

A0005

S0005 **I. DESCRIPTION**

P0005 Doxycycline (alpha-6-deoxytetracycline) is a second-generation tetracycline with increased oral bioavailability and tissue penetration as a result of its improved lipophilicity compared with earlier tetracyclines. It is a semisynthetic derivative of oxytetracycline and became available in 1967. It is available as both doxycycline monohydrate and doxycycline hyclate (Doryx, Doxy-100, Doxsig, Vibramycin, Zadorin). The molecular formula of doxycycline is $C_{22}H_{24}N_2O_8 \cdot HCl$, $1/2 [C_2H_5OH \cdot H_2O]$; the molecular weight is 512.9 and the chemical structure is shown in Figure 67.1.

P0010 Its mechanism of action is inhibition of microbial protein synthesis through interaction with 30S ribosomal subunits. It is almost universally

administered orally, although also available intravenously, and has a prolonged serum half-life. As with the other tetracyclines, doxycycline has a wide spectrum of activity, but the development of widespread bacterial resistance and development of more bactericidal antibiotics has restricted its major uses to treatment of atypical, often intracellular, bacterial pathogens as well as malaria. Doxycycline is a crucial agent in the therapy of Q fever, brucellosis, melioidosis, atypical pneumonia, leptospirosis, and rickettsial infections. It is also an important agent for prophylaxis of many of the agents of biowarfare, such as anthrax.

S0010 **2. ANTIMICROBIAL ACTIVITY**S0015 **2a. Routine susceptibility**

P0015 Doxycycline has a wide range of activity. A summary of the *in vitro* activity of doxycycline against key clinical pathogens is shown in Table 67.1.

(Gutmann *et al.*, 1983; Dewsnup and Wright, 1984; Brown *et al.*, 1996), minocycline has greater activity against these organisms and against a larger number of *N. farcinica* isolates (Brown *et al.*, 1996). *Bacillus anthracis* is susceptible to doxycycline (Mohammed *et al.*, 2002; Frean *et al.*, 2003).

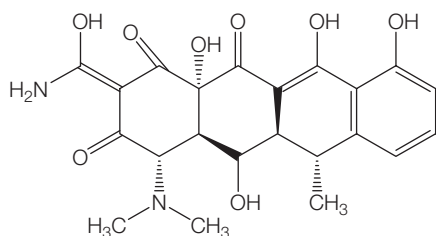
S0020 **Gram-positive bacteria**

P0020 Doxycycline has activity against most Gram-positive bacteria, but other drugs are used in preference for serious Gram-positive infections on account of the bacteriostatic activity of doxycycline. Nevertheless, doxycycline may be of value in treating skin and soft-tissue infections (Cenizal *et al.*, 2007; Ruhe and Menon, 2007) due to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA; Tsuji *et al.*, 2007), but generally the high rate of resistance in *S. aureus* precludes the use of doxycycline. There is increasing resistance to multiple antimicrobials among strains of *Streptococcus pneumoniae*, including tetracyclines. Recent doxycycline resistance rates in *S. pneumoniae* vary geographically between 2% and >15%, such that it is no longer used for severe pneumococcal infections (Zhanel *et al.*, 2003; Koeth *et al.*, 2004a). *In vitro* evidence of synergy between doxycycline and quinupristin-dalfopristin exists for vancomycin-resistant *Enterococcus faecium*, which may be of relevance in treating this highly resistant pathogen (Matsumura *et al.*, 1999; Eliopoulos and Wennersten, 2002). *Listeria monocytogenes* and *Actinomyces israelii* are susceptible (Holmberg *et al.*, 1977; Vitas *et al.*, 2007). Although doxycycline has activity against the *Nocardia asteroides* complex

S0025 **Gram-negative bacteria**

Although tetracyclines are active against Enterobacteriaceae, they are seldom used for severe intra-abdominal or urinary tract infections. *Yersinia pestis* is a notable exception among the Enterobacteriaceae, for which doxycycline is the mainstay of antimicrobial therapy (CDC, 1994; Hernandez *et al.*, 2003). *Yersinia pestis* is more susceptible to doxycycline than to tetracycline (Smith *et al.*, 1995). The broad-spectrum activity against gut organisms makes doxycycline a useful agent for prevention of traveler's diarrhea. Tetracyclines, mostly tetracycline itself, are used for treatment of *Vibrio cholerae*. The halophilic vibrios, *V. parahaemolyticus* and *V. alginolyticus*, which cause food-borne gastroenteritis, are nearly always susceptible to doxycycline (Joseph *et al.*, 1978; Morris *et al.*, 1985; Abbott and Janda, 1994). *Vibrio vulnificus*, which causes septicemia and marine-associated necrotizing skin and soft-tissue infection, is also susceptible (Morris *et al.*, 1985; French *et al.*, 1989; Midani and Rathore, 1994). Doxycycline has useful activity against *Campylobacter jejuni* and *C. fetus*, although in the presence of ciprofloxacin resistance, the frequency of cross-resistance to doxycycline increases significantly (Schonberg-Norio *et al.*, 2006). *Helicobacter cinaedi* and *Aeromonas hydrophila* are doxycycline susceptible (Janda *et al.*, 1994; Burman *et al.*, 1995).

Brucella spp. are still uniformly doxycycline susceptible, with synergy shown for the combination of doxycycline and streptomycin (Baykam *et al.*, 2004; Orhan *et al.*, 2005). *Burkholderia pseudomallei* is susceptible to doxycycline, with low rates of resistance in primary or relapse isolates (Jenney *et al.*, 2001; Thibault *et al.*, 2004; Sivalingam *et al.*, 2006). Where *B. pseudomallei* has persisted despite doxycycline therapy, resistance has developed to this agent (Jenney *et al.*, 2001). *Stenotrophomonas maltophilia* is susceptible to doxycycline (Nicodemmo *et al.*, 2004). Doxycycline is highly active against multiresistant strains of *Acinetobacter baumannii* *in vitro* and also in an *in vitro* model of *A. pneumonia* (Vila *et al.*, 1993; Rodriguez-Hernandez *et al.*, 2000).



F0005 **Figure 67.1** Chemical structure of doxycyclin.

T0005 **Table 67.1** Doxycycline susceptibility data emphasizing organisms for which this antibiotic is an important therapeutic choice. For atypical and intracellular pathogens, susceptibility testing is nonstandardized and involves cell culture and PCR methodologies.

	MIC ₅₀ (mg/l)	MIC ₉₀ (mg/l)	Range (mg/l)	Reference
Gram-positive bacteria				
<i>Staphylococcus aureus</i>	0.25	4	0.03 to >16	Tsuji <i>et al.</i> , 2007
<i>Streptococcus pyogenes</i>	0.12	8		Koeth <i>et al.</i> , 2004b
<i>Streptococcus pneumoniae</i>	0.25	8	0.06–8	Koeth <i>et al.</i> , 2004b
<i>Enterococcus faecalis</i> – vancomycin resistant	16	32	0.12–64	Eliopoulos and Wennersten, 2002
<i>Bacillus anthracis</i>	0.063	0.063	0.031–0.125	Frean <i>et al.</i> , 2003
<i>Listeria monocytogenes</i>	0.25	0.25	0.125–1	Martinez-Martinez <i>et al.</i> , 2001
<i>Nocardia asteroides</i>	2	32	<0.125–32	Gutmann <i>et al.</i> , 1983; Dewsnup and Wright, 1984
<i>Nocardia farcinica</i>	8	16	2–16	Brown <i>et al.</i> , 1996
Gram-negative bacteria				
<i>Escherichia coli</i>	0.5	32	0.5–64	Sweet <i>et al.</i> , 1982
<i>Klebsiella</i> spp.	1.5	64	1–64	Sweet <i>et al.</i> , 1982
<i>Haemophilus influenzae</i>	0.5	1		Koeth <i>et al.</i> , 2004b
<i>Burkholderia pseudomallei</i>	1	1.5	0.125–4	Thibault <i>et al.</i> , 2004; Sivalingam <i>et al.</i> , 2006
<i>Burkholderia mallei</i>	0.5	2	0.125–4	Kenny <i>et al.</i> , 1999
<i>Stenotrophomonas maltophilia</i>	1	2	0.5–4	Nicodemo <i>et al.</i> , 2004
<i>Leptospira interrogans</i>		1.56	0.1–12.5	Murray <i>et al.</i> , 2004
<i>Yersinia pestis</i>	0.5	1	0.125–2	Hernandez <i>et al.</i> , 2003
<i>Neisseria meningitidis</i>	0.5	1	0.12–2	Jorgensen <i>et al.</i> , 2005
<i>Brucella melitensis</i>	0.032	0.064	0.0156–0.094	Baykam <i>et al.</i> , 2004
<i>Mycoplasma pneumoniae</i>	0.12	0.25	0.06–0.25	Bebear <i>et al.</i> , 2000a; Bebear <i>et al.</i> , 2000b
<i>Legionella pneumophila</i>	1	2	0.5–2	Schulin <i>et al.</i> , 1998
<i>Chlamydia pneumoniae</i>	0.12	0.25	0.06–0.50	Roblin and Hammerschlag, 2000; Critchley <i>et al.</i> , 2002
<i>Chlamydia trachomatis</i>	0.125	0.25	0.125–0.25	Roblin and Hammerschlag, 2000; Samra <i>et al.</i> , 2001
<i>Chlamydia psittaci</i>	0.1		0.05–0.2	Butaye <i>et al.</i> , 1997
<i>Rickettsiae</i>			0.06–0.125	Rolain <i>et al.</i> , 1998
<i>Coxiella burnetii</i>			2–4	Boulos <i>et al.</i> , 2004a
<i>Bartonella</i> spp.	0.03	0.12	<0.016–0.12	Dorbecker <i>et al.</i> , 2006
<i>Plasmodium falciparum</i>	1.2–5.4			Pradines <i>et al.</i> , 2000; Menard <i>et al.</i> , 2005; Newton <i>et al.</i> , 2005; Pradines <i>et al.</i> , 2006
<i>Mycobacterium marinum</i>	2	6	0.5–12	Rhombert and Jones, 2002

P0035 Doxycycline displays activity against *Legionella pneumophila* *in vitro*, but this is dependent on inoculum size (Schulin *et al.*, 1998). The anti-*Legionella* activity of doxycycline is confirmed in cellular model systems (Havlicek *et al.*, 1987), but evidence of clinical activity is scarce. Doxycycline therapy reduces mortality in guinea-pigs infected with *L. micdadei* (Pasculle *et al.*, 1985).

P0040 *Bartonella* spp., such as *B. henselae*, *B. bacilliformis* and *B. quintana*, are susceptible to doxycycline (Schwartzman, 1992; Regnery and Tappero, 1995). Their doxycycline MIC is usually ≤ 0.12 $\mu\text{g/ml}$ (Maurin *et al.*, 1995; Dorbecker *et al.*, 2006).

