

Is Single-dose Ceftriaxone the best treatment for Ophthalmia Neonatorum in a Resource Poor Setting?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What are appropriate first-line antibiotics for septicemia in children in developing countries?*

The **WHO Pocketbook of Hospital Care for Children** states that severe conjunctivitis (a lot of pus and/or swelling of the eyelids) is often due to gonococcus. Wash the eyes to clear as much pus as possible.

► Ceftriaxone (50 mg/kg up to total of 150 mg IM ONCE)

OR

► Kanamycin (25 mg/kg up to total of 75 mg IM ONCE).

ALSO use as described above:

► Oxytetracycline eye ointment OR

► Chloramphenicol eye ointment (Pocketbook chapter 3.12.2, page 59).

Introduction:

Ophthalmia Neonatorum (ON) is a purulent eye infection affecting neonates in the first weeks of life. It is caused by a variety of different organisms that are usually acquired from the maternal genital tract during birth but may be acquired postnatally. The condition is potentially sight threatening and can progress to neonatal

sepsis and death. The risk of developing ON and its sequelae has been addressed by two different approaches; prophylaxis of all newborn infants using disinfectant or antibiotic preparations versus treatment of affected neonates with topical or systemic antibiotics.

The prevalence of different organisms responsible for ON varies across the world. Globally, *Neisseria gonorrhoea* and *Chlamydia trachomatis* are the most significant causes due to prevalence of infection and potential for sequelae in infected cases. ON due to *Neisseria gonorrhoea* can progress rapidly and result in corneal ulceration with loss of sight and neonatal sepsis. ON due to *Chlamydia* can be complicated by corneal scarring and later respiratory disease. Rates of *Neisseria gonorrhoea* genital infection in pregnant women in Africa have been estimated to range from 7.5 to 14% (1, 2). Rates of *Chlamydia trachomatis* genital infection in pregnant women in Africa have been estimated to range from 6.9 to 29% (3) (1). Co-infection rates are estimated to be around 2%. (1) Maternal transmission of disease at delivery is multifactorial and high in a resource poor setting. (1). With both organisms, extraocular colonisation (particularly pharyngeal) is common (1). Other organisms implicated in ON are *Staphylococcus aureus*, *Neisseria meningitidis* and Group B *Streptococcus*.

Diagnosis of gonorrhoeal and chlamydial infections in studies in resource poor settings has relied on culture of *N. gonorrhoeae* and culture or direct fluorescent antibody identification of *C. trachomatis*. Testing for these pathogens using DNA detection techniques is recognised as being superior to culture and DFA assays and has increased sensitivity of gonorrhoea and chlamydia diagnosis in developed countries (4) (5). In resource poor settings, microbiological

screening of pregnant women for genital infections and microbiological testing of neonates presenting with ophthalmic infections is cost and resource prohibitive. Any recommended treatment for ON in this setting needs to be empiric and effective against the most likely organisms. Therefore, this review will focus on treatment of ON due to Chlamydia and Gonorrhoea.

Prenatal treatment for ON due to Chlamydia or Gonorrhoea

Because the causative organism for ON is usually acquired from the mother's genital tract during the birthing process, some studies have looked at treatment of infected mothers pre-delivery. A recent Cochrane review "Antibiotics for gonorrhoea in pregnancy" concluded that single therapy with Amoxicillin (with probenecid) or Ceftriaxone was safe and effective at delivering 'microbiological cure' for Gonorrhoea in the mother (6). This review identified no studies that assessed neonatal outcomes post maternal treatment for gonorrhoea. With regard to Chlamydia, the Cochrane Review "Interventions for treating genital Chlamydia trachomatis infection in pregnancy" concluded that single therapy with Amoxicillin or Erythromycin was safe and resulted in 'microbiological cure' for Chlamydia in the mother (7). Erythromycin was less well tolerated by the mother due to nausea and vomiting. This review identified only one study assessing neonatal outcomes for maternally treated Chlamydia. In this study, 'microbiological cure' was demonstrated in 152 neonates where the mothers were treated with either Amoxicillin or Erythromycin for 7 days. Swabs were taken from neonates' eyes, nose, pharynx, rectum and genitals for Chlamydia culture at one week of age and all were negative. There was no other outcome data for neonates in any of the studies reviewed.

It is not clear whether or not 'microbiological cure' in the mother or neonate correlates well with absence of neonatal disease. Potential for reinfection of the mother post treatment is significant if sexual partners are not concurrently treated.

