A CONTROLLED TRIAL OF POVIDONE–IODINE AS PROPHYLAXIS AGAINST OPHTHALMIA NEONATORUM

SHERWIN J. ISENBERG, M.D., LEONARD APT, M.D., AND MARK WOOD, M.D.

Abstract *Background.* Neonatal conjunctivitis (ophthalmia neonatorum) continues to cause blindness, because the agents used prophylactically to prevent this condition are not completely effective and are not widely available in many parts of the world. Povidone–iodine ophthalmic solution is an effective antibacterial agent with broad antibacterial and antiviral activity to which no bacteria are known to be resistant, and it is far less expensive and less toxic than the agents currently used to prevent neonatal conjunctivitis.

Methods. We conducted a masked, prospective trial involving 3117 infants born over a period of 30 months in a hospital in Kenya. Shortly after birth each infant received a 2.5 percent solution of povidone–iodine (n = 1076), a 1 percent solution of silver nitrate (n = 929), or 0.5 percent erythromycin ointment (n = 1112) in both eyes. Randomization was achieved by rotating the three medications after each was used for a week.

Results. Of the neonates treated with povidone–iodine, 13.1 percent had infectious conjunctivitis, as compared with 17.5 percent of those treated with silver nitrate ($P<0.001$) and 15.2 percent of those treated with erythromycin ($P = 0.01$). Povidone–iodine was more effective against *Chlamydia trachomatis* than was silver nitrate ($P<0.001$) or erythromycin ($P = 0.008$). There were 104 cases of noninfectious conjunctivitis (9.7 percent) in the povidone–iodine group, as compared with 129 in the silver nitrate group (13.9 percent, $P<0.001$) and 148 in the erythromycin group (13.3 percent, $P = 0.004$). Many cases of noninfectious conjunctivitis were probably due to a toxic reaction to the treatment itself. The incidence of *Neisseria gonorrhoeae* and *Staphylococcus aureus* infections was similar in the three groups.

Conclusions. A 2.5 percent ophthalmic solution of povidone–iodine as prophylaxis against ophthalmia neonatorum is more effective than treatment with silver nitrate or erythromycin, and it is less toxic and costs less. (N Engl J Med 1995;332:562-6.)

CONJUNCTIVITIS in the first month of life, known as ophthalmia neonatorum, can cause blindness. In Africa between 1000 and 4000 newborns are blinded by this disease annually.[1] The worldwide potential for blindness from neonatal conjunctivitis is enormous, since the incidence ranges from 1.6 percent or less (in the United States) to 23 percent among the 80 million babies born annually throughout the world.[2]

Ophthalmia neonatorum was the main cause of childhood blindness in 19th-century Europe, but treatment with an instillation of silver nitrate solution on the conjunctiva at birth reduced the incidence by a factor of 20 to 30.[3] This innovation may be the single greatest advance toward preventing blindness. Many centers have switched from silver nitrate to erythromycin or tetracycline preparations because of their allegedly superior activity against *Chlamydia trachomatis* and their lower toxicity.[4] Today, some form of prophylaxis is legally required in the United States and in many other countries.

Povidone–iodine has many potential advantages over the two currently used drugs, including a broader antibacterial spectrum. In a concentration as low as 0.1 percent, povidone–iodine is effective against *Neisseria gonorrhoeae;* in a concentration as low as 1 percent it is effective against *C. trachomatis*[5]; and in a concentration of 0.5 percent or lower its antiviral spectrum includes the human immunodeficiency virus and herpes simplex virus.[5,6] Povidone–iodine turns the surface of the eye brown for a few minutes, a characteristic that can serve as an indicator that it has been properly applied. The possibility of misapplication is greater with the other two agents because they are colorless. With povidone–iodine, unlike antibiotics, bacterial resistance has not been encountered. Finally, it is cheaper than the other agents (Table 1). In many developing countries, where ophthalmia neonatorum is most common, no prophylaxis is used, mainly because of the expense and lack of availability.