P0045 Gastrointestinal anaerobes, such as the *Bacteroides fragilis* group and *Clostridium* spp., are doxycycline susceptible, although their MIC_{90s} are at the breakpoints for the drug (Schaumann *et al.*, 2000). *Fusobacterium* spp. (Schaumann *et al.*, 2000) and *Prevotella* spp. are also susceptible to doxycycline (Chow *et al.*, 1975; Sutter and Finegold, 1976).

S0030 *Mycoplasma* spp.

P0050 *Mycoplasma pneumoniae* is highly susceptible to doxycycline. *M. hominis* is also usually susceptible, but strains with tetracycline resistance are being encountered in recent years (Bebear *et al.*, 2000a; Bebear *et al.*, 2000b). *Mycoplasma genitalium* is commonly doxycycline resistant (Wikstrom and Jensen, 2006; Bjornelius *et al.*, 2008). Doxycycline-resistant *Ureaplasma urealyticum* have been recognized for some time (Evans and Taylor-Robinson 1978; Magalhães and Veras, 1984); however, they remain susceptible to other antimicrobials, including azithromycin (Bebear *et al.*, 2000a).

Chlamydia spp.

Chlamydia trachomatis is mostly susceptible to doxycycline, but MBCs may be very high for this organism (Samra *et al.*, 2001). It is important to appreciate that susceptibility testing methodologies for *Chlamydia* spp. are not standardized (Wang *et al.*, 2005). *Chlamydia pneumoniae* is also susceptible to the tetracyclines (Roblin and Hammerschlag, 2000; Critchley *et al.*, 2002), as is *C. psittaci* (Khatib *et al.*, 1995; Butaye *et al.*, 1997).

Spirochetes

P0060 Doxycycline is one of the major therapeutic choices for treatment of spirochetal infections, including leptospirosis (Murray *et al.*, 2004) and Lyme disease (Wormser *et al.*, 2000). Tetracycline is active against *Treponema pallidum*, with doxycycline not formally tested, but the tetracycline MIC against *T. pallidum* (0.2 $\mu\text{g/ml}$) is much higher than that of penicillin G (0.0005 $\mu\text{g/ml}$) (Norris and Edmondson, 1988). In rare circumstances, doxycycline is used for the treatment of syphilis.

Rickettsiae and *Coxiella*

P0065 Doxycycline is active against the rickettsiae and is the agent of choice for adult infections due to pathogens such as the spotted fever group (*Rickettsia rickettsii*, *R. conorii*, *R. australis*, and *R. honei*), scrub typhus (*R. tsutsugamushi*), and epidemic typhus (*R. prowazekii*). Doxycycline is not only the most active of the tetracyclines but, in a comparison with other anti-rickettsial antibiotics, it was clearly the most active overall agent with MICs of 0.06–0.25 $\mu\text{g/ml}$ (Raoult *et al.*, 1987; Raoult and Drancourt, 1991). These data come from testing antimicrobial

susceptibility for almost all rickettsiae in cell culture systems (Rolain *et al.*, 1998). Thirteen strains of *Coxiella burnetii* were shown to be susceptible to doxycycline in shell vial cell culture, with no growth detected in any strain in the presence of 4 µg/ml of the antibiotic, which represents the lower range of agreed susceptibility (Raoult *et al.*, 1991). *In vitro* models of chronic *C. burnetii* infection indicate that the organism is less susceptible to doxycycline than in acute infection (Yeaman *et al.*, 1989; Raoult *et al.*, 1991; Maurin and Raoult, 1999). The benefit of adding hydroxychloroquine to enhance the bactericidal activity of doxycycline by alkalinizing the phagolysosome is shown in these cell culture models of chronic *C. burnetii* infection (Maurin *et al.*, 1992b).

S0050 **Bartonella spp.**

P0070 Doxycycline has good activity against *B. henselae*, *B. quintana*, *B. elizabethae*, and *Bart. vinsonii*, with MICs <0.12 µg/ml and complete agreement between agar dilution and E-test methodologies (Dorbecker *et al.*, 2006). Doxycycline is bacteriostatic for *B. quintana*, although MBCs > 4 µg/ml have been shown both in axenic media and in systems utilizing red blood cells (Rolain *et al.*, 2003). By contrast, rifampicin and, to a lesser extent, gentamicin were bactericidal.

S0055 **Mycobacteria spp.**

P0075 Doxycycline is an important agent in the treatment of rapidly growing mycobacteria as it has activity against *Mycobacterium fortuitum*, *M. chelonae*, and *M. abscessus* (De Groot and Huitt, 2006). *Mycobacterium fortuitum* may acquire tetracycline resistance determinants similar to those found in Gram-positive bacteria and become doxycycline resistant (Pang *et al.*, 1994). A high proportion (86.5%) of strains of *M. marinum* were susceptible to doxycycline, with minocycline being even more active (Rhomberg and Jones, 2002). In the era of advancing multi-drug and extensive drug resistance in *M. tuberculosis*, second-line agents need to be investigated for activity. Doxycycline has previously been regarded as having no clinically significant activity against *M. tuberculosis*, but a single recent study suggests it may be worthwhile testing for doxycycline sensitivity as 63/68 Russian MDRTB isolates were doxycycline susceptible (Balabanova *et al.*, 2005). *Mycobacterium kansasii* is resistant to doxycycline (da Silva Telles *et al.*, 2005).

S0060 **Malaria and other parasites**

P0080 The tetracyclines affect the expression of apicoplast genes in *Plasmodium falciparum*, leading to altered function of merozoites and

slow but complete killing of the parasite (Dahl *et al.*, 2006). The *in vitro* activity of doxycycline for *P. falciparum* has been studied in Senegalese isolates (Pradines *et al.*, 2000), in which the geometric mean IC₅₀ was 5.43 µg/ml, and Thai isolates (Newton *et al.*, 2005), in which MIC₅₀ was 4.86 µg/ml. Doxycycline levels above these were found in only a minority of a small sample of Thai patients with severe *P. falciparum*, calling into question the adequacy of current doxycycline dosing recommendations (Newton *et al.*, 2005). No difference in IC₅₀ was shown for chloroquine-susceptible and -resistant isolates, indicating the absence of cross-resistance with other antimalarials (Pradines *et al.*, 2000). Doxycycline breakpoints for *P. falciparum* have not been determined so it is not possible to determine resistance rates. In two endemic African sites with high rates of chloroquine resistance, doxycycline IC₅₀s for *P. falciparum* ranged between 1.2 µg/ml (Menard *et al.*, 2005) and 4.2 µg/ml (Pradines *et al.*, 2006). Synergy between doxycycline and artemisinin can be demonstrated *in vitro* (Spencer *et al.*, 2002).

Doxycycline shows some activity against *Toxoplasma gondii* *in vitro* and in animals *in vivo* (Chang *et al.*, 1990), along with *Giardia lamblia* *in vitro* activity (Edlind, 1989).

2b. Emerging resistance and cross-resistance

Doxycycline resistance is becoming more common in *S. pneumoniae*, particularly in isolates with reduced penicillin susceptibility. Although the overall frequency of doxycycline resistance in *S. pneumoniae* in 2004 was 24%, rates of up to 63% doxycycline resistance were seen in penicillin-resistant isolates in Spain and Australia (Koeth *et al.*, 2004b). This same international study identified a high rate (15%) of doxycycline resistance in *S. pyogenes*.

Tetracycline resistance is widespread in many aerobic and anaerobic Gram-negative species. Mobile genetic elements encode resistance mechanisms, commonly conferring multiresistance to tetracyclines and other chemotherapeutic agents. No doxycycline resistance has been found in *Chlamydia* or *Rickettsia* species, although susceptibility testing is not standardized for these obligate intracellular pathogens (Wang *et al.*, 2005). The potential for development of *Chlamydia* resistance is shown by the discovery of tetracycline-resistant *C. suis* in pigs (Lenart *et al.*, 2001). This organism is sufficiently similar to *C. trachomatis* that inclusion bodies of both species can be experimentally induced to occupy the same intracellular vacuole, a situation that could lead to doxycycline resistance in *C. trachomatis* (Roberts, 2003). A more extensive discussion can be found in Chapter 66, Tetracycline.

S0070 3. MECHANISM OF DRUG ACTION

P0100 Tetracyclines, including doxycycline, inhibit bacterial protein synthesis through reversible binding to the ribosomal complex, preventing the association of aminoacyl-tRNA with the bacterial ribosome and interfering with protein synthesis. Access to Gram-negative bacterial ribosomal binding targets on the 30S subunit is through porins and via an energy-dependent process. Additional inhibition of protein synthesis occurs in mitochondria through binding to the 70S

ribosomes. Although some doxycycline-susceptible parasites have mitochondria that are inhibited by this drug, these are not the only parasitic target. Apicoplast ribosomal subunits in *P. falciparum* appear to be inhibited by doxycycline (Dahl *et al.*, 2006). This process occurs late in the malarial cell cycle, explaining the slow antimalarial effect of doxycycline (Batty *et al.*, 2007). The apicoplast houses enzymes involved in fatty acid synthesis and heme biosynthesis pathways.

S0075 4. MODE OF DRUG ADMINISTRATION AND DOSAGE

S0080 4a. Adults

P0105 Doxycycline is almost always administered orally and only in rare situations, such as rickettsial infection, ehrlichiosis, or severe psittacosis, is intravenous use required. The usual adult dosage is

100 mg 12-hourly; it should be taken with at least 100 ml water (see below). The adult dosage of doxycycline for malaria chemoprophylaxis is 100 mg orally daily.

An i.v. preparation of doxycycline is available. The adult dosage is 200 mg initially, followed by 100 mg every 12 hours. Each dose should

be dissolved in 500 or 1000 ml of glucose–saline fluid for slow i.v. infusion over a period of 0.5–1.0 hours.

S0085 4b. Newborn infants and children

P0115 Doxycycline may need to be given to children, particularly for rickettsial, *Y. pestis*, Ehrlichia or *B. pseudomallei* infection, in whom the benefits of its use outweigh side-effects such as staining of teeth (Shetty, 2002; see below under 6. Toxicity). The pediatric dosage is 2.2 mg/kg bd.

S0090 4c. Altered dosages

S0095 Renal impairment

P0120 Doxycycline is safe in patients with renal impairment (Whelton *et al.*, 1974). Unlike other tetracyclines, its use is not associated with deteriorating renal function in patients with renal disease (Little and Bailey, 1970; George and Evans, 1971; Alestig, 1973; Stenbaek *et al.*, 1973; Mahony and Lloyd-Jones, 1975). Its half-life is mildly increased but its C_{max} is unchanged. Although there is reduced urinary excretion in renal impairment, it does not accumulate in the serum because its

gastrointestinal elimination is increased (Heaney and Eknoyan, 1978). Another factor that mitigates against doxycycline accumulation in renal impairment is reduced protein binding (Houin *et al.*, 1983). Negligible amounts of doxycycline (~10%) have been shown to be removed by hemodialysis (Whelton *et al.*, 1974).

