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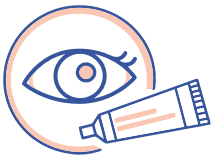

Evidence on: Erythromycin Eye Ointment for Newborns

What is the history of using erythromycin eye ointment for newborns?

The use of erythromycin eye ointment in newborns has its roots in the late 1800s. Back then, about 10% of newborns born in hospitals across Europe developed an illness called ophthalmia neonatorum. This illness caused blindness in 3% of affected infants (Schaller & Klauss, 2001).

Ophthalmia neonatorum (ON), also known as neonatal conjunctivitis, is an infection that causes inflammation of the conjunctiva during the first four weeks of life. The conjunctiva is a layer of thin tissue that covers the inner part of the eyelid and the white part of the eye. During the late 1800s, before antibiotics were discovered, 0.3% of infants (3 out of 1,000) were blinded from ON (Schaller & Klauss, 2001).

This article was updated on August 3, 2017 by Rebecca Dekker, PhD, RN, APRN and Anna Bertone, MPH

Doctors had suspected since the early 1800s that newborns caught ON after being exposed to something in the birth canal, but for many years nobody knew what the infants caught or how to prevent it. In 1879, a German physician named Albert Neisser discovered that gonorrhea—a sexually transmitted infection – was causing the ON (Dunn, 2000). The following year, another German physician, Carl Credé, introduced a breakthrough treatment to prevent ON. Instead of waiting for signs of infection to treat with silver nitrate solution, as doctors had been doing with little success since the 1830s, he realized that ON could be prevented by putting silver nitrate into the eyes of all newborns at birth. This new practice aimed at prevention was a great success. The number of ON infections in Dr. Credé's hospital

went from 30-35 cases per year to just one case in the first six months that he started using silver nitrate (Schaller & Klauss, 2001).

Today, more than 130 years after Dr. Credé made his discovery, quite a few things have changed. First, antibiotics have made it possible to treat pregnant people who have sexually transmitted infections as well as any infants who contract bacterial ON—making blindness highly unlikely in developed countries. Also today, gonorrhea has been replaced by chlamydia—another sexually transmitted infection—as the leading cause of ON, both globally and in the U.S. (Zloto et al. 2016; AAP, 2015). Another change is that silver nitrate is no longer used because it is extremely irritating to the eye and can cause severe pain, chemical pink eye (eye irritation), and temporary vision problems (Standler, 2006). Silver nitrate is no longer available in the U.S. (neither is tetracycline eye ointment, another antibiotic that was used in the past to prevent ON). Instead, most newborns in the U.S. will have 0.5% erythromycin ointment put in their eyes at birth in hopes of preventing ON.

What causes ophthalmia neonatorum (ON)?

Conjunctivitis is also commonly called *pink eye* due to the redness and swelling that can come with the infection. Pink eye can be caused by viruses (e.g., herpes), bacteria, chemicals, and blocked tear ducts. As we have stated, today the most common cause of ON is chlamydia–a sexually transmitted infection responsible for 2% to 40% of reported cases of ON in the U.S. The sexually transmitted disease gonorrhea now accounts for less than 1% of cases.

Among U.S. women, chlamydial infection is about six times more common than gonorrheal infection. In 2015, the rate of chlamydia was 646 per 100,000 females in the U.S., and the rate of gonorrhea was 107 cases per 100,000 females in the U.S. (CDC, 2015). Although chlamydia is the most *common* cause of ON, gonorrhea results in the most *serious* type of ON.

Other types of bacteria that come from the mother, hospital, or home environment are thought to cause 30% to 50% of cases, and the herpes virus causes less than 1% (AAP, 2015).

This article focuses on ON from gonorrhea and chlamydia, since that has always been the emphasis in public health prevention. The other bacteria that cause ON were never the targets of eye ointment prophylaxis ("pro-fuh-LAX-is"). *Prophylaxis* means taking action ahead of time to try and prevent something bad from happening. However, some care providers claim that the eye ointment also offers protection from infection with bacteria like staph and strep. We will discuss the evidence for this practice later in the article.

The only way for a newborn to contract ON from chlamydia or gonorrhea is if the mother has an untreated infection at the time of giving birth. Of newborns born to mothers with untreated gonorrhea, between 1 in 2 to 1 in 3 of them risk developing gonorrheal ON, which carries with it a high risk of blindness. Left untreated, gonorrheal ON can begin to cause vision loss in as little as 24 hours. The risk of a newborn getting chlamydia from an infected mother ranges from 8% to 44%, with the best estimate around 15%. Chlamydia has a low risk of blindness but can still cause eye damage and, rarely, loss of vision if not treated (Kapoor et al. 2016).