Povidone–iodine was more effective than silver nitrate or erythromycin against the conjunctival bacteria found in 100 healthy newborns in California and was less toxic than silver nitrate.[7] No previous study, however, has investigated the relative efficacy of all three drugs as prophylaxis against ophthalmia neonatorum. We chose Kenya as the site of a study examining the ability of povidone–iodine ophthalmic solution to prevent ophthalmia neonatorum because the frequency of the disease there is as high as 23.2 percent when no prophylaxis is used.[2,8] In a masked fashion, we compared the incidence and type of conjunctivitis in neonates after the application of povidone–iodine, silver nitrate, or erythromycin.

METHODS

Patients

The protocol was reviewed and approved by the Human Subjects Committee of the Harbor–UCLA Medical Center and the Ministry of Health of Kenya. All babies born at the Presbyterian Church Hospital in Kikuyu, Kenya, from March 1991 through August 1993 were candidates for the study. Infants were excluded if they had any obvious ocular malformations, the mother had received antibiotics during the last month of pregnancy, or the mother was unable to bring the infant back to the hospital in the event that conjunctivitis developed. Verbal consent was obtained from each child's mother.[9]

All infants in the study received one of three ophthalmic prepara-

From the Department of Ophthalmology, Jules Stein Eye Institute, Harbor–UCLA Medical Center, UCLA School of Medicine, Los Angeles and Torrance, Calif. (S.J.I., L.A.); and the Eye Department, Presbyterian Church Hospital, Kikuyu, Kenya (M.W.). Address reprint requests to Dr. Isenberg at the Jules Stein Eye Institute, UCLA School of Medicine, 100 Stein Plaza, Los Angeles, CA 90024-7001.

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tions in both eyes within 20 minutes of birth, after the eyes and face were cleaned: a drop of 2.5 percent povidone–iodine solution, a 1-cm strip of 0.5 percent erythromycin ophthalmic ointment, or a drop of 1 percent silver nitrate ophthalmic solution. The three medications were rotated after each was used for a week in the maternity unit. Thus, each infant was assigned to receive a drug according to the week of birth. This allocation system was easier to use in a busy maternity unit in a developing country, resulting in less confusion and possible misallocation, than a strict randomization of infants. Each mother was shown pictures of inflamed eyes and instructed to return to the hospital with her infant if the child's eye began to have a discharge or became red within a month of birth. The instructions were the same regardless of the allocation group.

Specimen Collection

Infants returning with conjunctivitis were taken to the clinical laboratory of the Nairobi Hospital for microbiologic analysis of the inflamed eyes. Because the cultures were plated at the laboratory, no transport mediums were necessary. Conjunctival specimens obtained for detection of bacteria were inoculated immediately onto plates containing blood and Thayer–Martin medium, the inocula were streaked across the plates to promote isolation of the bacteria, and the plates were incubated in an atmosphere of 5 to 10 percent carbon dioxide at 35°C for 24 to 48 hours. Cultured organisms were identified by standard procedures. Two smears were made, stained with Gram's and Giemsa stains, and observed for *C. trachomatis* inclusions and bacteria. For direct fluorescent-antibody assay for *C. trachomatis,* specimens were collected, fixed, stained with fluorescein-conjugated monoclonal antibody (Syva Microtrak, Palo Alto, Calif.), and observed for elementary bodies. The laboratory technicians had no knowledge of which prophylactic ocular medication was given to any particular infant.

Statistical Analysis

Logistic regression was used to determine the effect of the medications on the risk of infection. The infants with conjunctivitis were grouped according to the results of the bacteriologic culture and direct fluorescent-antibody assay as having infection with *C. trachomatis,* all bacteria under study, coagulase-negative staphylococci, *Staphylococcus aureus,* or *N. gonorrhoeae*. The infants were considered to have noninfectious conjunctivitis if no organisms were cultured. Each group was compared with the group of infants with no inflammation. The model included sex and the presence or absence of prenatal care, maternal vaginal infection, and birth in an unhygienic environment (indicated by the presence of meconium, among other factors) as covariates.

Results

The characteristics of the 3117 newborns according to treatment group are presented in Table 2. The risk factors were distributed evenly across the groups. Table 3 shows the distribution and percentages of infants with infectious and noninfectious conjunctivitis. The most frequently identified organism was *C. trachomatis* (found in 50.5 percent of all infected infants), and *S. aureus* was the second most common (found in 39.7 percent of all infected infants). *N. gonorrhoeae* was cultured in 5 percent of all infected infants. Table 4 shows the distribution of the risk factors according to the development of conjunctivitis.

