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How safe is doxycycline for young children or for pregnant or breastfeeding women?

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ABSTRACT

Tetracycline antimicrobials entered into clinical usage in the late 1940s. Permanent dental staining from tetracyclines was first appreciated in 1956, eventually leading to avoidance of this class of antibiotics whenever possible in young children and pregnant or breastfeeding women. Doxycycline, introduced in 1967, binds calcium less avidly than prior tetracyclines and is regarded by some authorities as safe to prescribe for pregnant women and young children. Review of the available data, however, suggests that this interpretation may be incorrect or at least premature. In conclusion, until more definitive data are developed, doxycycline should continue to be only selectively prescribed for young children and pregnant or breastfeeding women for whom alternative, safer antibiotics are not available, and courses of treatment should be of as short a duration as possible.

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Tetracyclines are polycyclic naphthacene carboxamide compounds that include 4 benzene rings (Guggenheimer, 1984; Johnson, 1964; Nelson and Levy, 2011; Toaff and Ravid, 1963). Chlortetracycline, the first tetracycline, was discovered in the 1940s and was approved by the United States Food and Drug Administration (FDA) in 1948 (Nelson and Levy, 2011). The bacterium that produced this antibiotic was named *Streptomyces aureofaciens*, and the brand name of the antibiotic was Aureomycin (Nelson and Levy, 2011). These names were chosen to reflect the golden yellow color of the bacterial colony, as well as that of the drug itself (Nelson and Levy, 2011). Oxytetracycline was FDA approved in 1951. Tetracycline was derived from chlortetracycline and FDA approved in 1953 (Nelson and Levy, 2011). These first-generation tetracyclines are structurally similar (Agwuh and MacGowan, 2006; Johnson, 1964; Nelson and Levy, 2011).

Because of their broad spectrum of antimicrobial activity that included many respiratory pathogens and an apparent excellent safety profile, they were initially widely used to treat young children with respiratory tract infections and otitis media. Although the first report of tooth discoloration appeared in 1956 (Schwachman and Schuster, 1956), this class of drugs remained in wide usage and resulted in intrinsic dental staining for large numbers of children (Frankel and Hawes, 1964; Guggenheimer, 1984; Hennon, 1965; Storey, 1967). Tetracycline-induced dental staining is not reversible and may result in adverse psychologic effects on the individual affected and lead to sizeable costs

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in the efforts expended to try to correct the problem (Guggenheimer, 1984; Keitel and Soentgen, 1965). The FDA issued a statement about this adverse effect in 1963 (Guggenheimer, 1984; Johnson, 1964). Because of the risk of dental staining, tetracycline is usually not prescribed for children less than 8 years of age and for breastfeeding women (Boast et al., 2016; Cross et al., 2016; Morganti et al., 1968). Tetracycline is also usually avoided in the second half of pregnancy because of the same concern (Genot et al., 1970; Porter et al., 1965). Besides the issue of dental staining, pregnant women also have a greater risk of hepatotoxicity from tetracycline (Heaton et al., 2007; Nahum and Kennedy, 2006). Furthermore, tetracycline administration to premature infants can transiently inhibit bone growth (Cohlan et al., 1963; Toaff and Ravid, 1963).

It is believed that tetracyclines affect tooth development and cause irreversible dental staining because of binding to calcium at physiologic pH, resulting in the formation of a tetracycline-calcium orthophosphate complex (Guggenheimer, 1984; Moffitt et al., 1974; Toaff and Ravid, 1963). Tetracycline deposition in teeth occurs primarily in the dentin. Somewhat more controversial is whether tetracycline may also cause enamel hypoplasia (Frankel and Hawes, 1964; Patterson, 1979; Porter et al., 1965; Toaff and Ravid, 1963). The amount of drug given with respect to daily dosage, combined with duration of therapy, appears to impact the risk of dental staining (Ayaslioglu et al., 2005; Guggenheimer, 1984; Hamp, 1967; Storey, 1967). The frequency with which dental staining occurs is dependent on the timing of administration with regard to tooth development (Brearley and Storey, 1968; Moffitt et al., 1974; Storey, 1967). A greater number of courses of this antibiotic class may increase the chances of administration during active tooth mineralization (the calcifying activity in human dentition is slow and intermittent) (Brearley and Storey, 1968; Grossman et al., 1971; Guggenheimer, 1984; Toaff and Ravid, 1963). Particularly high-risk time periods for staining of primary dentition are the third trimester of pregnancy and during the neonatal period (Kutscher et al., 1966; Porter et al., 1965). In general, permanent teeth are affected more diffusely and less intensely, possibly due to slower mineralization of permanent teeth and thicker enamel (Guggenheimer, 1984; Hamp, 1967). Also, permanent teeth may have a naturally occurring yellow coloration, which might obscure the staining effects of treatment with tetracyclines (Hennon, 1965). In ground sections of pigmented teeth, the thickness of the pigmented bands is proportional to the duration of tetracycline administration, the intensity of the color is related to dosage, while the number of bands is related to cycles of drug administration (Toaff and Ravid, 1963).

