this purpose. Pyrimethamine plus clindamycin is used for patients who cannot tolerate sulfa drugs. • Atovaquone with or without pyrimethamine also can be considered for children. • Limited data support the use of SMX/TMP for secondary prophylaxis

Clinical Guideline	Recommendation
<p>American Academy of Ophthalmology: Conjunctivitis Preferred Practice Pattern (2008)⁶⁶</p>	<p>and should only be used for patients who do not tolerate pyrimethamine plus sulfadiazine or clindamycin.</p> <ul style="list-style-type: none"> • Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without specific treatment in immune-competent adults. • Use of topical antibacterials is associated with earlier clinical and microbiological remission compared to placebo in days two to five of treatment. • Advantages of topical antibacterials persist over days six to 10, but the extent of benefit lessens over time. • Choice of antibacterial is usually empirical; generally based on convenience and price. • For the treatment of severe bacterial conjunctivitis, choice of antibacterial is guided by the results of laboratory tests. • Systemic antibacterials are necessary to treat conjunctivitis due to <i>N gonorrhoeae</i> and <i>C trachomatis</i>. Topical therapy, while not necessary, is usually used.
<p>American Academy of Dermatology: New Insights into the Management of Acne: An Update from the Global Alliance to Improve Outcomes in Acne Group (2009)⁴⁶</p>	<ul style="list-style-type: none"> • Acne vulgaris should be managed early and aggressively as a chronic disease to limit scarring; the disease is self-limiting in only 60% of cases. • Oral isotretinoin, the most effective acne vulgaris treatment developed to date, is administered during a 20 week period and sometimes must be given in repeated courses. • The combination of a topical retinoid and antimicrobial agent remains the preferred treatment approach for the majority of patients with acne vulgaris, especially in the presence of inflammatory lesions. • Due to the risk of bacterial resistance, antibiotics should be used for the shortest duration and should not be used as monotherapy but in combination with benzoyl peroxide. • Topical antibiotics combined with benzoyl peroxide and a topical retinoid may be used in mild to moderate acne vulgaris; oral antibiotics are recommended for moderate to moderately severe acne vulgaris. • Topical retinoids alone or in combination with benzoyl peroxide is recommended for the maintenance of acne vulgaris. • Long term antibiotic use may be required in the rare cases in which the patient experiences acne vulgaris flares when oral antibiotics are discontinued. <p><u>Global alliance acne vulgaris treatment algorithm</u></p> <ul style="list-style-type: none"> • For mild acne vulgaris (comedonal), treatment with a topical retinoid is considered first line; treatment with an alternative topical retinoid or azelaic acid or salicylic acid are considered alternatives. • For mild acne vulgaris (mixed and papular/pustular), treatment with a topical retinoid and a topical antimicrobial is considered first line. Treatment with alternative topical retinoid and alternative topical antimicrobial or azelaic acid are considered alternatives. • For moderate acne vulgaris (mixed and papular/pustular), treatment with oral antibiotic and a topical retinoid with or without benzoyl peroxide is considered first line. Treatment with an alternative oral antibiotic and alternative topical retinoid with or without benzoyl peroxide are considered alternatives. • For moderate acne vulgaris (nodular), treatment with an oral antibiotic and a topical retinoid and benzoyl peroxide is considered first line.

Clinical Guideline	Recommendation
	<p>Treatment with oral isotretinoin or alternate oral antibiotic and an alternate topical retinoid (with or without) benzoyl peroxide/azelaic acid are considered alternatives.</p> <ul style="list-style-type: none"> • For severe acne (nodular/conglobate), treatment with oral isotretinoin is considered first line. Treatment with high dose oral antibiotic and a topical retinoid and benzoyl peroxide are considered alternative. • For maintenance therapy (mild to severe acne vulgaris), treatment with a topical retinoid with or without benzoyl peroxide is considered first line.
<p>American Academy of Dermatology: Guidelines of Care for Acne Vulgaris Management (2007)⁴⁷</p>	<p><u>Standard of care</u></p> <ul style="list-style-type: none"> • Topical therapy is the standard of care in acne vulgaris treatment. • Systemic antibiotics are used in moderate to severe acne vulgaris and treatment-resistant forms of inflammatory acne vulgaris. • Intralesional corticosteroid injections are effective for large inflammatory lesions. <p><u>Topical therapy</u></p> <ul style="list-style-type: none"> • Topical retinoids reduce obstruction within the follicle and are useful in the management of both comedonal and inflammatory acne vulgaris. • The relative efficacy between topical retinoids (i.e., tretinoin, adapalene, tazarotene, isotretinoin [not available topically in the United States]) is unclear. • Benzoyl peroxide is a bactericidal agent with the ability to prevent or eliminate the development of <i>Propionibacterium acnes</i> resistance, and is therefore used in combination with oral or topical antibiotics. • Topical antibiotics (i.e., erythromycin, clindamycin) are effective in the treatment of acne vulgaris but are more effective when used in combination with benzoyl peroxide due to a synergy as well as the resulting elimination or reduction of bacterial resistance. • Salicylic acid has moderately effective and less potent comedolytic properties than topical retinoids and is therefore used in patients intolerant to dermatological effects caused by topical retinoids. • Azelaic acid has shown to be effective, with comedolytic and antibacterial properties. • The role of aluminum chloride, resorcinol, sodium sulfacetamide, sulfur and zinc in the management of acne vulgaris is unclear due to limited clinical evidence and/or peer-reviewed literature. <p><u>Systemic antibiotics</u></p> <ul style="list-style-type: none"> • Doxycycline and minocycline are more effective than tetracycline. • Minocycline has been shown to be superior to doxycycline in reducing <i>P. acnes</i>. • Erythromycin is effective but associated with bacterial resistance and therefore its use should be limited to those who cannot tolerate tetracyclines (i.e., pregnant women and children less than eight years old due to the potential damage to the skeleton or teeth). <p><u>Hormonal agents</u></p> <ul style="list-style-type: none"> • Oral contraceptives containing norgestimate with ethinyl estradiol and norethindrone acetate with ethinyl estradiol are Food and Drug Administration approved for the management of acne vulgaris. <p><u>Isotretinoin</u></p>