In developing countries, such as those in sub-Saharan Africa, ON remains a major cause of blindness, mostly due to untreated gonorrheal ON (Whitcher et al. 2001). Serious complications from ON are rare in the U.S. and other countries with high rates of prenatal screening and treatment for sexually transmitted infections and quick access to oral or injectable antibiotics should ON develop. In fact,

we could not find any published reports of blindness in newborns with ON who had been treated with antibiotics after getting an infection. Antibiotics are highly effective at treating bacterial ON and eye damage can be avoided if antibiotics are given promptly after an infant develops ON (Darling & McDonald, 2010).

Can a baby get ON after a Cesarean?

If a baby is born by Cesarean then it is extremely unlikely that the baby could develop ON, especially if the mother's water never broke before surgery (Medves, 2002). However, the current recommendation of the American Academy of Pediatrics (AAP) is that erythromycin be put into the eyes of all newborns to prevent gonorrheal ON, including infants born by Cesarean, since ascending infection can occur (AAP, 2015).

By *ascending infection*, the AAP means that gonorrhea and chlamydia are physically able to infect the fetus even before the fetus passes through the birth canal. We found four cases of gonorrheal ON after Cesarean (Thompson et al. 1974; Strand & Arango, 1979; Diener, 1981; Jacobsen et al. 1991). In all four cases, the mother's water had been broken for 18 to 24 hours or more before the surgery. Other rare case reports provide evidence that gonorrhea can infect the placenta even before the mother's water has broken and cause an infection of the membranes called chorioamnionitis, and sepsis (Yvert et al. 1985; Smith et al. 1989). Chlamydial ON has also occurred after Cesarean in at least 26 babies (Givner et al. 1981; Sato et al. 1990; Yescas-Buendía et al. 1993; Wu et al. 2003; Amini et al. 2008) and at least one of these transmissions is thought to have occurred even though the mother's water had not broken at the time of surgery (Shariat et al. 1992).

So, in summary, it is possible for a newborn to get gonorrheal or chlamydial ON after a Cesarean, but the actual risk is unknown because it's so rare.

Which is a better strategy: Worrying about sexually transmitted infections during pregnancy or after birth?

Untreated gonorrheal and chlamydial infections during pregnancy have been associated with many other complications. Gonorrhea has been linked to miscarriages, stillbirths, premature birth, low birth weight, premature rupture of membranes, chorioamnionitis, and bloodstream infections. Chlamydia has been linked to preterm labor, premature rupture of membranes, low birth weight, and newborn lung infections (CDC, 2016).

The fact that gonorrhea and chlamydia can cause harm long before birth means that it is far better to catch an infection early in pregnancy rather than to only wait until after the birth to worry about the consequences of these infections. An ON prevention strategy that emphasizes screening, treatment, and counseling in pregnant people could help to decrease the risk of pregnancy-related complications, as well as newborn ON.

How do you know if a mother is at risk for chlamydia or gonorrhea?

Anyone who is sexually active can get chlamydia or gonorrhea through vaginal, anal, or oral sex. A male partner does not have to ejaculate in order to give the infection to his partner. Re-infection is possible after a previous treated infection. Most people have either no symptoms or mild symptoms (CDC, 2016).

You can avoid both chlamydia and gonorrhea if you are in a monogamous relationship in which both partners have been tested and are uninfected. If that is not your situation, then you can reduce your

risk by using latex condoms the right way (http://bit.ly/2lM3Oo2) every time you have sex. Your risk of getting chlamydia or gonorrhea is higher if you are young (under the age of 25), if you have multiple sexual partners, if your partner has other sexual partners, or if you live in an area where there are high rates of infection. Washington, D.C. has the highest rates of gonorrheal and chlamydial infection in the U.S.; it reports 416 cases of gonorrhea and 1,198 cases of chlamydia per 100,000 people (CDC, 2015). Outside of D.C., the southeastern states report the highest rates of these infections. In Africa and in some developing countries, their rates are much higher than in the U.S.

Why is erythromycin eye ointment used to prevent ON in newborns?

Care providers in some countries try to prevent ON by giving all newborns eye ointment (such as erythromycin). The eye ointment is intended to kill or weaken bacteria in the eye–particularly gonorrhea–to protect the infant from getting pink eye, since pink eye from gonorrhea can cause serious eye damage and blindness if left untreated.