Staining of teeth from tetracyclines varies from a pale yellow to dark brown; factors that appear to influence the color include the particular tetracycline homologue taken, the thickness of the enamel, and the degree of light exposure of the teeth (Bridges et al., 1969; Hamp, 1967; Moffitt et al., 1974; Toaff and Ravid, 1963). Among the older tetracyclines, some studies have suggested that oxytetracycline was less likely than other tetracycline homologues to lead to more severe dental staining (Bridges et al., 1969; Kowalewska et al., 1966; McIntosh and Storey, 1970; Wallman and Hilton, 1962a, 1962b), whereas others did not (Swallow et al., 1967; Toaff and Ravid, 1963; Zegarelli et al., 1963). If teeth fluoresce a yellow or yellow-orange color under ultraviolet (UV) light, it is suggestive of tetracycline discoloration and can be helpful diagnostically if the pigmentation is slight (Frankel and Hawes, 1964; Porter et al., 1965). Gray-brown pigmented teeth, however, are less likely to fluoresce.

Newer tetracycline derivatives such as doxycycline introduced in 1967 (sometimes referred to as second-generation tetracyclines) have also been available to treat patients (Cross et al., 2016; Todd et al., 2015). Doxycycline is a semisynthetic derivative of oxytetracycline. There are, however, many differences between doxycycline and older tetracyclines, such as oxytetracycline, including markedly different pharmacokinetic properties, resulting in both lower doses and less frequent administration with doxycycline (Table 1) (Agwuh and MacGowan, 2006; Cross et al., 2016; Cunha and Cunha, 2017; Eisen, 2010). In addition, doxycycline appears to bind calcium less avidly than tetracycline (Schach von Wittenau, 1968). The question of whether doxycycline can be safely given to the groups of patients for whom tetracycline is relatively contraindicated has been a topic of considerable interest (Nahum and Kennedy, 2006). In one study performed with rats, tooth discoloration from doxycycline was less than that observed from either tetracycline or oxytetracycline (McIntosh and Storey, 1970). In this study, administration of doxycycline resulted in a lemon yellow shade of tooth discoloration when it occurred.

Table 1
Selected pharmacokinetic features of tetracycline and oxytetracycline (both first-generation tetracyclines) compared with that of doxycycline (second-generation tetracycline).

Features	Tetracycline	Oxytetracycline	Doxycycline
Usual adult dose and route of administration	250–500 mg orally 4 times per day	250–500 mg orally 4 times per day	100 mg orally twice daily[a]
Total daily dose	1–2 g	1–2 g	200 mg
Bioavailability after oral administration	77–88% (without food)	~ 60% (without food)	~95%
Serum half-life ($t½$)	6–11 h	~ 9 h	12–25 h
Plasma protein binding	55–64%	27–35%	82–93%

[a] Initial dose often 200 mg to reach steady-state concentrations more quickly.

Boast et al. (2016) published a literature review addressing the available data on the risk of dental staining from doxycycline in young children and concluded that the risk is <1% from up to a 10-day course of doxycycline in children <8 years of age. These authors stated that longer courses of treatment or doxycycline dosages exceeding 2.9 mg/kg twice daily require further study. They also concluded that there are insufficient data on dental adverse effects if antibiotic exposure occurs in the neonatal period.

Cross et al. (2016) also published a review article on the safety of doxycycline in pregnancy and early childhood. These authors concluded that no correlation existed between the use of doxycycline and teratogenic effects during pregnancy. The authors stated that doxycycline is safe in early pregnancy and possibly throughout pregnancy. However, in 2017 Muanda et al. (2017a) reported on a nested case–control study based on the Quebec Pregnancy Cohort (1998–2009) and observed that the use of doxycycline when administered before the 20th week of pregnancy was associated with a significantly increased risk of spontaneous abortion, whereas amoxicillin and cephalosporins were not. In another study, the same investigators also found that doxycycline administration during the first trimester was associated with the development of major congenital malformations of the heart and circulatory system, whereas the use of amoxicillin or cephalosporins was not (Muanda et al., 2017b).

