Tetracycline and doxycycline frequently are prescribed to women for a number of different infectious diseases. Although both are considered to be broad spectrum, many common pathogens have acquired resistance to them, leaving a fairly finite list of indicated uses. This list includes the treatment of several sexually transmitted diseases, pelvic inflammatory disease and endometritis, and acne. The principal contraindications to their use are breast feeding, pregnancy, age less than 8 years, and impaired renal or hepatic function. The main toxicities are staining of teeth, stippling of bones, and photosensitivity. Renal, central nervous system, hepatic, and gastrointestinal disturbances also have been documented. When taken with food or certain medications, tetracycline is poorly absorbed, making adequate serum concentrations difficult to attain. Doxycycline is better absorbed. The volume of distribution for both drugs is essentially that of the body's serum, including small amounts in breast milk, secretions, cerebrospinal fluid, and amniotic fluid. The drugs are metabolized in the liver and then eliminated in the urine (tetracycline) or feces (doxycycline). Subtle differences in the metabolism and side effects of the two medications favor the use of doxycycline over tetracycline in most instances. In spite of their limitations, when used properly, tetracycline and doxycycline are safe, effective, and inexpensive antimicrobials. (Prim Care Update Ob/Gyns 1996;3:224-227)

The optimal and judicious selection of antimicrobial agents for the therapy of infectious disease is a complex procedure that requires clinical judgment and detailed knowledge of pharmacological and microbiological factors. The goal is to choose a drug that is selectively active for the most likely infecting microorganism(s) and that has the least potential to cause toxicity or allergic reactions in the individual being treated. Tetracycline and doxycycline are antibiotics commonly prescribed by primary care physicians in the treatment of a number of infections. The objective of the following discussion is to review the pharmacology, toxicity, spectrum of activity, clinical application, and cost of these important, and occasionally misused, antimicrobial agents.

**Pharmacology**

**Origin and Structure**

The development of tetracycline antibiotics was the result of a systematic screening of soil specimens collected from many parts of the world for antibiotic-producing organisms. A number of tetracyclines exist, all very much alike in structure and function. Tetracycline and doxycycline are semisynthetically produced from a species of Streptomyces and differ only by the position of a single hydroxy moiety on carbon #5.  

Absorption and Excretion

Tetracycline is absorbed incompletely from the gastrointestinal tract; only 60% is absorbed under optimal conditions. Plasma concentrations of doxycycline, however, essentially are equivalent whether given orally or intravenously because the drug's absorption is nearly complete. The absorption of both drugs is much greater in the fasting state and is impaired substantially by food, milk products, antacids, calcium, and iron preparations. Tetracycline is affected much more by these factors than doxycycline. Both tetracycline and doxycycline should be taken 3 hours before, or 2 hours after, taking iron or antacids, and tetracycline should not be taken with meals. Once in the serum, the half-lives of tetracycline and doxycycline are 6–12 hours and 16–18 hours, respectively. Hence, tetracycline requires four-times-a-day dosing, whereas doxycycline only needs to be taken twice daily.  

The volume of distribution of tetracyclines includes not only that of the extracellular serous fluid but the tears, saliva, cerebrospinal fluid, and amniotic fluid. Concentrations in these secretions and fluids are only 10–25% of those found in the serum, and only doxycycline is known to accumulate in the cerebrospinal fluid. All tetracyclines are concentrated in the liver and excreted by way of the bile into the intestine. Because of the effects of the enterohepatic circulation, the tetracyclines are excreted and resorbed continually and thus may be present in the blood for a long time after cessation of therapy. Tet-
TETRACYCLINE/DOXYCYCLINE

Tetracycline is eliminated primarily through the kidney. Doxycycline, on the other hand, is eliminated almost exclusively in the feces and is, therefore, one of the safest of the antibiotics in the presence of renal failure.

MECHANISM OF ACTION
The site of action of tetracycline and doxycycline is the bacterial ribosome. The drugs bind primarily to 30 S ribosomes and block access of bacterial aminoacyl tRNA to the acceptor sites on mRNA, preventing the addition of amino acids to the growing peptide chain. Resistance is mediated by a plasmid that prevents the intracellular accumulation of tetracyclines. These drugs are primarily bacteriostatic, preventing the organism from reproducing but not killing it outright. Thus, an intact immune system is necessary for eradication of the infection.

Toxicity

REPRODUCTION
Tetracyclines are pregnancy category D, mainly due to their effects on fetal bone and teeth (see below). Tetracyclines may reduce the effectiveness of oral contraceptives; however, this effect has not been confirmed in all investigations.