Logistic-regression analysis revealed that there were more infections in the silver nitrate and erythromycin groups than in the povidone–iodine group ($P<0.001$ and $P=0.001$, respectively) (Table 5). Table 5 also shows that the incidence of maternal infection and the absence of prenatal care were significantly higher among the infected infants. Newborns treated with silver nitrate had an overall rate of infection that was 34 percent higher than that among the infants treated with povidone–iodine, and newborns receiving erythromycin had an overall infection rate that was 16 percent higher than that among the infants treated with povidone–iodine (Table 3).

Table 1. Cost in Kenya of a 5-ml Container of Agents Used for Prophylaxis against Ophthalmia Neonatorum.

Medication	Cost (U.S. Dollars)
Povidone–iodine	0.10
Tetracycline	0.31
Erythromycin	0.74
Silver nitrate	7.30

There were fewer infections with *C. trachomatis* in the povidone–iodine group than in either the silver nitrate group ($P<0.001$) or the erythromycin group ($P=0.008$). Infants treated with silver nitrate had more chlamydial infections than infants given erythromycin ($P=0.01$). Newborns treated with silver nitrate had a rate of chlamydial infections that was 92.5 percent higher than that among infants treated with povidone–iodine, and neonates receiving erythromycin had a rate of chlamydial infections that was 34.5 percent higher than that among the infants given povidone–iodine.

Fewer infections with coagulase-negative staphylococci were seen in the povidone–iodine group than in the erythromycin group ($P=0.01$), but the rate was virtually identical to that in the group given silver nitrate. With respect to infections caused by *S. aureus* or *N. gonorrhoeae,* no difference in effectiveness was found among the three agents. The povidone–iodine group had fewer cases of noninfectious conjunctivitis than either the silver nitrate group ($P<0.001$) or the erythromycin group ($P=0.004$).

Babies whose mothers had infections had more bacterial infections overall ($P=0.009$), as shown in Table 5, and more gonococcal infections in particular ($P<0.001$). Female infants had marginally more *S. aureus* infections than male infants ($P=0.045$). No significant difference in the frequency or type of infection was seen whether the infant was delivered vaginally or

Table 2. Characteristics of the Treatment Groups.

Characteristic	Povidone–Iodine (N = 1076)	Erythromycin (N = 1112)	Silver Nitrate (N = 929)	Total (N = 3117)
	number (percent)			
Female sex	486 (45)	535 (48)	431 (46)	1452 (47)
Birth by cesarean section	82 (8)	68 (6)	50 (5)	200 (6)
Mother received no prenatal care	1009 (94)	950 (85)	768 (83)	2727 (87)
Born to a mother with vaginal infection	12 (1.1)	12 (1.1)	2 (0.2)	26 (0.8)
Birth in an unhygienic environment	19 (1.8)	24 (2.2)	15 (1.6)	58 (1.9)

Table 3. Distribution of Types of Conjunctivitis among the Infants According to Treatment Group.

Variable	Povidone–Iodine (N = 1076)	Erythromycin (N = 1112)	Silver Nitrate (N = 929)	Total (N = 3117)
	number (percent)			
Infectious conjunctivitis*	141 (13.1)	169 (15.2)†	163 (17.5)‡	473 (15.2)
C. trachomatis	59 (5.5)	82 (7.4)	98 (10.5)	239 (7.7)
N. gonorrhoeae	9 (0.8)	11 (1.0)	4 (0.4)	24 (0.8)
S. aureus	66 (6.1)	59 (5.3)	63 (6.8)	188 (6.0)
Coagulase-negative staphylococci	15 (1.4)	28 (2.5)	14 (1.5)	57 (1.8)
Gram-negative bacteria	17 (1.6)	11 (1.0)	3 (0.3)	31 (1.0)
Noninfectious conjunctivitis§	104 (9.7)	148 (13.3)	129 (13.9)	381 (12.2)
Positive cultures*	166	191	182	539
Microorganisms per infected infant	1.18	1.13	1.12	1.14¶

*The infants may have had more than one type of infection.