Cross et al. (2016) also concluded from their analyses that there was no evidence that doxycycline leads to permanent dental staining when administered to children provided that the daily dose does not exceed 200 mg and the drug is given for a maximum duration of 14 days. The American Academy of Pediatrics in the Red Book published in June of 2018 concluded that even longer courses of doxycycline, up to 21 days, were safe and could be prescribed for any indication without regard to the patient's age (Committee on Infectious Diseases and American Academy of Pediatrics, 2018).

Remarkably, Cross et al. (2016) also stated that doxycycline is the preferred antibiotic for treatment of early Lyme disease (because of possible co-infection with *Anaplasma phagocytophilum*), and thus, the reader might infer from their publication that it is now safe to use doxycycline routinely to treat pregnant women and young children with erythema migrans. However, unlike for Rocky Mountain spotted fever (Biggs et al., 2016), amoxicillin and cefuroxime axetil are equally as effective as doxycycline for treatment of patients with erythema migrans, both with respect to resolving the skin lesion and for prevention of later complications of Lyme disease (Cerar et al., 2010; Dattwyler et al., 1990; Eliassen et al., 2017, 2018; Luger et al., 1995; Massarotti et al., 1992; Nadelman et al., 1992; Sanchez et al., 2016; Strle et al., 2018; Weber et

al., 1988). In addition, confirmed *A. phagocytophilum* co-infections in children are extremely rare (Schotthoefer et al., 2018; Sigurjonsdottir et al., 2017).

Furthermore, although just 10 days of doxycycline is effective for patients with erythema migrans, it is not at all unusual in clinical practice to see such patients treated with longer courses of antibiotics of at least 21 days (Kowalski et al., 2010); and those with residual symptoms are sometimes retreated with an equally long course of treatment (Arvikar et al., 2017; Tseng et al., 2015). If there are 300 000 cases of Lyme disease in the United States (Hinckley et al., 2014; Nelson et al., 2015) and if 70% present with erythema migrans (Bacon et al., 2008), that would result in 210 000 cases of erythema migrans per year. If approximately 15% of these individuals were <8 years old (based on an extrapolation from those cases reported to the Centers for Disease Control and Prevention (Bacon et al., 2008)), for this manifestation of Lyme disease alone, over 30 000 young children could now potentially be treated with doxycycline each year. Of this group, how many cases of permanent dental staining would be expected? How many would be an acceptable number, assuming that all of those patients who were not allergic to beta lactam antibiotics or azithromycin could have been treated differently?

There are only 6 relatively small cohort studies that have addressed the safety of doxycycline in young children, and each has certain limitations (Forti et al., 1967; Forti and Benincori, 1969; Lochary et al., 1998; Poloczek, 1975; Poyhonen et al., 2017; Todd et al., 2015; Volovitz et al., 2007) (Table 2). Overall, the studies included 438 children who were exposed to doxycycline. Six children out of 438 (1.4%) developed tooth staining potentially due to doxycycline (95% CI: 0.6–3.0%). Although data published in the peer-reviewed medical literature are limited, or unavailable, on the blood levels and pharmacokinetics of doxycycline given orally to young children (as well as pregnant women) (Cross et al., 2016; Forti et al., 1967; Nahum and Kennedy, 2006; Reeves et al., 2009), a dosage of 2.2 mg/kg twice daily is recommended to treat Rocky Mountain spotted fever up to a maximum of 100 mg/dose (Biggs et al., 2016). However, only 1 of the 6 studies definitely followed this dosage schedule, with at least 3 of the 5 other studies giving less than one-half of this dosage, whereas 1 study exceeded this dosage (Poyhonen et al., 2017). In 4 of the studies, the mean age of the children when they were first prescribed doxycycline was between 4 and 5.1 years of age (Lochary et al., 1998; Poyhonen et al., 2017; Todd et al., 2015; Volovitz et al., 2007). Calcification of permanent teeth begins around 3–4 months of life and is largely complete by 5–6 years of age, suggesting that children who are under 4 years of age would be the highest-risk group. Even with tetracycline, the risk of cosmetically objectionable dental staining is considered negligible after the age of 5 years, especially if treatment duration is short and multiple courses of treatment are not prescribed (Ayaslioglu et al., 2005; Grossman et al., 1971; Shetty, 2002).