BREASTFEEDING
Available data suggest that an insignificant amount of tetracycline is excreted into breast milk. In addition, one study showed that the drug that is excreted is bound to calcium, which retards its absorption in the fetus. Review of the literature shows that no cases of tooth staining in breastfed infants subsequent to maternal ingestion of tetracyclines have been well documented. Assays on infants breastfed by mothers using tetracyclines all showed concentrations less than the lower limit of the sensitivity of the assay. Nevertheless, the standard of care presently is that tetracyclines should not be used by breastfeeding mothers because alternative therapies are available and the potential implications are significant.

CALCIFIED TISSUES
Retardation of bone growth and discoloration of teeth may occur in children due to the formation of a tetracycline- or doxycycline-calcium complex. Whereas the effects on bone are reversible with cessation of treatment, the tooth discoloration is permanent. Tetracyclines are impregnated into tooth dentin and will fluoresce a bright yellow when exposed to ultraviolet radiation and later stain a darker yellow or brown. Deciduous tooth calcification occurs from the 14th week in utero to 2–3 months of age. Tetracycline exposure during this time will affect only the deciduous teeth. Permanent tooth calcification takes place between the ages of 4 months and 6 years.

SKIN
Phototoxicity was noted to occur in 40 of 2,682 (1.6%) patients treated with tetracycline and six of 15 (40%) using doxycycline. This photosensitivity was evident only when skin was exposed to sunlight containing rays in the range of 270–320 nm range. This type of radiation is filtered out by ordinary window glass. All photosensitization effects are reversible, and permanent injury to the skin does not occur.

GASTROINTESTINAL
The high antibiotic concentrations reached in the intestine after enteric flora, and stool may become soft, odorless, and yellow-green in color. Epigastric burning, nausea, vomiting, and diarrhea may occur. Several studies cite tetracycline and doxycycline as the cause of reversible esophageal ulcerations, preventable, in part, by taking the medications in a sitting position and with a full glass of water. Alterations in bowel flora may also cause bacterial overgrowth that can be life-threatening (see Superinfections). Overall, doxycycline is less irritating to the gastrointestinal tract than tetracycline.

SUPERINFECTIONS
Like all antimicrobial agents, the tetracyclines may lead to superinfections caused by resistant bacteria or yeasts. The incidence of these infections appears to be much higher with the tetracyclines than with the penicillins. Pseudomembranous enterocolitis may occur with either oral or intravenous administration of tetracycline and doxycycline.

HEPATIC
In general, tetracyclines should be avoided in patients with hepatic disease because of the catabolic or antianabolic effects that may yield a nitrogen load requiring hepatic metabolism. Fine vacuoles, cytoplasmic changes, and increased deposition of fat have been noted to occur in the liver of patients treated with these drugs. Pregnant women are particularly susceptible to severe tetracycline-induced hepatic injury.

NERVOUS SYSTEM
Dizziness, tinnitus, and vertigo have been reported and are completely reversible. Case reports of pseudotumor cerebri have also been associated with tetracycline use.