Clinical Guideline	Recommendation
	<ul style="list-style-type: none"> • Isotretinoin, a vitamin A derivative, is approved for the treatment of severe recalcitrant nodular acne vulgaris and possibly effective in treatment-resistant acne vulgaris or acne vulgaris producing physical or psychological scarring. • Since isotretinoin is a potent teratogenic, females of child-bearing age must only be treated if they are participating in the approved pregnancy prevention and management program (iPLEDGE).
<p>American College of Obstetricians and Gynecologists: Practice Bulletin: Treatment of Urinary Tract Infections in Nonpregnant Women (2008)⁶⁷</p>	<ul style="list-style-type: none"> • Most urinary tract infections are caused by <i>E coli</i> (80 to 90%). • Other causes of urinary tract infections include <i>Staphylococcus saprophyticus</i>, <i>Proteus</i>, <i>Pseudomonas</i>, <i>Klebsiella</i> and <i>Enterobacter</i> species. • Treatment options include SMX/TMP (preferred), trimethoprim, ciprofloxacin, levofloxacin, norfloxacin, gatifloxacin (all three-day regimens), nitrofurantoin macrocrystals, nitrofurantoin monohydrate/macrocrystals (seven-day regimens) and fosfomycin tromethamine (single dose). • First generation cephalosporins and amoxicillin are less effective than the above agents due to resistance and rapid excretion from the urinary tract. • B-lactams are not first-line therapy in acute cystitis unless the causative organism is gram-positive, in which case amoxicillin or amoxicillin/clavulanate may be used. • Women with frequent recurrences may be treated with once daily nitrofurantoin, norfloxacin, ciprofloxacin, trimethoprim, SMX/TMP or any other agent listed above for six to 12 months and then be reassessed. • SMX/TMP is considered the preferred treatment for uncomplicated cystitis except in areas where resistance is common. • Fluoroquinolones should not be used first-line in areas where SMX/TMP resistance is uncommon. • Acute pyelonephritis in acutely ill patients should be treated with parenteral broad-spectrum antibiotics. If gram-positive organisms are suspected, amoxicillin, ampicillin or a cephalosporin may be used. In other cases β-lactams are no longer recommended. • First-line treatment for pyelonephritis is now a fluoroquinolone. SMX/TMP may be used in areas of low resistance. • Parenteral treatment options include an aminoglycoside with ampicillin or piperacillin, a first generation cephalosporin, aztreonam, piperacillin/tazobactam, or a parenteral fluoroquinolone alone or in combination.
<p>Infectious Diseases Society of America: International Clinical Practice Guidelines for the Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women: A 2010 Update by the Infectious Disease Society of America and the European Society for Microbiology and</p>	<p><u>Acute uncomplicated bacterial cystitis</u></p> <ul style="list-style-type: none"> • Taking into consideration availability, allergy history and tolerance the following antimicrobials are recommended: nitrofurantoin monohydrate/macrocrystals, SMX/TMP, fosfomycin, pivmecillinam[‡]. • Fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) are recommended as alternative agents if the above agents cannot be used. Although highly efficacious, fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) should be reserved for important uses other than acute cystitis due to increasing resistance. • β-lactams (amoxicillin/clavulanate, cefdinir, and cefpodoxime) are also recommended as alternative agents. Due to poor efficacy and antimicrobial resistance, amoxicillin and ampicillin should not be used as monotherapy.

