EH85415 Email submission from Dr Hand

From: Hand K. [redacted]
Sent: 17 August 2017 11:13
To: [redacted] (Chief operating officer, National Clinical Guideline Centre)
Subject: Antibiotics for children with Lyme disease

Dear [redacted], (Chief operating officer, National Clinical Guideline Centre)

Please forgive the delay in responding – your message arrived when I was on holiday and I am also juggling work for the NICE guidelines on managing common infections.

1. Anecdotally, doxycycline is used occasionally in the 8-12y age group in my experience, but I have not looked into the evidence myself and our local guidelines recommend a threshold of >12y in line with the EU licence.
2. I am aware of one study examining the impact of doxycycline on dental staining in children <8y (attached) but, whilst reassuring, no patient had longer than 10 days of doxycycline. This is a useful study however, summarising the background information on teeth staining resulting in the FDA warning not to use in children under 8 years of age. It doesn't consider any impact of doxycycline on bone development.

I have copied text below from a couple of standard reference sources. I would offer to carry out a literature search but NICE employs experts in literature searching who would do a much better job than I.

The text below is taken from Toxbase.

Tooth discolouration
Tetracyclines are incorporated into calcifying teeth and have been associated with discolouration of the teeth and hypoplasia of the enamel.[2, 24, 25] Calcification of deciduous teeth occurs from approximately 16 weeks gestation to 14 months of age and exposure to tetracyclines during this period results in staining of the dentine and enamel.[26] During the third trimester exposure to 1g/day tetracycline for three days can produce grey-brown, yellow, or brown staining of deciduous teeth.[26] Permanent teeth are not affected by prenatal exposure to tetracycline as calcification does not begin until after birth.[26, 27]
Inhibition of bone growth
Tetracyclines are deposited in the calcifying bones and have been associated with inhibition of bone growth in preterm neonates and skeletal changes in animal reproductive toxicity studies.[2, 24] In the neonate, administration of tetracycline at either 7mg/kg or 25mg/kg every six hours for 9-12 days to 37 premature infants produced a transient 40% depression in skeletal growth rate that normalised once tetracycline was discontinued. No effect on bone growth was observed for control infants given neomycin.[28] While data do not demonstrate a long-term effect on bone growth, there are theoretical concerns that in utero exposure to tetracyclines may also be associated with effects on the developing bones.

24. Apgar, V., Drugs in Pregnancy. JAMA, 1964. 190: p. 840-1.
25. Toaff, R. and Ravid, R., Tetracyclines and the teeth. Lancet, 1966. 2(7457): p. 281-2.
26. Cohlan, S.Q., Tetracycline staining of teeth. Teratology, 1977. 15(1): p. 127-9.
27. Anthony, J.R., Effect on deciduous and permanent teeth of tetracycline deposition in utero.

Postgrad Med, 1970. 48(4): p. 165-8.
28. Cohlan, S.Q., Bevelander, G., and Tiamsic, T., Growth inhibition of prematures receiving tetracycline. Am J Dis Child, 1963. 105

The text below is taken from Kucers standard textbook: the Use of Antibiotics (6th edition, online e-book).

4b. Newborn infants and children

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 bid.

Shetty AK. Tetracyclines in pediatrics revisited. Clin Pediatr (Phila). 2002 May;41(4):203-9. PubMed PMID: 12041715.

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**).

Dumler JS, Madigan JE, Pusterla N, Bakken JS. Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment. Clin Infect Dis.
2007 Jul 15;45 Suppl 1:S45-51. Review. PubMed PMID: 17582569.

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**).

Walker DH. Rocky Mountain spotted fever: a seasonal alert. Clin Infect Dis. 1995 May;20(5):1111-7. Review. PubMed PMID: 7619984

Yagupsky P, Gross EM, Alkan M, Bearman JE. Comparison of two dosage schedules
of doxycycline in children with rickettsial spotted fever. J Infect Dis. 1987
Jun;155(6):1215-9. PubMed PMID: 3572036.

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**).

Mwengee W, Butler T, Mgema S, Mhina G, Almasi Y, Bradley C, Formanik JB, Rochester CG. Treatment of plague with gentamicin or doxycycline in a randomized
clinical trial in Tanzania. Clin Infect Dis. 2006 Mar 1;42(5):614-21. Epub 2006
Jan 25. PubMed PMID: 16447105.

I hope this is somewhat helpful but it is far from a systematic literature search.

Best wishes,

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