Impaired hepatic function

There are no data on the pharmacokinetics of doxycycline in hepatic failure. In contrast to minocycline and tetracycline, doxycycline does not cause hepatitis (Thiim and Friedman, 2003). Although tetracyclines are excreted in the bile, this is not a major pathway for their excretion, and patients with pre-existing liver damage do not appear to be more prone to the toxic effects of tetracyclines (Alestig, 1974).

The elderly

Doxycycline pharmacokinetics have been studied in the elderly – a longer half-life, greater AUC, and smaller volume of distribution have been shown in a group of patients with a mean age of 76 years (Bocker *et al.*, 1986).

S0110 5. PHARMACOKINETICS AND PHARMACODYNAMICS

S0115 5a. Bioavailability

P0135 Doxycycline is almost completely absorbed in the duodenum after oral administration, and it has a prolonged serum half-life (12–16 hours). Eighty-two percent to 93% of doxycycline is protein bound (Agwuh and MacGowan, 2006). Co-administration with food has minimal impact on doxycycline levels – these being reduced by only 20%. All tetracyclines form complexes with metal ions in food, but doxycycline complexes are unstable in the acid contents of the stomach, so that the drug enters the duodenum in a free state, where it is absorbed. However, metal complexes formed in the alkaline contents of the small bowel, into which doxycycline diffuses as part of its mode of excretion, are stable and are not absorbed. The net effect is that the total absorption of doxycycline is partially impaired by the presence of multivalent cations, such as ferrous sulphate (Neuvonen *et al.*, 1970), and by subsalicylate bismuth given simultaneously or 2 hours before doxycycline (Ericsson *et al.*, 1982). Iron reduces the AUC_{0-24} by 10% (Newton *et al.*, 2005).

P0140 The bioavailability of doxycycline is not reduced by proton pump inhibitors or H₂ blockers but serum levels are lowered and bioavailability reduced by 85% if the drug is taken together with aluminum magnesium hydroxide (Maalox) (Deppermann *et al.*, 1989). Aluminum hydroxide taken orally also lowers the serum levels after i.v. doxycycline administration. This interaction may be due in part to an interference of aluminum ions with the enteric reabsorption of doxycycline (Nguyen *et al.*, 1989). Co-administration of doxycycline and cytochrome P450 3A4 inducers, including phenytoin, carbamazepine and rifampicin, reduce serum doxycycline levels presumably because of increased hepatic metabolism of the drug (Colmenero *et al.*, 1994) (see below under 5e. Drug interactions).

5b. Drug distribution

The key pharmacokinetic features of doxycycline are summarized in Table 67.2. After oral administration, the peak serum level is usually attained 2–3 hours later. After a 200 mg oral dose of doxycycline, peak serum levels of 5.0–5.4 µg/ml at 3–4 hours were found in fasted subjects, with subsequent levels of 2.9–4.0 and 1.3–2.2 µg/ml after 8 and 24 hours, respectively (Welling *et al.* 1977). There are few data on dose linearity with regards to doxycycline. When a single oral dose of 500 mg doxycycline was administered after food, a mean peak serum level of 15.29 µg/ml was obtained at 4 hours, and this fell to levels of 6.60, 3.42, 1.24, and 1.0 µg/ml after 24, 48, 72, and 96 hours, respectively (Adadevoh *et al.*, 1976). After a 200 mg i.v. infusion of doxycycline, a peak serum level of 5–10 µg/ml is usually attained (Alestig, 1973), which falls slowly and levels, ranging between 1–2 µg/ml persisting for 24 hours (Klastersky *et al.*, 1972). After a 100 mg single oral dose the AUC is 37–40 mg h/l (Malmberg, 1984), and after a 200 mg single dose, 90 ± 16 mg h/l (Welling *et al.*, 1977).

Doxycycline is more highly lipid soluble than earlier tetracyclines, and thus it has better tissue penetration. In dogs, lipophilicity of the tetracyclines has been correlated with many of their transport characteristics; it facilitates their transport across lipid-rich cell membranes and, therefore, doxycycline penetrates more readily than tetracycline into the brain, eyes and intestinal epithelium. Doxycycline also penetrates more readily into bacterial cells (Nikaido and Thanassi, 1993).

Interstitial fluid concentrations of doxycycline are 54% of serum levels, as shown by a blister fluid model study in healthy volunteers (Schreiner and Digranes, 1985). Doxycycline is concentrated in the bile with levels 10–25 times that in serum (Alestig, 1973). Doxycycline

T0010 **Table 67.2** Summary of doxycycline pharmacokinetics after a 200-mg dose.

C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)	AUC (µg/ml/h)	Comments	Reference
5.2 ± 1.5	2.7 ± 0.8	13 ± 5	90 ± 16		Welling <i>et al.</i> , 1977
9.3	–	14	112	i.v. dose	Heaney and Eknoyan, 1978
3.17 (1.63–7.72)	2 (1.5–4)	10.5 (6.9–17.9)	32 (18.7–79.7)	Acute phase <i>P. falciparum</i>	Newton <i>et al.</i> , 2005
4.44 (1.52–8.64)	3 (1.5–8)	11.6 (8.5–17.2)	48.6 (18.3–69.8)	Convalescence <i>P. falciparum</i>	

concentrations in thoracic duct lymph and peritoneal fluid are maintained at about 75% of simultaneous serum levels (Andersson *et al.*, 1976), and those in colonic tissue and particularly ileal tissue are equivalent to or exceed serum levels (Höjer and Wetterfors, 1976). Prostatic concentrations are up to 60% of serum levels (Eliasson and Malmberg, 1976; Oosterlinck *et al.*, 1976). Pleural fluid penetration was determined after 200 mg i.v. doxycycline was given to patients with pleurisy, with levels up to 25% of serum detected at 2 hours (Lode, 1979). Salivary concentration of doxycycline is poor, and, after an oral dose of 600 mg doxycycline, peak salivary concentrations occurred at 8 hours and were only 8% of the mean serum level at the time (Marlin and Cheng, 1979). After oral doses of 100 mg daily, mean salivary levels were 0.1–0.5 µg/ml (Heimdahl and Nord, 1983), and such concentrations were unaffected by parotitis (Eneroth *et al.*, 1978). Penetration into sputum is poor, having been shown to be 8–28% over multiple time-points (Marlin *et al.*, 1981). Low concentrations of doxycycline are achieved in bone (Dornbusch, 1976), skin, subcutaneous fat, and tendon tissue, but levels in muscle are higher (Gnarpe *et al.*, 1976).

P0160 Therapeutic concentrations of doxycycline may occur in the aqueous humor, but cerebrospinal fluid (CSF) concentrations do not exceed 1 µg/ml in subjects with noninflamed meninges (Andersson and Alestig, 1976). Effective concentrations of doxycycline may be achieved in the CSF, as the range of CSF penetration in patients with central nervous system (CNS) disease is broad. In patients with Lyme disease treated with doxycycline 200 mg orally 12-hourly, CSF penetration 2–3 hours after a dose was 15% with a concentration of 1.1 µg/ml. With a doxycycline dose of 100 mg 12-hourly, the CSF concentration at that time was only 0.6 µg/ml (Dotevall and Hagberg, 1989). Yim *et al.* (1985) detected a mean CSF doxycycline level of 1.3 µg/ml (range 0.8–2.0) in five patients with latent or neurosyphilis receiving 200 mg twice daily for 7 days.

P0165 Doxycycline penetrates well into breast milk (Chow and Jewesson, 1985), with levels of up to 40% of plasma (British Columbia's Children's and Women's Pharmacy, 2003). As it is less bound to calcium than other tetracyclines, there is the potential for toxicity in the breast-fed infant.

S0125 5c. Clinically important pharmacokinetic and pharmacodynamic features

P0170 The pharmacodynamics of doxycycline are poorly studied, but the available data indicate that there is concentration-dependent killing of *S. aureus*, *S. pneumoniae*, and *Escherichia coli* (Cunha *et al.*, 2000). Doxycycline has a postantibiotic effect for these same bacteria (Cunha *et al.*, 2000). There are no AUC/MIC static effect targets published currently to aid in determining clinical breakpoints. Breakpoints, if available, are therefore largely determined by epidemiologic MIC distributions and clinical experience (Sader *et al.*, 2007; EUCAST, 2008).

S0130 5d. Excretion

P0175 Renal excretion of doxycycline occurs solely by glomerular filtration. Urinary excretion accounts for 30–65% of an orally administered dose of doxycycline (Steigbigel *et al.*, 1968; Alestig, 1973; Alestig 1974; Mahon *et al.*, 1976). In renal impairment this is reduced, but increased fecal excretion prevents accumulation of the drug.

P0180 High concentrations of doxycycline, up to 14 µg/ml, are attained in bile, but this route of elimination normally accounts for only a small percentage of an administered dose (Mahon *et al.*, 1970; Alestig, 1974). A large proportion of doxycycline excreted in bile is reabsorbed from the intestine.

With doxycycline, that part of an administered dose which is not excreted in the urine is excreted in the feces. Doxycycline diffuses from blood across the small bowel wall into the lumen, where cationic chelation occurs, preventing absorption (Whelton *et al.*, 1974). The contents of the small bowel, being constantly added to from the stomach and other secretions, easily cope with the binding of successive amounts of doxycycline. Biliary excretion contributes only a small amount to the fecal excretion of doxycycline. In the presence of renal impairment, increased amounts of doxycycline are excreted in the feces, thereby preventing accumulation of the drug in the serum (Alestig, 1974; Whelton *et al.*, 1974; Mahon *et al.*, 1976). For instance, Whelton *et al.* (1974) found that 77% of an orally administered dose given to end-stage renal failure patients was excreted in the feces.

Doxycycline is not substantially metabolized or inactivated by enzymatic means *in vivo*, with no human biometabolites identified. However, concomitant administration of barbiturates, phenytoin or carbamazepine (Penttilä *et al.*, 1974) and rifampicin (Colmenero *et al.*, 1994) shorten the serum half-life of doxycycline, suggesting that these drugs increase the metabolism of doxycycline potentially through liver metabolism. It is also possible that these drugs interfere with the protein binding of doxycycline, thereby encouraging its excretion.

5e. Drug interactions

Doxycycline is a substrate of CYP3A4 enzymes and a moderate inhibitor of the same cytochrome P450 drug-metabolizing system. Therefore, its levels may be decreased by CYP3A4 inducers. Phenytoin, carbamazepine (Penttilä *et al.*, 1974) and barbiturates apparently induce the metabolism of and reduce the serum concentration of doxycycline (Neuvonen and Penttilä, 1974). Other drugs that can reduce doxycycline levels by this mechanism include nafcillin, nevirapine, and rifampicin. Cholestyramine binds doxycycline. Doxycycline has been shown to increase methotrexate levels in one patient, precipitating neutropenia and gut toxicity (Tortajada-Ituren *et al.*, 1999). In patients treated for acne with both doxycycline and retinoic acid derivatives, the risk of benign intracranial hypertension is increased. Failure of the oral contraceptive pill (OCP) and increased risk of pregnancy has been suggested to be a consequence of doxycycline therapy. A pharmacokinetic study of women showed no reduction in serum ethinyl estradiol levels with concomitant doxycycline use. Furthermore, no progesterone rise was found, showing that breakthrough ovulation did not occur (Neely *et al.*, 1991). Reported failure of the OCP while taking doxycycline may be due to antibiotic-associated diarrhea or reduced compliance consequent on nausea and vomiting, all of which may reduce serum ethinyl estradiol levels.