Clinical Guideline	Recommendation
Infectious Disease (2011)⁶⁸	<u>Acute pyelonephritis</u> <ul style="list-style-type: none"> • In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, oral ciprofloxacin with or without an initial intravenous loading dose is appropriate. • An initial one-time intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended if prevalence of fluoroquinolone resistance exceeds 10%. • In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, a once-daily fluoroquinolone (e.g., ciprofloxacin, levofloxacin) is appropriate. • If the pathogen is known to be susceptible, oral SMX/TMP is recommended. When the susceptibility is not known, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. • Oral β-lactam agents are less effective than other available agents. Therefore if an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. • For women with pyelonephritis requiring hospitalization, an intravenous antimicrobial regimen, such as a fluoroquinolone; an aminoglycoside, with or without ampicillin; an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside; or a carbapenem should be initial treatment.

*The 2006 Lyme disease guidelines by the Infectious Disease Society of America were the subject of an antitrust investigation by the Connecticut Attorney General in 2006 to examine potential conflicts of interest among panelist and whether the panelist failed to consider divergent medical opinion. An independent review panel was convened and, in 2010, agreed that no changes needed to be made to the 2006 guidelines.

†Not commercially available in the United States. Available through the Centers for Disease Control and Prevention's malaria hotline.

‡Not available in the United States.

Conclusions

The tetracyclines (demeclocycline, doxycycline, minocycline, tetracycline) are all Food and Drug Administration (FDA) approved for use in the treatment of various infectious diseases, and have all demonstrated efficacy in the treatment of acne vulgaris.^{1,3-17} The class of antibiotics works by inhibiting bacterial protein synthesis and has a broad spectrum of activity.¹ Within the class no major clinically significant differences exist among the various agents; however, doxycycline and minocycline appear to be the most highly utilized.²⁻¹⁷ Furthermore, doxycycline possesses some advantages that could potentially make it a more preferred tetracycline for clinical use. Specifically, doxycycline can be administered twice daily, achieves reasonable concentrations even if administered with food, is less likely to cause photosensitivity and binds calcium to a lesser extent compared to tetracycline reducing the risk for tooth discoloration and bony growth retardation.² Despite these advantages, results from clinical trials have not consistently demonstrated superiority of one tetracycline over another.¹⁹⁻⁴³ In addition, all available tetracyclines are available generically in at least one dosage form and/or strength.

In terms of treatment guidelines, the tetracyclines potentially play a role in the treatment of various infectious diseases based on their established susceptibility to certain microorganisms and FDA approved indications.^{3-17,45-47,52-67} Of note, the tetracyclines play a major role in the treatment of Lyme disease and various sexually transmitted diseases, as well as in the eradication of *Helicobacter pylori* infections (when used as combination therapy).^{45,58,59}

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Doxycycline hyclate	1,791	2,380	62.24%	\$22,289.91	\$9.37
Minocycline	299	766	20.03%	\$23,082.63	\$30.13
Tetracycline	275	490	12.81%	\$3,826.76	\$7.81
Doxycycline monohydrate	120	172	4.50%	\$8,787.20	\$51.09
Vibramycin [®]	5	9	0.24%	\$2,001.71	\$222.41
Doryx [®]	2	5	0.13%	\$1,766.06	\$353.21
Doxycycline hyclate [®]	1	2	0.05%	\$504.90	\$252.45
Class Total:	2,493	3,824	100%	\$62,259.17	\$16.28

Recommendations

At this time, all generic tetracycline products are preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL). All branded products require prior authorization. Of note, minocycline SR, doxycycline SR products (brand and generic), Adoxa[®] Pak and doxycycline monohydrate Pak are not covered. In recognition of the established safety and efficacy of tetracyclines, consensus clinical guideline recommendations, availability of generics and cost considerations, no changes to the current criteria (below) are proposed.

Brand name minocycline products:

- The patient has had a documented side effect, allergy, or treatment failure with generic minocycline. If a product has an AB rated generic, the trial must be the generic formulation.

Brand name doxycycline products (see below for Oracea[®] and Vibramycin[®] Suspension):

- The patient has had a documented side effect, allergy, or treatment failure with generic doxycycline. If a product has an AB rated generic, the trial must be the generic formulation.

Oracea[®]:

- The patient has a diagnosis of Rosacea.
AND
- The patient has had a documented side effect, allergy, or treatment failure with doxycycline, minocycline, and tetracycline.

Vibramycin[®] Suspension, Syrup:

- The patient has a medical necessity for a liquid dosage form.

Brand name tetracycline products:

- The patient has had a documented side effect, allergy, or treatment failure with generic tetracycline. If a product has an AB rated generic, the trial must be the generic formulation.

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