Automatic prophylaxis with eye ointment for all newborns within 24 hours of birth is currently recommended by several health organizations in the United States (U.S.), including the U.S. Preventive Services Task Force, the American Association of Family Physicians, and the American Academy of Pediatrics. However, the Canadian Pediatric Society recently recommended that routine, required prophylaxis with erythromycin be stopped. In their recommendation, they stated that their colleagues at the AAP are also planning to review their opinion, which may lead to changes in the AAP recommendations (Moore and MacDonald, 2015).

As you can see in the table below, some countries use ON prophylaxis, while others have stopped this practice:

Still carry out ON prophylaxis	No longer recommend ON prophylaxis
Brazil	Australia
Canada*	Belgium
France	Denmark
Italy	Great Britain
Slovenia	The Netherlands
Spain	Norway
Turkey	Sweden
United States	
Some areas in Central America	
Some areas in Central Asia	
Some areas in the Far and Middle East	
Some countries in Africa	

Data from Kapoor et al., 2016

**The Canadian Pediatric Society recommended in 2015 that prophylaxis for ON be discontinued; legislative changes are underway but not yet adopted.*

State law in most U.S. states requires newborn eye prophylaxis. In 2006, a search of state law databases found that at least 32 U.S. states had laws requiring newborn prophylaxis against ON (Standler, 2006). In these states, health care providers are required to give the eye ointment to every newborn, regardless of the mother's status for chlamydial or gonorrheal infection, and regardless of whether or not the baby was born vaginally or by Cesarean. Some states, such as New York (http://on.ny.gov/2wB20Dq), do not allow parents to exercise their right to informed refusal, and hospital employees in New York can go so far as to call Child Protective Services if the parents do not want the erythromycin ointment (http://bit.ly/2fmdRBW). However, other states, such as Tennessee, have recently made changes to their state laws (http://bit.ly/2vGsDtz) to allow parents to decline the eye ointment for their infants.

What is the evidence for erythromycin prophylaxis to prevent newborn pink eye?

In 2010, researchers combined results from eight studies (called a meta-analysis) that looked at the effectiveness of various eye ointments to prevent ON (Darling & McDonald, 2010). The use of erythromycin was examined in four of those studies, including a total of 4,514 participants. As you can see from the table below, erythromycin was more effective than silver nitrate at preventing chlamydial ON – the researchers found a 29% decrease in the risk of chlamydial ON among the infants who received erythromycin compared to silver nitrate. They did not find any evidence that erythromycin is better than silver nitrate at preventing gonorrheal ON. However, finding no difference between the two types of prophylaxis does not mean that erythromycin was not effective. Researchers may consider it unethical to give no prophylaxis to infants in geographic areas with high rates of gonorrheal and chlamydial ON, so erythromycin is compared to silver nitrate instead of a no treatment group. Silver nitrate is no longer used in most developed countries but it's useful for comparing with erythromycin. Only one trial has ever randomly assigned babies who were potentially exposed to chlamydia and gonorrhea to receive erythromycin or no prophylaxis. The study of 4,544 newborns in China found that neither erythromycin, silver nitrate, nor tetracycline reduced the risk of chlamydial ON compared to no prophylaxis at all (Chen, 1992).

Study author (year)	Participants	Findings
Isenberg (1995)	3,117 newborns in a hospital in Kenya	When compared to silver nitrate, erythromycin resulted in a 30% reduced risk of chlamydial ON. Erythromycin resulted in no reduction in the risk of gonorrheal ON when it was compared to silver nitrate.
Chen (1992)	4,544 newborns in a hospital in Taiwan	Erythromycin did not make any difference in the rates of chlamydial ON when compared to no prophylaxis at all.
Hammerschlag (1989)	230 newborns born to mothers with chlamydia in the state of New York, as well as the overall 12,431 newborns born during the study period	When compared to silver nitrate, erythromycin did not reduce the risk of gonorrheal or chlamydial ON.
Hammerschlag (1980)	60 newborns born to mothers who all had chlamydia at the time of birth in Seattle, Washington	There were no cases of chlamydial ON, so researchers could not tell if erythromycin was more effective than silver nitrate.