An observation suggesting clinically relevant antagonism between penicillin and an early tetracycline, aureomycin arose from analysis of the outcome of pneumococcal meningitis patients. The 79% mortality seen in patients treated with the penicillin–tetracycline combination was significantly higher than in patients treated with penicillin monotherapy. More patients had adverse prognostic features in the penicillin group, and, although the study involved only 57 patients, it was adequately powered to provide a statistically valid result (Lepper and Dowling, 1951). Doxycycline has more recently been shown experimentally to have synergistic or additive effect with beta-lactams on clinical *Stenotrophomonas maltophilia* isolates (San Gabriel *et al.*, 2004) and *C. trachomatis* (How *et al.*, 1985). On balance, the concerns of antagonism between penicillin and tetracyclines, raised in 1951, have not been borne out by subsequent *in vitro* data and clinical experience.

S0140 **6. TOXICITY**S0145 **6a. Gastrointestinal side-effects**

P0205 Among reported doxycycline adverse effects, gastrointestinal side-effects were most common (Smith and Leyden, 2005). Doxycycline is prominent among the causes of pill esophagitis and may even cause esophageal rupture (Smith and Leyden, 2005). Along with tetracycline and clindamycin, doxycycline accounts for half of all pill-associated esophagitis. Doxycycline typically induces mid-esophageal ulceration at the site of anatomical extrinsic compression by the left atrium and aortic arch (Kadayifci *et al.*, 2004). It is postulated that the drug either lodges in the esophagus or is refluxed from the stomach, and the high acidity of doxycycline in solution causes esophageal ulceration. Patients are required to take doxycycline with ample water (at least 100 ml of water) while standing and well before going to bed (Hey *et al.*, 1982). It is also recommended that doxycycline should not be given to patients with esophageal obstruction or compression. Doxycycline may cause pseudomembranous colitis (Gorbach and Bartlett, 1974) but its use was associated with a reduced risk of *Clostridium difficile*, associated diarrhea in comparison with other agents such as imipenem and clindamycin (Baxter *et al.*, 2008).

S0150 **6b. Photosensitivity**

P0210 Photosensitivity is second to esophageal irritation as the most common of doxycycline side-effects. The photosusceptible rash due to doxycycline consists of erythema in sun-exposed areas, which, if severe, may be associated with edema, papules, vesiculation, and onycholysis (Bethell, 1977; Glette and Sandberg, 1986). Doxycycline is one of the strongest photosensitizing drugs. This reaction is due to UVB light's action on lumidoxycycline (Shea *et al.*, 1993). Photo-onycholysis (separation of the nails due to sunlight) due to tetracyclines may rarely occur without an associated skin rash (Lasser and Steiner, 1978; Rabar *et al.*, 2004).

S0155 **6c. Teeth and other tissue pigmentation and effect on bones**

P0215 Doxycycline has a lower potential for staining of teeth and bone than other tetracyclines with greater avidity for calcium. Teeth staining is due to the formation of tetracycline-calcium orthophosphate complexes that darken on exposure to sunlight. Awareness of this complication in nonpermanent dentition is the major reason that tetracyclines are infrequently prescribed to children. Discoloration of permanent adult dentition following doxycycline may occur, especially in the presence of poor dental hygiene and with marked sunlight exposure (Ayaslioglu *et al.*, 2005).

P0220 Black pigmentation of the thyroid has been observed at thyroidectomy in one patient who had been taking doxycycline for a short time preoperatively (Miller *et al.*, 2006). This is more commonly observed with minocycline (see Chapter 68, Minocycline).

S0160 **6d. Teratogenicity**

P0225 Doxycycline readily crosses the placenta. In a large survey of 18,515 pregnancies, doxycycline was associated with a small increase in major fetal abnormalities (OR 1.6, 95% confidence interval 1.1–2.3) (Czeizel and Rockenbauer, 1997). There was no significant increase in fetal abnormalities if doxycycline was taken during organogenesis (Czeizel and Rockenbauer, 1997). Another study of 1795 doxycycline-exposed pregnancies concluded that there was no increase in the risk of fetal malformations (Rosa, 2002). Animal studies involving mice, monkeys, and rabbits have shown no teratogenic effects of doxycycline (Nahum *et al.*, 2006). On balance, although doxycycline is regarded as

nonteratogenic, it is categorized D and its use in pregnancy is restricted. This is based on the potential for dental staining (Nahum *et al.*, 2006).

6e. Hypersensitivity reactions

These are uncommon, and usually take the form of urticaria, asthma, or facial edema. Rare cases of acute anaphylaxis have occurred due to tetracyclines other than doxycycline (Fellner and Baer, 1965; Furey and Tan, 1969). Two cases of Stevens–Johnson syndrome due to doxycycline have been reported in the English medical literature (Cac *et al.*, 2007). The Jarisch–Herxheimer reaction may occur when doxycycline is used to treat spirochetal infections, such as leptospirosis and *Borrelia recurrentis* (see Chapter 1, Benzylpenicillin (Penicillin G)).

6f. Idiopathic intracranial hypertension

This uncommon complication, also known as benign intracranial hypertension, is due to doxycycline's interference with cyclic adenosine monophosphate metabolism at the arachnoid granules. Doxycycline-induced intracranial hypertension occurs at any age with no sex predilection or association with obesity, unlike the nondrug-induced idiopathic intracranial hypertension that occurs in obese women. Symptoms of raised intracranial pressure may become apparent from between 2 weeks and one year of doxycycline's commencement (Chiu *et al.*, 1998). Management consists of cessation of doxycycline and institution of medical therapy with acetazolamide or other diuretics if intracranial hypertension is persistent. Visual loss may result from this condition so optic nerve fenestration or CSF shunting may be required (Digre, 2003).

6g. Effects on immune response

In various experimental systems, doxycycline can be shown to alter different arms of the immune system. Doxycycline can depress leukocyte migration (Forsgren and Schmeling, 1977; Belsheim *et al.*, 1979), but suprapharmacologic concentrations of the drug are usually necessary to achieve this (Bäck and Norberg, 1984; Glette *et al.*, 1984). With high concentrations of doxycycline, chemiluminescence and glucose oxidation of polymorphs are also impaired. These *in vitro* effects on polymorph functions are due to doxycycline's divalent cation chelating effect (Glette *et al.*, 1984). The ability of human leukocytes to phagocytose yeasts and bacteria is decreased by doxycycline; this effect may be related to altered surface morphology of polymorphs incubated with tetracyclines (Forsgren and Gnarp, 1982). Doxycycline can suppress phytohemagglutinin-induced lymphocyte transformation *in vitro* (Hauser and Remington, 1982) at the top of or just above the pharmacologic range (Potts *et al.*, 1983). Proinflammatory cytokine release is decreased by tetracycline in lipopolysaccharide-challenged mice, protecting against shock in that experimental model (Shapira *et al.*, 1996). Doxycycline has been shown to have variable effects on different vaccines in experimental mice (Woo *et al.*, 1999). Although some of these effects could potentially be deleterious in immunosuppressed patients, this has not been clinically apparent to date. Conversely, beneficial immunomodulatory effects are being explored in novel applications that rely on these diverse effects of doxycycline.

6h. Hepatotoxicity

There is no evidence that doxycycline causes the severe hepatitis associated with tetracycline and minocycline usage (see Chapter 66, Tetracycline and Chapter 68, Minocycline).

S0185 **7. CLINICAL USES OF THE DRUG**

P0250 With the increase in resistance to the tetracycline class of antibiotics, their previous wide-scale use for respiratory, gastrointestinal, and genitourinary tract infections has been curtailed. Rather, doxycycline is now used for a select group of indications where its specific mode of action is necessary to treat atypical pathogens. Table 67.3 summarizes the current key clinical uses of doxycycline. This section will concentrate on these specific indications.

S0190 **7a. Respiratory tract infections**

P0255 Doxycycline in combination with a beta-lactam antibiotic is an alternative listed in some treatment guidelines for empirical treatment of mild community-acquired pneumonia (CAP) to cover atypical respiratory pathogens including *C. pneumoniae*, *M. pneumoniae*, *C. psittaci*, and *Legionella pneumophila* (Niederman *et al.*, 2001). Owing to the high rate of tetracycline resistance among *S. pneumoniae* and *Haemophilus influenzae*, doxycycline is not used as monotherapy for CAP in most countries.

P0260 Doxycycline, along with macrolides and quinolones, is concentrated within alveolar macrophages, potentiating its anti-*Legionella* activity (Cunha, 1991). Use of a loading regimen of high-dose doxycycline (200 mg bid for 72 hours before reverting to 100 mg bid) has been suggested for moderate to severe legionellosis (Klein and Cunha, 1998; Cunha, 2006). Azithromycin or respiratory quinolones are now widely used for *Legionella* treatment because of their superior *in-vitro* activity and long intracellular half-lives. Nonetheless, a combination of penicillin and doxycycline (100 mg bid) is still considered appropriate therapy for inpatient treatment of moderately severe community acquired pneumonia with empiric anti-*Legionella* cover. Doxycycline is as effective as erythromycin in the treatment of *M. pneumoniae* pneumonia (Shames *et al.*, 1970). Persistent symptoms of bronchitis

may occur in some patients associated with positive cultures for *C. pneumoniae* for several months, despite an adequate course of doxycycline for the acute illness (Hammerschlag *et al.*, 1992). Doxycycline is the most effective drug against psittacosis caused by *C. psittaci* (Jawetz, 1969; Yung and Grayson, 1988) and may need to be given i.v. in some cases (Khatib *et al.*, 1995). Atypical pneumonia due to *C. burnetii* is responsive to doxycycline (see below under 7j. Q fever (*Coxiella burnetii*)). Strain differences in *C. burnetii* are such that, although the most common presentation of acute Q fever in some countries including Canada and Spain is atypical pneumonia, in others such as France and Australia this organism does not frequently cause pneumonia (Marrie, 2004).

Doxycycline, along with erythromycin and co-trimoxazole, has been shown to be of benefit in treating acute bronchitis in otherwise well adults. However, the benefits of treatment, including a reduction in cough and sputum production of half a day, are inconsequential and generally do not warrant antibiotic therapy (Bent *et al.*, 1999).