RENAL
Tetracyclines may aggravate uremia in patients with renal disease because, at higher concentrations, the
Table 1. Clinical Application of Tetracycline and Doxycycline in Obstetrics and Gynecology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causative Organisms</th>
<th>Dose and Duration of Therapy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne (inflammatory type)</td>
<td>Skin flora</td>
<td>TCN 250–500 mg BID for 6–8 wk</td>
<td>Alternatives: topical tretinoin and 10% benzoyl peroxide, erythromycin 250–500 mg BID–TID, or minocycline 100 mg BID</td>
</tr>
<tr>
<td>Actinomycosis</td>
<td><em>Actinomyces israelii</em></td>
<td>DCN 100 mg BID for 2–6 mo</td>
<td>Alternative: penicillin V 500 mg QID</td>
</tr>
<tr>
<td>Cervicitis</td>
<td><em>Chlamydia trachomatis</em>, <em>Neisseria gonorrhoeae</em></td>
<td>DCN 100 mg BID for 7 d</td>
<td>Alternatives: erythromycin 500 mg QID for 7 d, ofloxacin 300 mg BID for 7 d, or azithromycin 1 g in a single oral dose. Ceftriaxone, 125–500 mg IM, or cefixime, 400 mg in a single oral dose, are recommended to eradicate gonorrhea</td>
</tr>
<tr>
<td>Endometritis</td>
<td>Vaginal flora</td>
<td>DCN 100 mg BID for 7 d</td>
<td>Alternatives: amoxicillin/clavulanate 500 mg TID or erythromycin 500 mg QID for 7 d</td>
</tr>
<tr>
<td>Granuloma inguinale (donovanosis)</td>
<td><em>Calymmatobacterium granulomatis</em></td>
<td>DCN 100 mg BID for 3–5 wk</td>
<td>Erythromycin 500 mg QID for 3–5 wk is used in pregnancy. Treatment with TMP-SMZ has been reported to be effective</td>
</tr>
<tr>
<td>Lymphogranuloma venerenum</td>
<td><em>C. trachomatis</em></td>
<td>DCN 100 mg BID for 21 d</td>
<td>Alternative: erythromycin 500 mg QID for 21 d</td>
</tr>
<tr>
<td>Lyme disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td>DCN 100 mg BID for 10–20 d</td>
<td>Alternatives: penicillin V or erythromycin, both 500 mg QID for 10–20 d</td>
</tr>
<tr>
<td>Nongonococcal urethritis</td>
<td><em>Ureaplasma urealyticum</em>, <em>C. trachomatis</em></td>
<td>DCN 100 mg BID for 7 d</td>
<td>Alternatives: see those listed for cervicitis (above)</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td><em>C. trachomatis</em>, <em>N. gonorrhoeae</em>, <em>C. trachomatis</em>, *N.</td>
<td>Outpatient: cefoxitin 2 g IM plus probenecid 1 g po once or ceftriaxone 250 mg IM once, followed by DCN 100 mg po BID or TCN 500 mg po QID for 10–14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>gonorrhoeae</em>, <em>C. trachomatis</em>, <em>N. gonorrhoeae</em>, *C.</td>
<td>Inpatient: cefotetan 2 g IV every 12 h or cefoxitin 2 g IV every 6 h plus DCN 100 mg IV or po every 12 h; DCN should be continued for 10–14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>trachomatis</em>, <em>N. gonorrhoeae</em>, <em>C. trachomatis</em>, *N.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TCN, tetracycline; BID, two times a day; TID, three times a day; DCN, doxycycline; QID, four times a day; IM, intramuscularly; TMP-SMZ, trimethoprim-sulfamethoxazole; po, orally; IV, intravenously.

**ALLERGIC**

Accounts of severe hypersensitive reactions are rare but have been known to occur.6

**HEMATOLOGIC**

Tetracycline can depress plasma prothrombin activity, requiring adjustment of dosing of anticoagulants. It also can cause severe thrombophlebitis when administered intravenously.1

**Spectrum of Activity and Clinical Applications**

The use of tetracyclines in animal feeds and in treatment of infectious diseases through the years has re-
sulted in increasing bacterial resistance to these drugs. Although tetracyclines are considered to have the broadest antibacterial spectrum of any class of antibiotics, many pathogenic organisms such as group-B and group-D streptococci, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, and *Bacteroides fragilis* are resistant to the drug. This resistance, along with the availability of superior antimicrobial agents, has limited the number of indications for the use of tetracyclines. Nevertheless, these agents are still of value in many infectious diseases that are of particular interest to the obstetrician/gynecologist.\(^1\)\(^-\)\(^4\) Table 1 summarizes the clinical application of tetracycline and doxycycline in clinical practice.\(^5\)\(^-\)\(^9\)\(^10\)

### Cost and Dispensing Information

Tetracycline is supplied in 250- and 500-mg capsules and doxycycline in 50- and 100-mg tablets and capsules. A typical 7-day course of generic tetracycline and doxycycline costs approximately $5 and $9, respectively. As a comparison, a 7-day course of generic cephalaxin or erythromycin, 500 mg four times a day, would cost $15 and $9, respectively. If a dose is missed, the patient should immediately take the missed dose and then the next dose as previously scheduled, unless the subsequent dose is due within the next 2 hours. In that case, the missed dose should not be taken to avoid double dosing, which increases the risk of toxic side effects, especially to the gastrointestinal tract.\(^6\)

### Conclusion

When used appropriately, tetracycline and doxycycline continue to be effective antimicrobials in the treatment of a number of infectious diseases. Although the two medications are similar, doxycycline may be taken with food, is better tolerated, and need only be administered twice daily. If these differences improve patient compliance, then it justifies the slightly higher cost of doxycycline and favors its use over tetracycline in most situations.

### References


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