In one study (Lochary et al., 1998), we interpreted the data to mean that 0/10 treated patients had dental staining from doxycycline, but the number could have been as high as 4/10. The investigators found a degree of staining that exceeded that found in the matched control subjects for those 4 individuals (each patient was matched with 2 controls) but did not assess whether the teeth showed the characteristic yellow fluorescence under UV light (Brearley and Storey, 1968). For 3 patients, the level of dental staining was higher in the matched controls, resulting in the interpretation by the investigators that dental staining attributable to doxycycline was not found.

In the largest United States study that involved 58 doxycycline-treated children (Todd et al., 2015), no information was provided on

Table 2
Studies that evaluated dental staining from doxycycline in young children.

Study (year of publication)	Patients who were treated with doxycycline	Dosage	Duration of treatment	Follow-up	Results	Comments
Forti and Benincori, 1969	25 premature infants 4–55 d of age	2 mg/kg po[a] day 1, 1 mg/kg po[a] day 2 onward	6–17 d	1 y postexposure	1/25 (4.0%) had dental staining	One course of treatment; route of administration not stated; evaluation at 1 y postexposure likely too short a time interval; doxycycline dosage less than that recommended for RMSF; no controls.
Poloczek, 1975	282 children, mean age 29 mo (range 1 mo to 12 y)	4 mg/kg po day 1, then 2 mg/kg daily	5–8 d; 40 patients were retreated	Last evaluation was 1 y postexposure	5/282 (1.8%) had dental staining	Evaluation at 1 y postexposure likely too short a time interval; No controls; doxycycline dosage less than that recommended for RMSF.
Lochary et al., 1998	10 children with RMSF; mean age 5.1 y (range 4.3–8.3 y)	15–100 mg twice daily	2–10 d but not reported for 4 cases	Mean age 13.7 y (11–19 y)	0/10 had dental staining[b]	One course of treatment; most took drug orally; 20 controls; although in 4/10 cases the color score was greater in the doxycycline-treated subjects compared with the average score found in the 2 matched controls, the reverse was true for 3 of the 10 doxycycline-treated subjects; UV fluorescence was not assessed.
Volovitz et al., 2007	31 children with atypical pneumonia and asthma; mean age 4.1 y (range 2.0–7.7 y) at time of initial treatment	4 mg/kg po twice daily on day 1, then 2 mg/kg po daily day 2 onward	10 d; mean of 2 courses of treatment (range 1–4)	Mean age 10.4 y (range 8–16 y); mean of 5.4 y (range 1–12 y) since last exposure to doxycycline	0/25 had dental staining	30 controls; 6 doxycycline-treated children excluded as not examined by study dentist; doxycycline dosage less than that recommended for RMSF.
Todd et al., 2015	58 children with RMSF; mean age 4.5 y (range 0.2–7.9 y)	Mean of 2.3 mg/kg po twice daily	Mean of 7.3 d (range 1–10 d); mean of 1.8 courses of treatment	Mean age 9.8 y (range 8.1–15.6 y)	0/58 had dental staining	213 controls; unclear how much doxycycline actually taken; whether timing of subsequent course(s) of doxycycline would have actually impacted the erupted teeth evaluated was not stated; all subjects Native Americans and whether risk of dental staining might be affected by genetic background unclear; UV fluorescence not assessed.
Poyhonen et al., 2017	38 children with suspected central nervous system infection, mean age 4.7 y (range 0.6–7.9 y)	10 mg/kg/d (range 8–10 mg/kg/d) po or iv for 2–3 d, then 5 mg/kg/d po or iv (range 2.5–10 mg/kg/d)	12.5 d (range 2–28 d), 37/38 received a single course of doxycycline	Mean age 14.2 y (range 8.3–22.6 y)	0/37 had dental staining attributed to doxycycline	No controls; UV fluorescence not assessed; doxycycline dosage higher than that recommended for RMSF.