†P = 0.01 for the comparison with povidone–iodine treatment.

‡P <0.001 for the comparison with povidone–iodine treatment.

§Many of these cases may represent toxic or chemical conjunctivitis.

¶The number is the average of the three values.

by cesarean section. Infants born in an unhygienic environment had a greater incidence of infections with coagulase-negative staphylococci than those born in a hygienic environment (P = 0.002).

Discussion

We undertook this test of the effectiveness of povidone–iodine as prophylaxis against ophthalmia neonatorum for two reasons. First, there is an increasing recognition of the inadequacy of the commonly used agents. When used prophylactically, topical erythromycin has a failure rate of 7 to 19.5 percent.[10] Ophthalmia neonatorum has been reported more often after erythromycin prophylaxis than after silver nitrate treatment[11] and more often after silver nitrate treatment than after tetracycline treatment (P<0.05).[12] Prophylaxis with erythromycin has resulted in outbreaks of erythromycin-resistant staphylococcal conjunctivitis in neonates.[13] Since the most dreaded pathogen of ophthalmia neonatorum is *N. gonorrhoeae,* the many reports of tetracycline resistance from such countries as the United Kingdom,[14] the Netherlands,[15] and the United States[16] are alarming. Tetracycline is no longer recommended as first-line therapy for gonococcal infections.[17] Ophthalmia neonatorum has occurred after the use of silver nitrate.[18,19] In addition, silver nitrate causes a serious toxic conjunctivitis, which may impede infant–mother bonding,[20] far more frequently than erythromycin or povidone–iodine.[7]

Table 4. Distribution of Risk Factors According to the Development of Conjunctivitis.

Type of Conjunctivitis	No. of Infants	Female Infant	Mother Received No Prenatal Care	Born to a Mother with Vaginal Infection	Birth in Unhygienic Environment
			number (percent)		
No conjunctivitis	2263	1034 (46)	1899 (84)	13 (0.6)	39 (1.7)
Culture-positive conjunctivitis*	473	232 (49)	455 (96)	8 (1.7)	11 (2.3)
Culture-negative conjunctivitis*	381	186 (49)	373 (98)	5 (1.3)	8 (2.1)

*Culture results also indicate the result of a direct fluorescent-antibody test for chlamydia.

The second reason to study povidone–iodine as prophylaxis against ophthalmia neonatorum is that its antibacterial spectrum exceeds that of any of the other agents. True bacterial resistance to povidone–iodine, unlike the other agents, has not been demonstrated.[21] In a controlled clinical trial of povidone–iodine given before ocular surgery, we showed that the application of a 5 percent solution reduced the number of bacterial colony-forming units by 91 percent and the number of species by 50 percent.[22] Subsequently, Speaker and Menikoff, using this ophthalmic solution preoperatively in 3489 adults undergoing cataract surgery, found that the incidence of postoperative endophthalmitis was significantly reduced.[23] In none of the thousands of patients treated by us and mentioned in the report of Speaker and Menikoff did this solution cause a discernible toxic or allergic reaction.

In a pilot study, we determined that a 2.5 percent solution of povidone–iodine was not irritating to the sensitive eyes of neonates, whereas the 5.0 percent solution that we had used in previous studies occasionally produced some conjunctival hyperemia. We then studied the antibacterial effect of a 2.5 percent solution of povidone–iodine on the eyes of 100 newborns in California.[7] Although both povidone–iodine and silver nitrate significantly reduced the number of both bacterial colony-forming units and species, povidone–iodine caused a greater decrease.[7] As compared with erythromycin, povidone–iodine caused a greater reduction in the number of colony-forming units (P<0.05) and in the number of bacterial species (P<0.002). Twenty-four hours after birth, there were more serious toxic reactions to silver nitrate than to povidone–iodine (P<0.001). Encouraged by these results, we decided to use the 2.5 percent concentration in the Kenyan trial.