7b. Gastrointestinal tract infections

Cholera

Most experience and data relating to antimicrobial therapy for cholera pertain to tetracycline (see Chapter 66, Tetracycline), but doxycycline may also be used to treat this condition. A single oral dose of doxycycline (300 mg for adults) is nearly as effective as 0.5 g tetracycline given every 6 hours for 2 days for the treatment of cholera (De *et al.*, 1976). If a daily oral dose of doxycycline is given for 4 days, then the results of treatment are as effective as those obtained by tetracycline given 6-hourly for 4 days, the only difference being that feces are cleared of vibrios within 3 days with doxycycline, compared with 2 days with tetracycline (Rahaman *et al.*, 1976).

T0015 **Table 67.3** Major clinical uses and outcome data for doxycycline.

Indication	Outcomes	Reference
Randomized controlled trials		
Non-gonococcal urethritis	Doxy ^a for 1 week equivalent to one dose azithromycin, cure <i>C. trachomatis</i> 97% versus 98%	
Pelvic inflammatory disease	Doxy plus one shot i.m. cefoxitin equivalent to inpatient doxy plus cefoxitin	Lau and Qureshi, 2002
Brucellosis	Doxy-gentamicin equivalent to doxy-streptomycin	Ness <i>et al.</i> , 2002
Lyme disease	Prevention; 200 mg doxy effective prevention after <i>Ixodes</i> tick bite	Hasanjani Roushan <i>et al.</i> , 2006
Leptospirosis	Doxy equivalent to penicillin G and cefotaxime for severe leptospirosis	Nadelman <i>et al.</i> , 2001
Q-fever endocarditis	Doxy-hydroxychloroquine superior to doxy-ofloxacin with reduced relapse	Suputtamongkol <i>et al.</i> , 2004
Malaria prophylaxis	Protective efficacy 93–100% for <i>P. falciparum</i> Equivalent protective efficacy to mefloquine Protective efficacy 99–100% for <i>P. vivax</i>	Raoult <i>et al.</i> , 1999 Andersen <i>et al.</i> , 1998; Sonmez <i>et al.</i> , 2005 Ohrt <i>et al.</i> , 1997; Sonmez <i>et al.</i> , 2005
Rickettsia	Mediterranean spotted fever (MSF); 2 days doxy equivalent to 2 days ciprofloxacin	Ohrt <i>et al.</i> , 1997; Taylor <i>et al.</i> , 1999
Onchocerciasis (Wolbachia)	Mild scrub typhus; 1 week doxy equivalent to one dose azithromycin	Gudiol <i>et al.</i> , 1989
Melioidosis	6 weeks of doxy 100 mg interrupts <i>O. volvulus</i> embryogenesis for 18 months Doxy combined with chloramphenicol and cotrimoxazole used for 20 weeks continuation treatment	Kim <i>et al.</i> , 2004 Hoerauf <i>et al.</i> , 2001; Hoerauf <i>et al.</i> , 2003b
Plague	Doxy equivalent to gentamicin (and streptomycin historical controls)	Rajchanuvong <i>et al.</i> , 1995
<i>Bartonella quintana</i>	Doxy-gentamicin reduces the risk of relapsed bacteremia compared with placebo	Foucault <i>et al.</i> , 2003; Mwengee <i>et al.</i> , 2006
Recommended therapy		
Community-acquired pneumonia	In combination with beta-lactam for mild to moderate CAP	Niederman <i>et al.</i> , 2001
Lyme disease		Wormser <i>et al.</i> , 2000
Ehrlichiosis		Dumler <i>et al.</i> , 2007
Rickettsia	5–15 days for infections other than mild epidemic typhus, MSF, and scrub typhus	
Cholera		Raoult and Drancourt, 1991
Prophylaxis biowarfare exposure	Active against <i>B. anthracis</i> , <i>B. melitensis</i> , <i>Y. pestis</i> , <i>F. tularensis</i> , <i>B. pseudomallei</i>	
Water-associated cellulitis	Active against marine vibrios, <i>A. hydrophila</i>	
Lymphogranuloma venereum		
Syphilis	Use only in patients with major hypersensitivity to penicillin	

^aDoxy: doxycycline.

S0205 **Traveler's diarrhea**

P0275 In one controlled trial, a 100 mg daily dose of doxycycline given for 3 weeks was effective in reducing the frequency of traveler's diarrhea among Peace Corp volunteers in Kenya (Sack *et al.*, 1978). At the time of this trial, the enterotoxigenic strains of *E. coli* (ETEC) in the area were nearly all susceptible to the drug. Subsequently, doxycycline resistance in ETEC has become widespread throughout the developing world, reducing, but not abolishing, its prophylactic efficacy (Ericsson, 2003). This is illustrated by other trials in areas where doxycycline-resistant ETEC were common, showing that doxycycline remained beneficial including in reducing the severity of traveler's diarrhea because of its action on other organisms (Echeverria *et al.*, 1984; Sack *et al.*, 1984).

S0210 **7c. Sexually transmitted infections and pelvic inflammatory disease**S0215 **Nongonococcal urethritis**

P0280 *Chlamydia trachomatis* is a common cause of infections involving the lower and upper genital tract. Doxycycline is a mainstay of treatment for these infections, often in combination with antibiotics that are effective against other bacteria found in these polymicrobial conditions. Uncomplicated genital *Chlamydia* infection is the most commonly notified infection in many developed countries (e.g. the USA, Australia) (McNabb *et al.*, 2007). Doxycycline 100 mg bid for 7 days is recommended for treatment of uncomplicated genital *Chlamydia* infection in nonpregnant patients, with azithromycin 1 g as a single dose as an alternative. Doxycycline and azithromycin are equally effective for this condition, with microbial cure rates of 97% and 98%, respectively (Lau and Qureshi, 2002). Doxycycline is cheaper, but compliance is inferior to that seen with azithromycin. Even so, where partial compliance with doxycycline has been documented, high cure rates have still been found (Bachmann *et al.*, 1999). Sexual partners should be treated to prevent reinfection of the index case and infection of other partners.

P0285 *Ureaplasma urealyticum* is another major cause of this disease. The activity of doxycycline against *U. urealyticum* has been shown to be less consistent than for *C. trachomatis* because resistant strains of *U. urealyticum* are increasingly common (Oriel and Ridgway, 1983). *Ureaplasma*, like *Chlamydia* spp., have been implicated in an expanding list of infections, including chorioamnionitis, infant pneumonia (Stagno *et al.*, 1981), septicemia and pelvic infection in women (Plummer *et al.*, 1987), septic arthritis in patients with hypogammaglobulinemia (Forgacs *et al.*, 1993), and chronic prostatitis (Brunner *et al.*, 1983).

P0290 *Mycoplasma genitalium* is a common cause of nongonococcal urethritis, particularly in men, but it is poorly responsive to doxycycline with low clearance rates (Wikstrom and Jensen, 2006; Bjornelius *et al.*, 2008). Azithromycin is superior to doxycycline for *M. genitalium* therapy (Bjornelius *et al.*, 2008). *Mycoplasma hominis* is also a cause of urogenital infection (Schlicht *et al.*, 2004) and can additionally cause septic arthritis (Luttrell *et al.*, 1994), neonatal CNS infections, salpingitis, postpartum fever, septicemia (Bøe *et al.*, 1983; Plummer *et al.*, 1987), and postoperative wound infections (Sielaff *et al.*, 1996) – all of which are responsive to therapy with doxycycline.

S0220 **Pelvic inflammatory disease**

P0295 pelvic inflammatory disease (PID), a polymicrobial infection commonly contributed to by *C. trachomatis*, is extremely common. Doxycycline is combined with broad-spectrum antimicrobials in a number of the recommended treatments for this condition.

P0300 There is considerable debate as to the necessity for parenteral therapy in patients with severe PID, such as those with tubo-ovarian abscesses. A randomized controlled trial has shown that, in mild to

moderate PID, a single i.m. dose of cefoxitin along with one oral dose of probenidic combined with doxycycline 100 mg bid for 14 days was equivalent to a minimum of 2 days i.v. cefoxitin combined with 14 days of oral doxycycline (Ness *et al.*, 2002). However, these study groups contained few patients with tubo-ovarian abscess on which to base conclusions of efficacy of oral therapy for this most severe end of the PID spectrum. Long-term outcomes from this study show that there were no differences in pregnancy rates or recurrence of PID between these two regimens (Ness *et al.*, 2002). A concern as to whether only a minority of patients studied truly had PID is addressed in a substudy of microbiologically proven cases, which also shows equivalence in these outcomes (Haggerty *et al.*, 2003).

Intravenous cefotetan or, more commonly, cefoxitin in combination with oral doxycycline is one recommended parenteral regimen for severe PID with tubo-ovarian abscess (Walker and Wiesenfeld, 2007). Alternatively, doxycycline may be combined with ampicillin–sulbactam. Other recommended regimens are clindamycin and gentamicin or ofloxacin–levofloxacin (Walker and Wiesenfeld, 2007).

Lymphogranuloma venereum

lymphogranuloma venereum (LGV) is a sexually transmitted infection that causes inguinal lymphadenopathy and proctitis with late sinus and scar formation at both sites in untreated disease. This is caused by *C. trachomatis* serovars L1, L2, and L3 and responds to treatment with the tetracyclines (Greaves *et al.*, 1957). Prolonged treatment is required because of the invasive nature of the disease. The recommended treatment for LGV is doxycycline 100 mg twice daily, given for 3 weeks. The only recommended alternative regimen for pregnant patients or patients intolerant of doxycycline is erythromycin (Workowski and Berman, 2006). Although azithromycin and fluoroquinolones have excellent activity against non-LGV chlamydiae, there are few reliable data on the use of these drugs to treat LGV and they are not currently recommended. Sexual contacts of LGV cases within a window of 60 days should be screened for chlamydial infection and treated with a standard *Chlamydia* regimen of doxycycline or azithromycin (Workowski and Berman, 2006).

Prostatitis

Chronic chlamydial prostatitis proven by detection of *C. trachomatis* in expressed prostatic secretions was treated in a randomized controlled trial with doxycycline or azithromycin. There was no difference in clinical response (69.8% vs 68.3%) or bacteriologic cure (76.7% vs 79.3%) with doxycycline 100 mg bid for 4/52 versus azithromycin 1 g weekly for 4/52 (Skerk *et al.*, 2004). Equivalence between doxycycline and azithromycin was also shown for chronic prostatitis due to *U. urealyticum* (Skerk *et al.*, 2006).

Gonorrhea, chancroid, and donovanosis (granuloma inguinale)

Doxycycline was used extensively for the treatment of gonorrhea and chancroid, but is no longer recommended because of the widespread resistance of *Neisseria gonorrhoeae* (Newman *et al.*, 2007) and *Haemophilus ducreyi* (Workowski and Berman, 2006). Donovanosis is a genital ulcerative disease due to *Klebsiella* (formerly *Calymatobacterium*) *granulomatis* infection. Donovanosis occurs in Papua New Guinea and South Africa and in Australian Aboriginals, presenting as beefy, nontender, ulcerative lesions of the genitalia or inguinal region. Azithromycin appears to be the drug of choice (O'Farrell, 2002), but doxycycline 100 mg bid for 3 weeks is also effective and is the CDC-recommended regimen (Workowski and Berman, 2006).