The overall quality of these trials was low (the Darling & McDonald reviewers agreed that all had at least one area of major weakness), so it is necessary to look at other types of studies to determine the effects of ON prophylaxis. A few studies have treated newborns with prophylaxis and compared their rates of gonorrheal or chlamydial ON to infants in the past who did not receive any prophylaxis. In a large observational study in South Africa, no eye prophylaxis was used for a certain amount of time, and then three hospitals started using silver nitrate and erythromycin. When they compared no prophylaxis to prophylaxis among 30,530 newborns, the number of gonorrheal ON infections dropped from 273 cases per 100,000 births to 34 cases per 100,000 births. However, within the prophylaxis group, there was a failure rate of 20%, in which the eye ointment did not work to prevent ON (Lund et al. 1987).

Hammerschlag et al. conducted a trial that included 230 infants born in Brooklyn, New York, to mothers with known chlamydial infections. They found that the rates of chlamydial ON were lower in the groups who had prophylaxis compared to newborns in the past whose mothers had chlamydia and did not receive any prophylaxis (11-20% versus 33%) (Hammerschlag et al. 1989).

Laga et al. also conducted a trial and found that chlamydial ON was reduced by 68% to 77% in the infants given prophylaxis compared to infants from the past who did not receive any prophylaxis (Laga et al. 1988).

The authors of the Darling & McDonald meta-analysis looked over these studies and concluded that, overall, prophylactic eye ointments may help to prevent chlamydial ON, but not as well as they help to prevent gonorrheal ON. Erythromycin was more effective than silver nitrate at preventing chlamydial ON, so that means it may offer some amount of protection. However, the evidence is so questionable that erythromycin (or any other prophylactic eye ointment) offers any amount of protection against chlamydial ON that groups like the American Academy of Pediatrics and the Canadian Pediatric Society have concluded that prophylactic eye ointments cannot prevent chlamydial ON (AAP, 2015; CPS, 2015).

As far as treatment goes after infants develop an infection, eye ointment is not effective for treating gonorrheal or chlamydial ON. Both require oral or IV antibiotics. To treat gonorrheal ON, infants need one dose of ceftriaxone (25-50 mg/kg, intravenously or intramuscularly, not to exceed 125 mg). To treat chlamydial ON, infants should receive oral erythromycin or ethylsuccinate (50 mg/kg/day in 4 divided doses daily) for 14 days or azithromycin (20 mg/kg as a single daily dose) for three days (AAP, 2015).

Does erythromycin prevent ON from other bacteria, such as staph?

The following bacteria are thought to cause 30-50% of ON infections:

- *Staphylococcus aureus*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae, nontypeable*
- *Group A and B streptococci*
- *Corynebacterium species*
- *Moraxella catarrhalis*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa* (AAP, 2015)

These bacteria live on the skin and in the lungs, vagina, stomach, and intestines. They are picked up during birth or from hospital or home exposures after the birth. Health care workers and other people

who handle newborns can have the above bacteria on their bodies and not have any symptoms. This means that every time a new person has contact with a baby, the newborn's risk of exposure increases (Sherertz et al. 2001).

Non-gonorrheal and non-chlamydial bacteria in the newborn's eyes are not dangerous and do not progress to blindness. However, these bacteria have been found in the eyes of newborns with pink eye (Bramantyo, et al. 2015). Whether or not they caused the pink eye is less well understood. Bacteria like *Staphylococcus aureus*, for example, are frequently found in the eyes of newborns who do not have pink eye (Kapoor et al. 2016).

Erythromycin eye ointment is a commonly prescribed treatment for non-gonorrheal, non-chlamydial conjunctivitis (Bremond-Gignac et al. 2011). The American Academy of Pediatrics recommends that it is also effective at preventing such pink eye from occurring during the first two weeks of life (AAP, 2015). However, they did not provide any research studies to back up this claim. Research has shown that erythromycin can prevent gonorrheal ON, and possibly chlamydial ON to some extent (although it is controversial), but there is little evidence that this is an effective prevention strategy for ON from other bacteria.

We did find a few studies that have looked at whether eye ointment can reduce the number of overall bacteria in the newborn's eyes, similar to how it reduces bacteria in petri dishes in a laboratory setting (Ibhanesebhor & Otobo, 1996).

One study measured the number of bacteria in newborn eyes after treatment with three types of eye ointments (Isenberg et al. 1995). In this study, newborns in Kenya were randomly assigned to three groups: povidone-iodine (1,076 newborns), erythromycin (1,112 newborns), or silver nitrate (929 newborns). *Povidone-iodine* is a disinfectant drop that can be placed into the newborn's eyes. The eye prophylaxis given within 20 minutes of the birth. Infants who returned to the hospital with pink eye were swabbed and the results were studied at the laboratory. If no organism could be found, then the infant was considered to have non-infectious, or chemical, pink eye.