Prophylaxis of ON and topical agents

Prophylaxis of ON is well described using a variety of topical agents. Prophylaxis

programmes are only cost effective in settings where the rate of maternal infection with *Neisseria gonorrhoea* and *Chlamydia trachomatis* is high. Adherence to and coverage of prophylaxis regimes is variable and health policy changeable so that global coverage of all infants at risk is unlikely to be achieved. Although several agents have been shown to be effective at eradicating the organisms from infants' eyes and preventing clinical progression to ON, there are problems with each method. First introduced in 1881, Crede's prophylaxis with 1% silver nitrate has been shown to cause chemical conjunctivitis in almost half of the infants. Prophylaxis with 1% Tetracycline ointment has been poorly adhered to in one study because it was considered "messy" by nursing staff. (8) More recently 2.5% povidone-iodine has been shown to be at least as effective as 1% silver nitrate and 0.5% erythromycin ointments. However, as demonstrated in Kenya, there is a significant failure rate with each method with a 0.4 to 0.8% incidence of gonococcal ON and a 5-10% incidence of chlamydial ON post prophylaxis with 2.5% povidone-iodine, 1% silver nitrate or 0.5% erythromycin ointment. (9)

Topical prophylaxis does not address the issue of extraocular carriage of organisms and potential serious sequelae of ON. There is a wide cost variation with the different prophylactic agents and health authorities need to consider whether prophylactic treatment is more cost and resource effective than identification and treatment of subsequent cases (9) (10).

Beta-lactams in sexually transmitted disease

Antimicrobial resistance to penicillin is widespread for various strains of *Neisseria gonorrhoea*. There is both chromosomally mediated penicillin resistance and resistance due to penicillinase (β -lactamase) producing *N. gonorrhoeae* (PPNG) (11). Penicillinase production is both chromosomally and plasmid mediated. Across Africa, rates of PPNG in ON range from 18 to 57% (12) (1) (13) (14). Treatment of genital or neonatal gonorrhoeal infections due to PPNG with penicillin is usually ineffective. Ceftriaxone demonstrates high in vitro activity against both PPNG and non-PPNG, with a low minimal inhibitory concentration (MIC) for resistant and non-resistant *Neisseria gonorrhoea* strains. Cefotaxime has a similar profile except that it has a shorter half-life than Ceftriaxone. Serum levels after a single adult

dose of Ceftriaxone 500mg IMI peak at up to 10000 times the MIC. This effect is sustained with levels still 1000 times the MIC at 24 hours post dose (11).

Beta-lactam antibiotics have a variable inhibitory effect on Chlamydia trachomatis. In in vitro studies, Ceftriaxone only has modest effect against C. trachomatis (11). Adult treatment regimes for urethritis using doses greater than 125mg have demonstrated a low incidence of post-gonococcal (presumed Chlamydial) urethritis. Amoxicillin demonstrates better in vitro activity but still cannot be recommended as primary treatment for Chlamydial infections (11).

Current treatment recommendations

Current WHO guidelines for the management of sexually transmitted infections recommends that all cases of ON be treated for both N. gonorrhoeae and C. trachomatis (15). Recommended treatments are as follows:

For ON due to N. gonorrhoeae

Ceftriaxone 50mg /kg IMI as a single dose (maximum 125mg). Alternative medications where Ceftriaxone is unavailable include Kanamycin 25mg/kg (maximum 75mg) as a single IMI dose or Spectinomycin 25mg/kg (maximum 75mg) as a single IMI dose

For ON due to C. trachomatis

Erythromycin orally at a dose of 50mg/kg/day in 4 divided doses for 14 days or Trimethoprim 40mg with sulphamethoxazole 200mg orally twice daily for 14 days.

This recommendation varies from advice given in the current “Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources” which does not mention concurrent infection with C trachomatis and advises systemic treatment with Ceftriaxone or Kanamycin together with topical tetracycline or chloramphenicol ointment (16).

Current WHO guidelines for the treatment of adult genital infection with Chlamydia trachomatis recommends using Doxycycline 100mg orally twice daily for 7 days or Azithromycin 1gm orally as a single dose (15). Single dose Azithromycin is a possible alternative to treatment with Erythromycin for neonates with ON due to Chlamydia trachomatis. Studies in trachoma endemic areas have shown a significant reduction in trachoma disease burden using

community treatments with single dose or 3 daily dose Azithromycin (17) (18). There is limited data suggesting that it is safe in pregnant women and neonates (19) (20) (21). Although microbiological cures rates are high in pregnant mothers when using single dose Azithromycin compared to a course of Erythromycin, this may not translate to lower rates of infection in their neonates (20).

Side effect profiles of these medications are varied. Ceftriaxone has a broad therapeutic range with a low incidence of allergic reactions. Kanamycin can potentially cause renal impairment and hearing loss. Spectinomycin also may cause renal impairment. Both Kanamycin and Spectinomycin may rarely cause neuromuscular blockade. Erythromycin in large sustained doses is frequently poorly tolerated due to nausea and vomiting and has potential to cause cardiac arrhythmias. Trimethoprim/Sulphamethoxazole has the potential to exacerbate neonatal jaundice and rarely causes severe allergic reactions and bone marrow suppression.