S0240 **Syphilis and other treponemal infections**

P0325 In patients who are highly allergic to beta-lactam antibiotics or who refuse parenteral therapy, doxycycline 200 mg daily for 14–28 days (Zenker and Rolfs, 1990) appears to be an appropriate alternative for primary and secondary syphilis. A recent case–control study of patients treated with doxycycline 100 mg bid for 14 days for early syphilis showed no increase in serologic failure with doxycycline over 400 days' follow-up. In fact, there were fewer failures of treatment and there was faster decline in reaginic antibodies with doxycycline (Ghanem *et al.*, 2006). Limited data on five patients with latent and neurosyphilis treated with doxycycline 200 mg twice daily for 21 days showed that the drug penetrated well into the CSF and suggested that doxycycline may be useful for these infections (Yim *et al.*, 1985). Even among this small series, one penicillin-allergic woman with early latent syphilis treated with two courses of doxycycline had no serologic response ten months later, as she had a repeat lumbar puncture that demonstrated asymptomatic neurosyphilis (Zenilman *et al.*, 1993). On balance, every effort must be made to treat patients with neurosyphilis with penicillin G because of poorer responses to doxycycline (Ali and Roos, 2002). Doxycycline 100 mg bid for 15 days is a satisfactory alternative for treating yaws (due to *Treponema pertenue*) in penicillin-allergic patients.

S0245 **7d. Brucellosis**

P0330 The current WHO guidelines for brucellosis treatment are a 6-week course of doxycycline 100 mg orally 12-hourly plus streptomycin 15 mg/kg i.m. daily for the first 2–3 weeks or rifampicin 600 mg daily for 6 weeks. These regimens were both endorsed as first-line *Brucella* treatment by an International Society of Chemotherapy Consensus Meeting (Ariza *et al.*, 2007). Both these combinations have been shown to be synergistic *in vitro* (Orhan *et al.*, 2005). The doxycycline–streptomycin regimen is clearly superior, with reduced relapses and improved clinical cure of osteoarticular, particularly spinal, manifestations of brucellosis (Solera *et al.*, 1994). Nonetheless, an international survey of treating physicians from *Brucella* high-endemicity nations has shown that the doxycycline–rifampicin combination is given far more frequently for convenience, despite its inferior efficacy (Pappas *et al.*, 2007). Doxycycline regimens shorter than the 6-week WHO recommended course have been shown to be associated with increased early post-treatment relapse (Solera *et al.*, 2004).

P0335 Alternative regimens are being investigated. Doxycycline and gentamicin 5 mg/kg daily for 7 days were shown to be equivalent to doxycycline and streptomycin in a single randomized controlled trial. Among the treatment failures there was a high proportion of patients with focal disease (3/6 had arthritis or orchitis) (Hasanjani Roushan *et al.*, 2006). This is recommended as the preferred alternative regimen to the WHO guidelines (Ariza *et al.*, 2007). A shorter, 30-day course of ofloxacin and rifampicin was compared with the standard, 45-day course of doxycycline and rifampicin in a small, randomized open-label study that showed no difference in outcome; the authors therefore concluded against the use of the more expensive, ofloxacin and rifampicin regimen (Karabay *et al.*, 2004).

P0340 Patients with osteoarticular complications of brucellosis can be treated with standard brucellosis drugs, but treatment needs to be more prolonged (Mousa *et al.*, 1987; Solera *et al.*, 1997). A recent meta-analysis indicates that *Brucella* spondylitis requires three months' therapy (Pappas *et al.*, 2004). Patients with *Brucella* meningitis or neurobrucellosis have been treated successfully by combining doxycycline with both rifampicin and co-trimoxazole. Some may respond to 6 weeks' treatment, but others may need treatment for up to eight months. For the first 2–3 weeks, i.m. streptomycin can also be added to the regimen (Al-Orainey *et al.*, 1987; Bouza *et al.*, 1987; McLean *et al.*, 1992; Al-Eissa, 1995). Combined medical and surgical therapy has been shown to be effective in a small case series of *Brucella* endocarditis (Keles *et al.*, 2001; Ozsoyler *et al.*, 2005). Doxycycline

combined with rifampicin and ceftriaxone or streptomycin were given preoperatively, and then doxycycline and rifampicin were continued post valve replacement with or without co-trimoxazole. In one case of aortic valve endocarditis, prolonged medical treatment alone with doxycycline plus rifampicin was successful (Cisneros *et al.*, 1989).

7e. Rickettsial infections

Doxycycline is the drug of choice for the treatment of epidemic louse-borne typhus, murine typhus, scrub typhus, tick typhus, Rocky Mountain spotted fever, and Mediterranean spotted fever (Ming-Yuan *et al.*, 1987; Gudiol *et al.*, 1989; Perine *et al.*, 1992). Chloramphenicol is also effective for these diseases, and has sometimes been preferred for very severe infections. The difficulty in sourcing either parenteral or oral chloramphenicol in many countries, and the availability of safe alternatives, currently makes this less relevant. Chloramphenicol remains the treatment of choice for pregnant women with rickettsial infection. In children with rickettsial infection, on balance, the risks of doxycycline therapy are less than those of chloramphenicol, and pediatric authorities recommend doxycycline (2.2 mg/kg up to 45 kg, adult dosage if >45 kg) (Walker, 1995).

Short courses of doxycycline are sufficient for specific rickettsial infections. Louse-borne typhus can be cured by a single dose of doxycycline, 100–200 mg for adults and 50 mg for children (WHO Working Group, 1982), but normally 7–15 days of doxycycline is recommended for this disease (Raoult and Drancourt, 1991). Mediterranean spotted fever has also been cured by an abbreviated course of doxycycline. In one trial, doxycycline was only continued for 24 hours after the patients were afebrile; this form of therapy compared favorably to a standard 7-day doxycycline course (Yagupsky *et al.*, 1987). In another trial, 200 mg doxycycline given 12-hourly for 1 day was as effective as a classic 10-day course with oral tetracycline for this disease (Bella-Cueto *et al.*, 1987). Short, non-doxycycline therapy is of benefit in mild scrub typhus in which single dose azithromycin 500 mg has been shown to have equivalent efficacy to doxycycline given for 1 week (Kim *et al.*, 2004). As spotted fever can have high morbidity and even cause rapid death, empiric doxycycline therapy should be administered promptly when the disease is suspected (Yagupsky and Wolach, 1993). There is a significant increase in mortality for patients treated later than 5 days after onset of symptoms of Rocky Mountain spotted fever (CDC, 2000). The other rickettsiae require tetracycline treatment for 5–15 days (Raoult and Drancourt, 1991).

Trials in Taiwan indicated that doxycycline 200 mg orally once a week was effective for prevention of scrub typhus (Olson *et al.*, 1980). This was confirmed in volunteers experimentally exposed to this infection.

7f. Melioidosis

This disease, caused by *B. pseudomallei*, has a spectrum of manifestations from fulminating septicemia with a high mortality to severe necrotizing pneumonia to a less severe, indolent form. Doxycycline is no longer used in the initial therapy of severe melioidosis as ceftazidime has been shown to be superior to combination therapy with chloramphenicol, doxycycline, and co-trimoxazole (White *et al.*, 1989; Sookpranee *et al.*, 1992). Imipenem is equivalent to ceftazidime (Simpson *et al.*, 1999), and meropenem, although not formally studied, appears equally effective (White, 2003). Treatment courses consist of at least 10 days of intravenous therapy followed by a long maintenance phase of oral chloramphenicol combined for an initial 8 weeks with doxycycline and co-trimoxazole (Rajchanuvong *et al.*, 1995), then continued as monotherapy for a total of 20 weeks. Compliance with the four-drug maintenance regimen described is relatively poor and, as a consequence, simpler regimens without the chloramphenicol have been studied and shown to be equivalent in efficacy and better

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tolerated (Chaowagul *et al.*, 2005). Even simpler, doxycycline-containing regimens are also being investigated; doxycycline monotherapy has been shown to be inferior to the four-drug regimen (Chaowagul *et al.*, 1999) and the combination of ciprofloxacin and azithromycin has been shown to be inferior to doxycycline and cotrimoxazole (Chetchotisakd *et al.*, 2001).

S0260 **7g. Trachoma**

P0365 The ocular *C. trachomatis* serotypes A, B, Ba, and C cause this blinding disease, which remains one of the three most common worldwide causes of loss of vision. Hyperendemic trachoma is transmitted from eye to eye and responds to topical treatment with tetracycline eye ointment given for 6 weeks (Mabey *et al.*, 2005). When oral doxycycline was added for 5 days' treatment each month for six months, the healing rates in children with severe trachoma were improved (Dawson and Schachter, 1985). Single dose azithromycin (20 mg/kg) appears to have equivalent efficacy to topical tetracycline with superior tolerability, and has largely replaced the topical therapy (Mabey and Solomon, 2003). A Cochrane systematic review of antibiotic treatment for trachoma found substantial heterogeneity in available studies that confounded analysis (Mabey *et al.*, 2005). Overall, there were no conclusive data to support the use of antibiotics, but their use was associated with reduced point prevalence of active disease and persistence of *C. trachomatis* at 3 and 12 months post treatment. No difference could be found between topical and various different oral antibiotics (Mabey *et al.*, 2005). *Chlamydia trachomatis* may be transmitted during childbirth, causing *ophthalmia neonatorum* in the newborn. Doxycycline does not have a role in treatment of this condition arising from pregnant women who have chlamydial cervicitis or urethritis. These women should be treated with a single dose of azithromycin. Erythromycin, orally for 2 weeks, should be used to treat established chlamydial conjunctivitis of the newborn, as topical treatment frequently fails to eliminate *C. trachomatis* from the eyes or from the pharynx of such patients (Baum, 1995).

S0265 **7h. Lyme disease and other Borrelia-related diseases**

P0370 Doxycycline has an important role in the prevention and treatment of Lyme disease. A randomized placebo-controlled study showed the benefit of prophylactic doxycycline. A single 200-mg dose of doxycycline prevented clinical Lyme disease and asymptomatic seroconversion in patients with *Ixodes scapularis* tick bite (Nadelman *et al.*, 2001). Doxycycline is recommended, along with oral amoxicillin, for treatment of early Lyme disease manifestations, such as erythema migrans, in a dose of 100 mg bid for 14–21 days (Wormser *et al.*, 2000). The oral doxycycline regimen is preferable in regions where ehrlichiosis is prevalent, as it is also effective against this disease. Longer courses of oral doxycycline (one month) are used to treat Lyme arthritis (Steere, 1995). Although parenteral penicillin or ceftriaxone-cefotaxime are the preferred regimens for severe neurological or cardiac Lyme disease, high-dose doxycycline (200 mg bd) may be required in some patients who are intolerant of beta-lactams. Although there is debate as to whether "chronic Lyme disease" with rheumatologic and neurologic manifestations is a true postinfectious entity, it is clear that antimicrobial therapy, including with i.v. ceftriaxone then oral doxycycline, is not beneficial for this condition and should be avoided (Klempner *et al.*, 2001). Single-dose oral doxycycline 100 mg is one of the effective regimens for louse-borne relapsing fever, an epidemic spirochetal infection due to *Borrelia recurrentis* (Perine and Teklu, 1983).