After the use of prophylaxis, infectious ON still occurred in 13%, 15%, and 18% percent of newborns treated with povidone–iodine, erythromycin, and silver nitrate, respectively. The most commonly found bacteria among the infants with pink eye was chlamydia (50%), followed by *Staphylococcus aureus* (40%). Compared to the group that received povidone-iodine, groups that received silver nitrate and erythromycin had overall rates of pink eye that were 34% and 16% higher, respectively. All three types of prophylaxis reduced the number of bacteria in the eyes of the newborns compared to the amount of bacteria typically found in newborn eyes before prophylaxis (Personal correspondence, Isenberg, 2017).

A study in Pakistan compared 2.5% povidone-iodine solution and 1.25% povidone-iodine solution in 100 healthy infants (Khan et al. 2016). A swab for bacterial culture was taken 30 minutes after birth. Then, a single drop of 2.5% concentration was put in the right eye and 1.25% concentration was put in the left eye. They found that both drops reduced the number of bacteria, and that the 1.25% concentration was as effective as the 2.5%. Similarly, a trial in Indonesia compared 2.5% povidone-iodine solution to 1% Chloramphenicol antibiotic ointment in 60 healthy newborns (Bramantyo et al. 2015). They found that both types of prophylaxis were equally effective at reducing the bacteria.

In 2014, researchers in Iran randomly assigned 300 newborns to one of three groups: two drops of colostrum (the mother's first breast milk after the birth), erythromycin, or nothing (Ghaemi et al. 2014). To be included in the trial, the newborns had to have no bacteria in their eyes immediately after the birth.

After receiving the prophylaxis (or none, in the group assigned to nothing), the infants were watched to see if they developed pink eye in the first 28 days after birth. All of the infants who developed pink eye were swabbed and found to have Staphylococcus aureus. ON was most common in the infants that did not receive any prophylactic treatment (33%), followed by the group receiving colostrum drops (24%) and the group receiving erythromycin (16%). This study provides evidence that erythromycin may offer some protection against ON from staph bacteria.

The idea behind this strategy to give eye ointment in order to prevent ON from non-gonorrheal and non-chlamydial bacteria is that by lowering the amount of overall bacteria in a newborn's eyes, we could potentially be lowering the risk of ON from bacteria such as staph and strep. One trial found that erythromycin reduced ON from staph compared to no treatment or drops of colostrum. However, the research on using erythromycin to prevent ON from non-gonorrheal and non-chlamydial bacteria is very limited. So, at this point, we don't know if this is an effective strategy or not. Also, this strategy may be limited by antibiotic resistant bacteria, which we will discuss in the next section!

Are bacteria becoming resistant to erythromycin?

Remember, non-sexually transmitted bacteria like *Staphylococcus aureus*, *Streptococcus pneumonia*, and group A and B streptococci are thought to cause 30% to 50% of ON infections. When care providers recommend erythromycin prophylaxis to prevent ON from these bacteria, they might not be considering that many strains of these bacteria are now resistant to the ointment they are putting in infants' eyes.

Erythromycin was first introduced in 1953, and by 1968, strains of Streptococcus bacteria had developed resistance. Of Streptococcus bacterial samples tested at the CDC in 2010 and 2011, 10% of group A were erythromycin-resistant, while half (49%) of Group B Strep strains were erythromycin-resistant (CDC, 2013). Resistant strains of *Staphylococcus aureus* have also been reported in newborns with ON who were given erythromycin prophylaxis (Hedberg et al. 1990).

Gonorrhea – the primary target of ON prevention campaigns – is also becoming resistant to erythromycin. In 2012, strains isolated in Canada showed a 23% resistance to erythromycin. It is not known whether this resistance can be overcome by using higher levels of antibiotics. The studies that show erythromycin to be effective prophylaxis for gonorrheal ON are not current and may not be as relevant today due to growing resistance (CPS, 2015).

Antibiotic resistance is rare in chlamydia, and people are not yet sick with antibiotic-resistant strains (Sandoz & Rockey, 2010). However, strains of chlamydia that are resistant to erythromycin have been found in a laboratory setting (Welsh et al. 1992).

Povidone-iodine is an alternative eye treatment that is thought to be effective against a wide variety of bacteria without encouraging the development of bacterial resistance (Kapoor et al. 2016).