Cost

Cost estimates for various treatment regimes vary according to the country, company supplying the drug and procuring agent (22). Current cost estimates for Ceftriaxone are between US\$ 0.39-3 for a single vial (250mg), compared to Kanamycin which costs between US\$ 0.16 and 0.4 per 1g vial. Cost estimates for a course of Erythromycin to treat a 3kg baby for 2 weeks range between US\$ 1-1.20. Price estimates for a single dose of Azithromycin at 20mg/kg for a 3kg baby range between US\$0.08 and 0.74 per treatment.

Methodology

The search strategy used was that of Haynes et al “Clinical Queries” in Pubmed. The search strategy utilized the Search by Clinical Category option identified therapy and used a broad search option as follows: (ophthalmia neonatorum or ophthalmia neonatorum) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

The search generated 343 abstracts with 219 remaining after limiting to English language and human studies. All 219 abstracts were read and 17 studies were identified with relevance to the topic. Studies were selected for review if they were conducted in developing countries and described the microbiological profile of ON and/or compared different antibiotic regimes for treatment of ON. Only 6 of the 17 studies met the review criteria. A further 6 relevant studies for review were identified by reviewing references of the 17 identified studies.

Results

Twelve studies were identified for review and the complete article sourced. Study aims and outcomes are summarised in the table. Ten studies were conducted in Africa and the remaining two studies were conducted in India. Two studies assessed the effectiveness of single dose IM Ceftriaxone in treating gonococcal ON (23,24). Two studies assessed the effectiveness of single dose Cefotaxime in treating gonococcal ON (25,26). Two studies assessed effectiveness of single dose IM Kanamycin together with different topical agents in treating gonococcal ON (12,14). Only one study compared single dose IM Ceftriaxone with single dose IM Kanamycin in treating gonococcal ON (27). The remaining 5 studies described prevalence and sensitivity of organisms responsible for ON in developing settings (1,13,28,29,30). None of the studies reported adverse events or side effects associated with treatment.

Microbiological profile

The large prospective study by Laga in Kenya (1) demonstrated that prevalence rates of *Neisseria gonorrhoea* and *Chlamydia trachomatis* in birthing mothers was 7 and 29% respectively with concurrent infection with both organisms in 2%. Transmission rates of *Neisseria gonorrhoea* and *Chlamydia trachomatis* from infected mothers to their infants' eyes were 42 and 31% respectively. Maternal to infant pharynx transmission rates for *Neisseria gonorrhoea* and *Chlamydia trachomatis* were 7 and 2% respectively. The studies overall demonstrated variable rates of *Neisseria gonorrhoea* and *Chlamydia trachomatis* infection amongst infants with ON. Poor tolerance or non-availability of Chlamydial testing (by conjunctival scraping) reduced *Chlamydia* identification rates in some studies (28,30). Rates

of *Neisseria gonorrhoea* and *Chlamydia trachomatis* eye infection in infants presenting with ON ranged from 0 to 43% for *Neisseria gonorrhoea* and 0 to 31% for *Chlamydia trachomatis*. Low rates of both *Neisseria gonorrhoea* and *Chlamydia trachomatis* were found in the two Indian studies (28,29). Across the studies, rates of concomitant *Neisseria gonorrhoea* and *Chlamydia trachomatis* infection in infants presenting with ON ranged from 3 to 15%. (1,13,28,29,30). Rates of PPNG in gonococcal isolates ranged from 18 to 52% in studies with $n > 100$ (1,13,30).

Single dose Ceftriaxone/ Cefotaxime for ON due to *Neisseria gonorrhoea*

Studies using Ceftriaxone and Cefotaxime were considered together as these drugs have very similar dosage and antibacterial profiles (23,24,25,26).

The four studies assessing effectiveness of Ceftriaxone/ Cefotaxime single dose therapy for treatment of ON included only cases of ON due to *Neisseria gonorrhoea*. Haase (23) required gram negative intracellular diplococci (GNICDC) on gram stain of eye discharge and the remaining three studies only reviewed cases that grew *N. gonorrhoeae* from eye swabs. Case numbers ranged from 7 to 21 per study. Haase (23) and Hoosen (24) used single-dose therapy with Ceftriaxone at a dose of 125mg and 62.5mg respectively. The two studies by Lepage (25,26) used Cefotaxime at a dose of 100mg/kg. The later study by Lepage (26) involved only 21 patients and included the nine patients from his earlier study (25). In the same study three of 21 cases were treated with more than one dose of Cefotaxime and three patients were over one year of age. Only one infant was lost to follow up (23). Microbiological cure rate (as demonstrated by repeat swab culture) for ON due to *Neisseria gonorrhoeae* was 100% in 6/6 infants (Haase, 23), 21/21 infants (Hoosen, 24), and 9/9 infants (Lepage, 25). Clinical cure (but not microbiological cure) was demonstrated in 19/19 treated with single dose Cefotaxime (Lepage, 26) and microbiological cure in 5/5 tested in that series.