7i. Leptospirosis

Severe leptospirosis requires antimicrobial therapy as, untreated, it has a mortality that may be as high as 22%. A randomized open-label study of patients with suspected severe leptospirosis in northern Thailand showed that doxycycline treatment was equivalent to penicillin G and cefotaxime with regards to mortality, time to defervescence, and hospital stay. These results pertained to patients with proven leptospirosis. The overall mortality in the study was 5%. Patients with rickettsial infections had superior outcomes with doxycycline (Suputtamongkol *et al.*, 2004).

7j. Q fever (Coxiella burnetii)

Acute Q fever, including pneumonia, is usually a self-limited febrile illness in which the value of any antibiotic therapy is hard to assess. Strain differences in *C. burnetii* are such that, although the most common presentation of acute Q fever in some countries, including Canada and Spain, is atypical pneumonia, in others such as France and Australia this organism does not frequently cause pneumonia (Marrie, 2004). A nonrandomized comparison between treatment regimens for acute Q fever showed that doxycycline reduced duration of fever more than tetracycline, but the effect was not profound (mean days of fever; untreated 3.3, tetracycline 2, doxycycline 1.7) (Spelman, 1982). It appears, based on a randomized study of tetracycline, that treatment with doxycycline must be commenced within 2 days of the onset of symptoms to be effective (Powell *et al.*, 1962). Many clinicians treat patients with moderately severe disease with doxycycline 100 mg bid for 14 days (Sawyer *et al.*, 1987; Lieberman *et al.*, 1995; Maurin and Raoult, 1999). Some patients may develop Q fever meningitis or meningo-encephalitis as part of acute Q fever. These respond to a 3-week course of doxycycline (Ferrante and Dolan, 1993). Antibiotic therapy for acute Q fever may prevent the development of endocarditis in patients with cardiac valvulopathy. One case-control study drawn from heterogeneous populations of acute Q fever assessed at the Unite des Rickettsies, Marseilles, showed that patients with valvulopathy and acute Q fever were significantly less likely to develop endocarditis if treated with a combination of doxycycline and hydroxychloroquine for between 1 and 15 months (Fenollar *et al.*, 2001).

Therapeutic regimens for Q fever endocarditis have always included tetracyclines due to the resistance of *C. burnetii* to beta-lactams and aminoglycosides. Before the introduction of a doxycycline-hydroxychloroquine regimen, there was an unacceptably high failure rate, despite prolonged therapeutic courses. The addition of hydroxychloroquine is necessary to alkalize the phagolysosome and increase the efficiency of antibiotic killing of intracellular *C. burnetii* (Maurin *et al.*, 1992a). The optimal phagolysosome pH for *C. burnetii* killing is 6.6 and chloroquine 1 mg/ml was able to increase the pH from 4.8 to 5.7 in an *in vitro* cellular model (de Duve *et al.*, 1974). Hydroxychloroquine is used in favor of chloroquine for its improved long-term tolerance. The doxycycline 100 mg bd/hydroxychloroquine 200 mg tds combination has been studied in a retrospective comparison with doxycycline-ofloxacin (Raoult *et al.*, 1999). Of 35 patients studied, 21 received the doxycycline-hydroxychloroquine combination. Fewer patients relapsed in the doxycycline-hydroxychloroquine group, and those that did received only 12 months' therapy. The doxycycline-hydroxychloroquine group could be treated with shorter durations (31 months versus 55 months of doxycycline-ofloxacin). The high dose of hydroxychloroquine used in this study is often poorly tolerated. Although the doxycycline-hydroxychloroquine regimen is now the standard of care for Q-fever endocarditis, there are only limited additional case reports of its successful use. Some of these reports include different regimens (doxycycline-chloroquine for two years) (Calza *et al.*, 2002) and this report and others (Madariaga *et al.*, 2004; Healy *et al.*, 2006) do not include information on follow-up after ceasing antibiotics.

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P0390 Before the introduction of this doxycycline–hydroxychloroquine regimen, prolonged doxycycline in combination with rifampicin, a fluoroquinolone, or co-trimoxazole was the standard of therapy, prescribed for a minimum of three years but often required lifelong to provide serologic evidence of controlled infection. Doxycycline and ofloxacin or perfloxacin were superior to doxycycline alone, but relapse rates of at least 50% occurred on ceasing therapy (Levy *et al.*, 1991; Raoult, 1993). Similar benefits of the doxycycline–rifampicin combination were shown over doxycycline monotherapy (Raoult, 1993).

S0280 **7k. Plague (*Yersinia pestis* infection) and tularemia (*Francisella tularensis* infection)**

P0395 Streptomycin has historically been the preferred drug for plague. *In vitro* susceptibility testing showed that doxycycline was effective against *Y. pestis* with MICs at the same level as comparator drugs (Hernandez *et al.*, 2003). A recent randomized open-label trial in adults and children with plague showed that doxycycline and gentamicin both have high efficacy equivalent to that previously reported for streptomycin (Mwengee *et al.*, 2006). For patients with meningitis, chloramphenicol is recommended (Butler, 1994; CDC, 1994).

P0400 Streptomycin is now replaced by the widely available gentamicin as the drug of choice for severe pneumonia due to tularemia (Enderlin *et al.*, 1994). In Europe, where milder forms of tularemia such as ulceroglandular disease are common, alternative drugs, doxycycline and chloramphenicol, can be safely used (Eliasson *et al.*, 2006). Although doxycycline use is associated with infrequent relapse, this does not predispose to poor outcomes with milder forms of tularemia (Eliasson and Back, 2007).

S0285 **7l. Ehrlichiosis**

P0405 This is a tick-borne infection caused by small obligate intracellular bacteria of the genus *Ehrlichia*. These organisms proliferate within white blood cells with *Anaplasma phagocytophilum* and *Ehrlichia ewingii* involving neutrophils where as *E. chaffensis* infects human monocytes (Dumler *et al.*, 2007). *Ehrlichia* infections occur during the summer months and cause undifferentiated fever with leukopenia, thrombocytopenia, and elevation in serum aminotransferase levels. *Ehrlichia chaffensis* and *E. ewingii* are restricted to the USA, but *A. phagocytophilum* has an international distribution that corresponds to the distribution of human-feeding *Ixodes pesculatus* ticks and includes areas of Europe and Asia. Severe infection and mortality are associated with delays in diagnosis and treatment. The treatment of choice is doxycycline, administered for 5–14 days (Dumler *et al.*, 2007). The absence of proven alternative antimicrobial regimens and necessity for prompt empirical therapy mandates doxycycline treatment in all patients with suspected ehrlichiosis, including in children <8 years of age (Dumler *et al.*, 2007). Concomitant *Ixodes* borne pathogens including Lyme disease and tick-borne encephalitis require diagnostic and management considerations.

S0290 **7m. Mycobacterial infections**

P0410 *Mycobacterium abscessus*, *M. chelonae*, and *M. fortuitum* are environmental, rapidly growing mycobacteria that predominantly cause cutaneous infections after nosocomial or accidental inoculation and, uncommonly, cause lung disease. These mycobacteria, particularly *M. fortuitum*, may be susceptible to doxycycline (De Groot and Huit, 2006). There are no randomized studies to definitively guide therapy for these infections. Antimicrobial susceptibility testing is helpful in assessing treatment options (Wallace *et al.*, 1985). Limited skin infections due to *M. chelonae* and *M. fortuitum* may be treated with prolonged oral antibiotics, of which doxycycline is one option. For patients with serious *M. abscessus* and *M. chelonae* infections, initial

therapy is with clarithromycin, potentially in combination with imipenem and an aminoglycoside. *Mycobacterium fortuitum* should be treated with surgical debridement, cefoxitin, and amikacin initially. Doxycycline may have a role in continuation therapy, postsurgical debridement. Infections due to *M. marinum* may be acquired, most typically, in patients injured during cleaning fish tanks. The infection presents with “sporotrichoid” nodules that advance up the involved limb. Doxycycline is one of the oral antimicrobial alternatives for treating *M. marinum* in a dose of 100–200 mg daily for three months (American Thoracic Society, 1997).

S0295 **7n. *Vibrio* and *Aeromonas* spp. infections, including water-associated cellulitis**

Marine cellulitis may be due to *Vibrio* spp. such as *V. vulnificus* or *V. parahaemolyticus*, whereas *Aeromonas hydrophila* can cause skin and soft-tissue infection in injuries contaminated by fresh water. *Vibrio* skin infections may cause overwhelming sepsis in patients with cirrhosis or iron-overload states. For serious water-associated cellulitis, a combination of doxycycline plus a broad-spectrum agent such as ticarcillin–clavulanate (see Chapter 16, Ticarcillin–Clavulanic Acid) or imipenem may be required. *Aeromonas hydrophila*, *A. caviae*, *A. veronii*, *A. jandaei* and other *Aeromonas* spp. can cause septicemia in patients with severe underlying diseases such as cancer. Most strains are susceptible to doxycycline, which can be administered orally to treat milder cases. *Aeromonas* spp. can also cause gastroenteritis, which is usually self-limiting and chemotherapy is not necessary (Jones and Wilcox, 1995).

S0300 **7o. Bartonella infections**

Many diseases are caused by infections with these bacteria, ranging from cat scratch disease (*B. henselae* and rarely *B. clarridgeiae* or *Afipia felis*) to bacillary angiomatosis and peliosis hepatis in AIDS patients (*B. henselae*) to bacteremia, particularly in the homeless (*B. quintana*), and endemic bartonellosis or Carrion’s disease (*Bart. bacilliformis*). Although macrolides are the mainstay of treatment for these infections, doxycycline can also be used. Indeed, when a series of patients with *B. quintana* bacteremia was analyzed, a combination of doxycycline with gentamicin was more likely to prevent relapse than either doxycycline or beta-lactam monotherapy (Foucault *et al.*, 2002). This series confirmed that *B. quintana* bacteremia may be prolonged and remain asymptomatic or may be intermittent. Further exploration of the role of antimicrobial therapy for *B. quintana* bacteremia was undertaken with a randomized placebo-controlled trial showing that doxycycline and gentamicin reduced the risk of recurrent bacteremia (Foucault *et al.*, 2003). Cat scratch disease is mostly treated with azithromycin, rifampicin, or co-trimoxazole, but the rare neuroretinitis manifestation (acute visual loss from optic nerve edema associated with macular exudates) of this condition appears to respond best to doxycycline and rifampicin (Reed *et al.*, 1998).