Povidone–iodine is also active against viruses, including herpes simplex. Herpetic keratoconjunctivitis can be an insidious infection. Fifty to 70 percent of neonates with herpes simplex are born to mothers with no history of genital herpes infection.[24] Although only 2 percent of cases of ophthalmia neonatorum are caused by herpes,[25] 17 percent of newborns with herpes simplex virus will have ocular involvement.[26] Benevento and associates showed povidone–iodine to be effective in a concentration as low as 0.1 percent against a challenge of 10 million plaque-forming units of herpes simplex virus type II.[5]

A final but important factor favoring the use of povidone–iodine is cost. Many hospitals in developing countries cannot afford to purchase the currently used medications, but povidone–iodine ophthalmic solution can be manufactured from powder available to pharmacies

Table 5. Results of Logistic-Regression Analysis.

VARIABLE	ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE	SIMPLE ODDS RATIO
Silver nitrate (vs. povidone–iodine)	1.76	1.37–2.27	<0.001	1.51
Erythromycin (vs. povidone–iodine)	1.38	1.08–1.76	0.001	1.25
Sex (female vs. male)	1.17	0.96–1.43	0.13	1.14
No prenatal care	5.47	3.36–8.91	<0.001	4.85
Maternal vaginal infection	3.46	1.37–8.74	0.009	2.98
Birth in an unhygienic environment	1.37	0.68–2.77	0.37	1.36

worldwide. The price of povidone–iodine, at least in Kenya, ranges from 1.4 percent to 30 percent of the cost of the other agents (Table 1). Producing the solution locally minimizes cost and maximizes the possibility that the newborns will receive proper prophylaxis.

Despite the use of prophylactic agents, the incidence of ophthalmia neonatorum in the present study was 13.1 percent, 15.2 percent, and 17.6 percent after prophylaxis with povidone–iodine, erythromycin, and silver nitrate, respectively. Although high for the developed world, where the incidence generally is less than 2 percent, these rates are not high for developing countries. After silver nitrate prophylaxis, the incidence of ophthalmia neonatorum was 10.5 percent in Gabon[27] and 19.4 percent in Cameroon.[28] Our high rate of positive cultures may also result from our methods. In many previous studies specimens were transported to the laboratory for analysis, whereas in our study all specimens and cultures were collected and processed at the laboratory.

From the 23 percent incidence of ophthalmia neonatorum reported in a Kenyan population similar to the one we studied when prophylaxis was not used,[8] it can be estimated that the incidence of ophthalmia neonatorum is reduced 44 percent by prophylaxis with povidone–iodine, 34 percent by prophylaxis with erythromycin, and 24 percent by prophylaxis with silver nitrate. A recent American study found that, as compared with no treatment, erythromycin decreased the incidence of ophthalmia neonatorum by 31 percent and silver nitrate decreased it by 39 percent,[29] whereas a Taiwanese study found that silver nitrate reduced the incidence by 31 percent ($P<0.05$) and erythromycin did not cause a significant reduction.[30]

The most feared cause of ophthalmia neonatorum is *N. gonorrhoeae,* because it can quickly cause blindness.[31] Laga and colleagues reported that the incidence of gonococcal and chlamydial infections in Kenya was 2.8 percent and 7.3 percent, respectively, when no prophylaxis was used.[8] In our study, all three agents were equally effective against gonococcus; the frequency of gonococcal infections in the three groups ranged from 0.43 percent to 0.99 percent. The second most feared microorganism, *C. trachomatis,* may decrease vision as a result of corneal and conjunctival scarring, vascularization,[32] and the formation of pseudomembranes.[33] Significantly fewer cases of *C. trachomatis* infection occurred in infants receiving povidone–iodine than in those receiving either silver nitrate ($P<0.001$) or erythromycin ($P=0.008$). This benefit is especially important because the incidence of chlamydial infections is escalating.[34] Erythromycin and silver nitrate were not superior to povidone–iodine against any other bacteria encountered in the study.