RMSF = Rocky Mountain spotted fever; po = taken orally; iv = intravenous administration.
[a] Presumably taken orally based on a prior publication by some of the same authors (Forti et al., 1967).
[b] Possibly up to 4/10, see text.

compliance with taking the medication. This study explicitly stated that the teeth examined had been developing at the time of doxycycline administration, but the authors did not comment if this also applied to the subjects for the time periods that they received retreatment with doxycycline. This study was conducted on an American Indian reservation in the Southwest, which raises a question as to whether it is appropriate to extrapolate the findings to persons with other genetic backgrounds. A study, however, in another geographic area in the Northern United States and Canada did document that Native American children from this region are susceptible to dental staining from tetracyclines (Rebich et al., 1983). One of the 6 studies did not provide complete data on either dosage or duration of doxycycline treatment (Lochary et al., 1998), both highly relevant variables. The only study involving premature infants had an insufficient duration of follow-up of only 1 year and did not include controls (Forti and Benincori, 1969). A second study similarly only evaluated teeth at up to 1 year of follow-up and also did not include control subjects (Poloczek, 1975). Therefore, both of these studies may have provided an incorrect assessment of the risk of dental staining. None of the studies evaluated dental staining in children exposed to doxycycline exclusively from breastfeeding.

In conclusion, whether doxycycline may cause permanent dental staining when prescribed for young children and pregnant women is unclear (Table 3) (Agwuh and MacGowan, 2006; Bridges et al., 1969; Cross et al., 2016; Cunha and Cunha, 2017; Eisen, 2010; Forti et al., 1967; Jaffe et al., 1974; Kowalewska et al., 1966; McIntosh and Storey, 1970; Nahum and Kennedy, 2006; Reeves et al., 2009; Schach von Wittenau, 1968; Swallow et al., 1967; Toaff and Ravid, 1963; Wallman and Hilton, 1962a, 1962b; Zegarelli et al., 1963), and if doxycycline should lead to dental staining, the exact frequency that this would occur is unknown. Until more definitive data are developed, doxycycline should continue to be only selectively prescribed for young children for whom alternative, safer antibiotics are not available, such as for children with Rocky Mountain spotted fever, a life-threatening infection that can often be successfully treated with just a 5–7-day course of doxycycline (Biggs et al., 2016). The risk to benefit ratio may also favor the use of doxycycline for young children with other infections as well (Committee on Infectious Diseases and American Academy of Pediatrics, 2018). To reduce the potential for dental staining, courses of treatment should be of as short a duration as possible.

Doxycycline treatment of young children with erythema migrans but without complicating factors (such as neurologic involvement, evidence of coinfection with *A. phagocytophilum*, or inability to tolerate oral beta lactam antibiotics), however, cannot be recommended based on available safety data. Rigorously conducted, additional studies in young children on the frequency of dental staining from doxycycline are needed to provide a more definitive assessment of the risk of this complication.

Table 3
Evaluation of whether doxycycline should be less likely than other tetracyclines to cause permanent dental staining.

Evidence	Limitations of evidence
Doxycycline is a semisynthetic derivative of oxytetracycline, and oxytetracycline is less likely to cause dental staining than other tetracyclines in some studies (Bridges et al., 1969; Kowalewska et al., 1966; McIntosh and Storey, 1970; Wallman and Hilton, 1962a, 1962b).	Evidence is inconsistent as to whether dental staining is less common from oxytetracycline (Swallow et al., 1967; Toaff and Ravid, 1963; Zegarelli et al., 1963).
Doxycycline binds to calcium less avidly than other tetracyclines (Schach von Wittenau, 1968).	Only limited published data to support this finding (Schach von Wittenau, 1968), and clearly doxycycline is able to bind calcium to some extent.
Doxycycline is less likely than other tetracyclines to cause dental staining in an animal system (McIntosh and Storey, 1970).	Clinical relevance of this animal study unclear.
Therapeutically effective blood levels of doxycycline require lower dosages than many other tetracyclines (Agwuh and MacGowan, 2006; Cross et al., 2016; Cunha and Cunha, 2017; Eisen, 2010).	Published pharmacokinetic data for all tetracyclines very limited in young children and pregnant women (Cross et al., 2016; Forti et al., 1967; Nahum and Kennedy, 2006; Reeves et al., 2009). Blood levels and other pertinent pharmacokinetic parameters of doxycycline and other tetracyclines have usually not been considered in studies on dental staining. For example, urinary pH affects the renal excretion of tetracyclines, which in turn affects the amount of antibiotic exposure. A relatively alkaline urinary pH (pH >6) increases oxytetracycline urinary excretion by 24% and by 54% for doxycycline (Cunha and Cunha, 2017; Jaffe et al., 1974).
Available clinical data show either low or no risk of dental staining (Forti and Benincori, 1969; Lochary et al., 1998; Poloczek, 1975; Poyhonen et al., 2017; Todd et al., 2015; Volovitz et al., 2007).	Data limited and no studies have included a direct comparison with other tetracyclines.

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