S0305 **7p. Acne and rosacea**

Acne vulgaris is a common disease of adolescence and results from increased sebum production and inflammation of the sebaceous follicles consequent on infection with *Propionibacterium acnes*. For mild disease, topical keratolytics may suffice, but, for more severe facial acne and truncal disease, antibiotics are of value. Doxycycline is used for both its antibiotic and antiinflammatory effects as it penetrates well into the pilosebaceous unit (Tan, 2003). Numbers of *P. acnes* can be shown to reduce by 90% with doxycycline treatment. Subinhibitory concentrations (e.g. 20 mg dose) of tetracyclines have been shown to reduce *P. acnes* lipase formation, lessening follicular inflammation through reduced sebum free fatty acids (Tan, 2003). Inhibition of neutrophil chemotaxis and other antiinflammatory effects are also present. The beneficial effect of doxycycline takes weeks to be obvious

- and treatment is prolonged for at least six months. Treatment is initiated at 100 mg bid and continued usually for 6 weeks until there is clear improvement, usually with reduction of at least 50% of lesions. Maintenance therapy is then continued with 100 mg daily. A number of factors may account for treatment failure, including poor compliance, high sebum formation, and the development of doxycycline resistance in *P. acnes*. Such resistance tends to occur in patients repeatedly treated with sequential antibiotics with intrinsically resistant disease.
- P0430 Rosacea is another common inflammatory skin condition that causes prominent flushing, facial pustulosis, and a papular eruption. Although doxycycline is commonly used to attempt to control rosacea, there are few high-quality studies supporting this practice (van Zuuren *et al.*, 2006). Current evidence supports the use of topical metronidazole or topical azelaic acid.
- S0310 **7q. Nocardiosis and actinomycosis**
- P0435 Minocycline (see Chapter 68, Minocycline) is more active than doxycycline against *Nocardia* although some patients intolerant of co-trimoxazole and minocycline may require maintenance therapy with doxycycline. Similarly, doxycycline can be used as an alternative to penicillin G for the treatment of actinomycosis in penicillin-allergic patients.
- S0315 **7r. Tropical sprue**
- P0440 Doxycycline may be used as a better tolerated alternative to long-term tetracycline administration for patients suffering from tropical sprue. A prolonged course of three to six months is used (Ramakrishna *et al.*, 2006).
- S0320 **7s. Whipple's disease**
- P0445 Doxycycline is active against *Tropheryma whipplei*, and synergy has been shown with hydroxychloroquine (Boulos *et al.*, 2004b). Thus, doxycycline may be useful for treatment of this disease in patients with severe allergy to co-trimoxazole (Knaapen and Barrera, 2007). Additionally, the benefit of the synergistic doxycycline–hydroxychloroquine combination may be required in treatment refractory cases (Boulos *et al.*, 2004b).
- S0325 **7t. Wolbachia endosymbiont infection**
- P0450 *Wolbachia* are rickettsiae family symbiotic bacteria that are important in the life cycle and fertility of filarial infections, such as onchocerciasis and Wucherian filariasis. These organisms, found in the hypodermis or cell wall of all life cycle stages of filarial, represent a new therapeutic target for these diseases as antihelminthic treatments such as ivermectin have a reversible and, therefore, relatively short-lived effect in suppressing the fertility of adult worms (Hoerauf *et al.*, 2003a). A 6-week course of doxycycline 100 mg daily was shown to deplete *Wolbachia* in *Onchocerca volvulus* worms and interrupt embryogenesis for 18 months (Hoerauf *et al.*, 2001; Hoerauf *et al.*, 2003b) – considerably longer than that shown for ivermectin. In a small study of lymphatic filariasis, adult *W. bancrofti* worms and microfilariae were both decreased by a 6-week course of doxycycline, with the effect persisting over 14 months of follow-up (Taylor *et al.*, 2005). The inability to give doxycycline to children under eight years of age or pregnant women, and the requirement for prolonged courses of the agent, are major current obstacles for this therapeutic approach, as population-based treatment is required to substantially control the carriage of filaria. Other antimicrobials are being investigated for their anti-*Wolbachia* activity.
- 7u. Malaria treatment and chemoprophylaxis** S0330
- Plasmodium falciparum* and *P. vivax* are both susceptible to doxycycline, which is combined with other antimalarials in the treatment of *P. falciparum*. Oral quinine and doxycycline remains the standard *P. falciparum* treatment in much of the developed world, with i.v. quinine used in the regimen for severe *P. falciparum* (Griffith *et al.*, 2007; Laloo *et al.*, 2007). Ease of administration, increased tolerability, and, in the case of artemether–lumefantrine (Riamet), superior outcomes (Alecrim *et al.*, 2006) now support the widespread use of Riamet and atovoquone–proguanil (Malarone) for uncomplicated *P. falciparum*. It is now also clear that i.v. artesunate is superior to quinine for severe *P. falciparum*, with a randomized controlled trial showing a survival benefit (Dondorp *et al.*, 2005). It is somewhat ironic that the preferred, artemisinin-derivative-based treatment is not readily available in the developed world because of lack of licensing due to noncompliance with Good Manufacturing Principles.
- P0455
- Although doxycycline has been shown to have anti-*P. vivax* activity, it is rarely used to treat this infection as it has a slower rate of parasite clearance than alternative antimalarials (Pukrittayakamee *et al.*, 2001). Rather, chloroquine is used unless there is evidence of resistance.
- P0460
- Doxycycline is an extremely effective prophylactic agent for protecting against *P. falciparum*. Doxycycline is as effective as mefloquine for *P. falciparum* prophylaxis as shown in studies in Indonesia (Ohr *et al.*, 1997) and Afghanistan (Sonmez *et al.*, 2005), with protective efficacy of 99–100%. A direct comparison between doxycycline and atovoquone–proguanil (Malarone) has not been undertaken, but, as mefloquine and Malarone have been shown to have equivalent prophylactic efficacy, doxycycline is assumed to have the same efficacy as Malarone. High protective efficacy rates for doxycycline have been also been shown in two comparative studies of azithromycin; 96.3% in Irian Jaya (Taylor *et al.*, 1999) and 92.6% in Kenya (Andersen *et al.*, 1998). As doxycycline has no causal prophylactic effect with no impact on preerythrocytic liver stages of malaria, it must be taken for 4 weeks after leaving a malaria-endemic area (Shmuklarsky *et al.*, 1994). In areas of high *P. vivax* prevalence such as Irian Jaya, doxycycline has been shown to have high protective efficacy against this species of malaria (Ohr *et al.*, 1997; Taylor *et al.*, 1999). Doxycycline is well tolerated for short-term malaria prophylaxis with rates of side-effects, including cutaneous reactions, lower than comparative antimalarials (Schlagenhauf *et al.*, 2003). The safety of long-term antimalarial prophylaxis using doxycycline has not been specifically studied for durations of more than six months (Knobloch, 2004). However, it is possible to extrapolate from other conditions, such as Q fever endocarditis, that durations of up to two years are safe (Maurin *et al.*, 1992a; Knobloch, 2004).
- P0465
- 7v. Prophylaxis for exposure to bioterrorism agents** S0335
- Doxycycline is an important agent for prophylaxis of individuals exposed to bacterial agents that are potential agents of bioterrorism. *Bacillus anthracis* (Mohammed *et al.*, 2002; Freaan *et al.*, 2003) is routinely susceptible to doxycycline, as is *Y. pestis* (Hernandez *et al.*, 2003), *Brucella* spp., and *Francisella tularensis* (the cause of tularaemia) (Bossi *et al.*, 2004). Doxycycline has equivalent *in vitro* efficacy to fluoroquinolones and is considerably cheaper, making it the preferred prophylactic agent (Brouillard *et al.*, 2006). *Burkholderia pseudomallei* is another potential bioterrorism weapon. Recommendations for prophylaxis for those exposed to *B. pseudomallei* include co-trimoxazole and, on the basis of *in vitro* susceptibility data, doxycycline (Thibault *et al.*, 2004; Sivalingam *et al.*, 2006).
- P0470

S0340 **7w. Anti-inflammatory and antitumour effects**

P0475 Although doxycycline appears to have numerous actions on immune effector mechanisms, its ability to inhibit matrix metalloproteinases (MMPs) is being actively investigated in various anti-inflammatory and antitumour settings (Pasquale and Tan, 2005; Weinberg, 2005). MMPs are proteolytic enzymes produced by inflammatory cells, often in response to bacterial infection. Their role in periodontitis was shown to be mediated by degradation of collagen, and they are inhibited by subantimicrobial concentrations of doxycycline (Golub *et al.*, 1998). Different effects of MMPs are involved in the pathogenesis of bony metastases, and the bony tropism of doxycycline makes it a useful agent for study of potential inhibitory effects on metastatic cancer (Saikali and Singh, 2003).

P0480 Subantimicrobial doses of doxycycline are a useful adjunct to local dental therapies for management of periodontitis as they have been shown to downgrade the action of gum destructive MMPs (Preshaw *et al.*, 2004). Through its ability to inhibit bony MMPs, doxycycline has a salutary effect on some tumours, particularly bony metastases (Saikali and Singh, 2003). Doxycycline may play a role in medical

therapy of abdominal aortic aneurysms through local inhibition of arterial wall MMPs (Rentschler and Baxter, 2007). This is supported by a number of animal studies (Pettrinec *et al.*, 1996) and preoperative doxycycline has been shown to reduce aneurysmal aortic wall MMPs in humans (Curci *et al.*, 2000). A single, small, randomized clinical trial showed that doxycycline-treated patients had less expansion of aortic aneurysms after a three-month treatment course (Mosorin *et al.*, 2001). Inflammatory arthropathies have been studied to see whether doxycycline may have a therapeutic role. One placebo-controlled randomized study of doxycycline plus methotrexate for two years in small numbers of rheumatoid arthritis patients showed superior treatment responses in those treated with doxycycline irrespective of whether high or sub-antimicrobial doses were used (O'Dell *et al.*, 2006). Alternately, seronegative arthropathies treated for three months were unresponsive to doxycycline (Smieja *et al.*, 2001). *Chlamydia psittaci* DNA is found in the majority of ocular adnexal lymphomas, and 3 weeks of doxycycline therapy has been shown in a number of small case series to cause resolution or substantial decrease in tumor in a substantial proportion of such patients (Ferreri *et al.*, 2005; Ferreri *et al.*, 2006). However, the value of doxycycline use in this manner requires further investigation.

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Author's Contact Information:

Damon P Eisen

Victorian Infectious Diseases Service and University of Melbourne
Royal Melbourne Hospital
Grattan St
Parkville
Victoria 3050
Australia
Fax: +61 3 9342 7277
Email: damon.eisen@mh.org.au

Author's Affiliation details:

Damon P Eisen MBBS MD FRACP

Professor
Victorian Infectious Diseases Service, Royal Melbourne Hospital
Victoria, Australia

List of Abbreviations:

CAP	community-acquired pneumonia
CSF	cerebrospinal fluid
ETEC	enterotoxigenic <i>Escherichia coli</i>
LGV	lymphogranuloma venereum
MMP	matrix metalloproteinase
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
OCP	oral contraceptive pill
PID	pelvic inflammatory disease

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