By convention, ophthalmia neonatorum is defined as conjunctivitis arising within one month after birth. Thus, an infection could have originated at home within a few weeks after the infant was discharged from the hospital and still be considered ophthalmia neonatorum. This may explain why there was no difference among the three drugs in the proportion of infections produced by *S. aureus* (about 6 percent). Krohn and colleagues found that some apparent cases of ophthalmia neonatorum were actually acquired from the infants' nasopharyngeal passages or from their care givers after birth.[35]

Of the 3117 infants we studied, 12.2 percent had signs of ocular inflammation, but no growth on cultures and a negative chlamydial antibody test. Toxic conjunctivitis, a reaction to the prophylactic medication, is generally seen within 24 hours of the instillation of the drug and resolves without treatment. We could not distinguish between cases of true infection with no bacterial growth and cases of toxic conjunctivitis. The povidone–iodine group had fewer infants with no evidence of any organism than did the silver nitrate group ($P<0.001$) or the erythromycin group ($P=0.004$). Since in infants the ophthalmic solution of povidone–iodine is less toxic than silver nitrate ($P<0.001$),[7] we believe that many of the cases of noninfectious conjunctivitis represent toxic reactions.

Consistent with the report of Laga and associates,[8] the presence of maternal infection predisposed a baby to the development of conjunctivitis in general ($P=0.009$) and gonococcal conjunctivitis in particular ($P<0.001$). A lack of prenatal care was also associated with an increased incidence of conjunctivitis ($P<0.001$). Thus, health professionals should be especially cautious to administer prophylaxis properly to such babies and to those born in unhygienic environments, because of the greater incidence of infections with coagulase-negative staphylococci ($P=0.002$) in these situations.

In conclusion, prophylaxis with a 2.5 percent ophthalmic solution of povidone–iodine resulted in fewer cases of ophthalmia neonatorum overall and, notably, fewer cases of chlamydial conjunctivitis than did prophylactic treatment with either erythromycin or silver nitrate. In contrast to other prophylactic agents, which are colorless, povidone–iodine turns the surface of the eye brown, which indicates that the medication has been properly administered. Povidone–iodine is less expensive than the other drugs and can be prepared locally. For these reasons, povidone–iodine deserves serious consideration as prophylaxis against ophthalmia neonatorum, especially in developing countries.