Post gonococcal ON was not reported in Lepage's two studies (25,26). Two infants in Haase's study (23) and 7 infants in Hoosen's study (4) were identified at time of screening as having concomitant *C. trachomatis* and were treated with 7 to 14 days of Erythromycin at a dose of

20mg/kg QID. There is no outcome data relating to Chlamydial cure rates in either study. Overall, PPNG rate in these studies was 10% to >60% (23,24,25,26).

Single dose Kanamycin for ON due to Neisseria gonorrhoea

Two studies reviewed effectiveness of single dose Kanamycin together with different topical eye regimes (saline, gentamicin ointment, chloramphenicol ointment) (12,14). Cases were infants with GNICDC on eye swab (14) or proven *N. gonorrhoeae* on swab culture. (12) The number of cases in the two studies was 117 (divided into 3 arms) and 219 respectively. Kanamycin doses used were 75mg, 100mg and 150mg IMI. There were significant failures in treatment for the two lower doses of Kanamycin in combination with saline eye washes. One baby (1/117) treated with 75mg Kanamycin and saline washes developed corneal ulceration and sepsis (14). Three of 219 babies treated with 100mg Kanamycin and saline irrigation were still culture positive for *N. gonorrhoeae* on day three (12).

Rates of post gonococcal ON in both studies were approximately 10%. Of 117 infants with GNICDC on eye swab gram stain, 13 had concomitant infection with *Chlamydia trachomatis* as demonstrated by culture (14). In the other study, 22 of 219 infants with culture proven *Neisseria gonorrhoeae* developed post-gonococcal ON (presumed chlamydial) and were treated with oral Erythromycin and Tetracycline ointment (12). Outcomes were not reported for infants with chlamydial infections. PPNG rates varied between 18 and 25%.

Single dose Ceftriaxone compared to single dose Kanamycin for ON due to Neisseria gonorrhoea

Only one study compared effectiveness of single dose Ceftriaxone with single dose Kanamycin in combination with topical gentamicin or tetracycline in the treatment of ON due to *N. gonorrhoea* (27). This was a randomised non-blinded trial with 122 participants and 61 cases randomised to either Ceftriaxone or Kanamycin. Cases were identified by purulent eye discharge and GNICDC on eye swab. Seventeen patients were lost to follow-up. Three infants treated with Kanamycin had persistent *N. gonorrhoeae* on culture of eye swab compared to none of 61 infants treated with Ceftriaxone.

Nearly 15% of cases had concomitant infection with *C. trachomatis*. Outcomes were not reported for these infants with chlamydial infection. PPNG rates were 28%.

Treatment of ON due to Chlamydia trachomatis

None of the studies reviewed directly assessed treatment outcomes for infants with ON due to concomitant infections with *Neisseria gonorrhoea* and *Chlamydia trachomatis*. In several studies, Erythromycin was used to treat ON due to both proven and presumed (post-gonococcal) *Chlamydia trachomatis* in high doses of 20mg/kg/dose QID for 7 to 14 days (12,23,24,30). The studies reviewed did not assess compliance with or side effects of Erythromycin treatment. Nor did they assess cure rates for ON due to *C. trachomatis*.

Summary

Studies assessing effectiveness of single dose Ceftriaxone in the treatment of ON in resource poor settings are few and case numbers are small. None of the studies identified utilise more sensitive diagnostic techniques for identification infection due to *Neisseria gonorrhoea* and *Chlamydia trachomatis*. The few clinical studies reviewed suggest that single dose Ceftriaxone at doses as low as 62.5mg were effective in treating ON due to *Neisseria gonorrhoeae* and may be superior to Kanamycin. This conclusion is reinforced when combined with data from other studies that show high efficacy in treating adult gonorrhoeal infections and consistent in vitro efficacy for Ceftriaxone against *N. gonorrhoeae*.

In the studies reviewed, rates of eye infection with *C. trachomatis* both demonstrated by microbiological testing and presumed because of post-gonococcal conjunctivitis were high. None of the studies directly assessed effectiveness of Ceftriaxone in treating ON due to *Chlamydia trachomatis*. When combined with data from in vitro studies showing only modest efficacy of Ceftriaxone against *C. trachomatis*, Ceftriaxone cannot be recommended for the treatment of ON due to *Chlamydia trachomatis*.

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