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REFERENCES

1. Foster A. Childhood blindness. Eye 1988;2:Suppl:27-36.
2. Whitcher JP. Neonatal ophthalmia: have we advanced in the last 20 years? Int Ophthalmol Clin 1990;30:39-41.
3. Credé CSR. Die verhütung der augenentzündung der neugeborenen. Arch Gynaekol 1881;18:367-70.
4. Christian JR. Comparison of ocular reactions with the use of silver nitrate and erythromycin ointment in ophthalmia neonatorum prophylaxis. J Pediatr 1960;57:55-60.
5. Benevento WJ, Murray P, Reed CA, Pepose JS. The sensitivity of Neisseria gonorrhoeae, Chlamydia trachomatis, and herpes simplex type II to disinfection with povidone–iodine. Am J Ophthalmol 1990;109:329-33.
6. Harbison MA, Hammer SM. Inactivation of human immunodeficiency virus by Betadine products and chlorhexidine. J Acquir Immun Defic Syndr 1989; 2:16-20.
7. Isenberg SJ, Apt L, Yoshimori R, Leake RD, Rich R. Povidone-iodine for ophthalmia neonatorum prophylaxis. Am J Ophthalmol 1994;118:701-6.
8. Laga M, Plummer FA, Nzanze H, et al. Epidemiology of ophthalmia neonatorum in Kenya. Lancet 1986;2:1145-9.
9. IJsselmuiden CB, Faden RR. Research and informed consent in Africa — another look. N Engl J Med 1992;326:830-4.
10. Black-Payne C, Bocchini JA Jr, Cedotal C. Failure of erythromycin ointment for postnatal ocular prophylaxis of chlamydial conjunctivitis. Pediatr Infect Dis J 1989;8:491-5.
11. Mooney BR, Green JA, Epstein BJ, Hashisaki PA. Non-gonococcal ophthalmitis associated with erythromycin ointment prophylaxis of gonococcal ophthalmia neonatorum. Infect Control 1984;5:138-40.
12. Laga M, Plummer FA, Piot P, et al. Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum: a comparison of silver nitrate and tetracycline. N Engl J Med 1988;318:653-7.
13. Hedberg K, Ristinen TL, Soler JT, et al. Outbreak of erythromycin-resistant staphylococcal conjunctivitis in a newborn nursery. Pediatr Infect Dis J 1990;9:268-73.
14. Ison CA, Terry P, Bendayna K, Gill MJ, Adams J, Woodford N. Tetracycline-resistant gonococci in UK. Lancet 1988;1:651-2.
15. van Klingeren B, Dessens-Kroon M, Verheuvel M. Increased tetracycline resistance in gonococci in The Netherlands. Lancet 1989;2:1278.
16. Knapp JS, Zenilman JM, Biddle JW, et al. Frequency and distribution in the United States of strains of Neisseria gonorrhoeae with plasmid-mediated, high-level resistance to tetracycline. J Infect Dis 1987;155:819-22.
17. Schwarcz SK, Zenilman JM, Schnell D, et al. National surveillance of antimicrobial resistance in Neisseria gonorrhoeae: the Gonococcal Isolate Surveillance Project. JAMA 1990;264:1414-7.
18. Hammerschlag MR, Cummings C, Roblin PM, Williams TH, Delke I. Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. N Engl J Med 1989;320:769-72.
19. Zanoni D, Isenberg SJ, Apt L. A comparison of silver nitrate with erythromycin for prophylaxis against ophthalmia neonatorum. Clin Pediatr 1992; 31:295-8.
20. Butterfield PM, Ende RN, Platt BB. Effects of silver nitrate on initial visual behavior. Am J Dis Child 1978;132:426.
21. Houang ET, Gilmore OJA, Reid C, Shaw EJ. Absence of bacterial resistance to povidone iodine. J Clin Pathol 1976;29:752-5.
22. Apt L, Isenberg S, Yoshimori R, Paez JH. Chemical preparation of the eye in ophthalmic surgery. III. Effect of povidone-iodine on the conjunctiva. Arch Ophthalmol 1984;102:728-9.
23. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. Ophthalmology 1991;98:1769-75.
24. Arvin AM, Hensleigh PA, Prober CG, et al. Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. N Engl J Med 1986;315:796-800.
25. Sandstrom I. Ophthalmia neonatorum with special reference to Chlamydia trachomatis: diagnosis and treatment. Acta Paediatr Scand Suppl 1986;330: 1-27.
26. Nahmias AJ, Visintine AM, Caldwell DR, Wilson LA. Eye infections with herpes simplex viruses in neonates. Surv Ophthalmol 1976;21:100-5.
27. Frost E, Yvert F, Ndong JZ, Ivanoff B. Ophthalmia neonatorum in a semi-rural African community. Trans R Soc Trop Med Hyg 1987;81:378-80.
28. Buisman NJF, Mwemba TA, Garrigue G, Durand JP, Stilma JS, van Balen TM. Chlamydial ophthalmia neonatorum in Cameroon. Doc Ophthalmol 1988;70:257-64.
29. Bell TA, Grayston JT, Krohn MA, Kronmal RA. Randomized trial of silver nitrate, erythromycin, and no eye prophylaxis for the prevention of conjunctivitis among newborns not at risk for gonococcal ophthalmitis. Pediatrics 1993;92:755-60.
30. Chen JY. Prophylaxis of ophthalmia neonatorum: comparison of silver nitrate, tetracycline, erythromycin and no prophylaxis. Pediatr Infect Dis J 1992;11:1026-30.
31. Laga M, Meheus A, Piot P. Epidemiology and control of gonococcal ophthalmia neonatorum. Bull World Health Organ 1989;67:471-7. [Erratum, Bull World Health Organ 1990;68:690.]
32. Mordhorst CH, Dawson C. Sequelae of neonatal inclusion conjunctivitis and associated disease in parents. Am J Ophthalmol 1971;71:861-7.
33. Sandstrom I. Etiology and diagnosis of neonatal conjunctivitis. Acta Paediatr Scand 1978;76:221-7.
34. Hobson D. Chlamydial infections in neonates and older children. Br Med Bull 1983;39:128-32.
35. Krohn MA, Hillier SL, Bell TA, Kronmal RA, Grayston JT. The bacterial etiology of conjunctivitis in early infancy. Am J Epidemiol 1993;138:326-32.