As a side note, there is no evidence that routine eye ointment prophylaxis with erythromycin is causing the increase in drug resistant strains of bacteria. The drug resistance is more likely an effect of oral antibiotics that many people are taking, rather than the one time use of a topical ointment in newborns (Personal correspondence, Dr. Arbeter, 2017). However, the drug resistance is probably making the eye ointment less effective.

It may be helpful to summarize the risks and benefits of erythromycin prophylaxis like this:

Benefits:

- Erythromycin has been shown in the past to reduce the risk of gonorrheal ON – thereby reducing the risk of blindness from the infection – and possibly, chlamydial ON (Darling & McDonald, 2010)
- Some evidence suggests that erythromycin reduces overall bacteria in the eye and may help to prevent ON from non-sexually transmitted bacteria like staph (Isenberg et al. 1995; Ghaemi et al. 2014)
- Erythromycin prophylaxis may be helpful if the mother and her partner(s) did not receive adequate screening and treatment for gonorrhea/chlamydia during the pregnancy *and* it's not possible to test the mother at the time of birth and treat the infant as needed (CPS, 2015)
- Erythromycin prophylaxis may help to protect a newborn from gonorrheal ON if the mother was infected after a negative screening result earlier in the pregnancy (for example, due to a partner's infidelity)
- Erythromycin prophylaxis may be helpful in geographic areas where rates of chlamydia and gonorrhea are very high, especially combined with low rates of prenatal care (Medves, 2002)
- Erythromycin ointment is inexpensive (Darling & McDonald, 2010)

Risks:

- Adverse effects can include chemical pink eye, or eye irritation (http://bit.ly/2uhZ4v0). A study in Kenya found that 13% of infants who received erythromycin developed pink eye with no evidence of infection (culture-negative) (Isenberg et al. 1995). If chemical pink eye is mistaken for bacterial pink eye, it could lead to treatment (http://bit.ly/2wBd1EQ) with more antibiotics while waiting for culture (test) results.
- Blurred vision (http://bit.ly/2uhZ4v0) could potentially interfere with bonding by disrupting early eye gazing between the newborn and parents (Personal correspondence, Brazelton Institute, 2017; Bruschweiler-Stern, 2009). Although bonding is difficult to study, it's been shown that from birth, newborns can tell between direct and indirect eye contact, and that newborns prefer when they can mutually gaze with their parent (Farroni et al. 2002).
- Erythromycin is not 100% effective at preventing gonorrheal ON – it had a 20% failure rate in the past and might be less effective now due to growing resistance (Lund et al. 1987)
- Erythromycin may not be effective at preventing chlamydial ON or ON from other non-gonorrheal bacteria (CPS, 2015)

Are there any other options beside the erythromycin?

One option is for the mother to be screened for sexually transmitted infections during pregnancy and receive antibiotic treatment, along with her sexual partner(s), if needed. If the mother is treated, then she would need follow-up testing to make sure the treatment was effective. If a mother is not infected with chlamydia or gonorrhea and is in a monogamous relationship with an uninfected partner, then newborn eye ointment may be reasonably declined (Medves, 2002).

The benefit of this option is that a potentially harmful sexually transmitted infection can be found and treated, improving the health of both the mother and the newborn (Coutanceau et al. 2015). The disadvantage is that if this is done on a large scale, it requires a well-organized maternity care system in which all pregnant people have access to prenatal care that includes screening for sexually transmitted infections and receiving treatment as needed. Although this is possible in some countries, it may not be in others. And even in developed societies, not all pregnant people receive the same prenatal care. In the U.S., the Centers for Disease Control recommends that all pregnant people under 25 years of age be screened for chlamydia and gonorrhea at the first prenatal visit, and that those over 25 at high risk for either infection be screened as well (CDC, 2016).

Another disadvantage of the screen-and-treat method is that a person may test negative for chlamydia or gonorrhea early in pregnancy, but then be infected by a partner before giving birth. According to research from the National Opinion Research Center's General Social Survey (http://bit.ly/2vG8RhS), 20%-25% of married men anonymously reported to ever having cheated on their spouse. It's important to remember that given the potential for infidelity, any sexually active pregnant person could be at risk for gonorrheal infection, and their newborn could also be at risk for gonorrheal ON. Some care providers may feel that it is a leap of faith to ask pregnant people about their sexual history, if they and their partner(s) have been tested for sexually transmitted infections, and if they are in a monogamous relationship.

The Canadian Pediatric Society recently recommended discontinuing the routine use of eye ointment prophylaxis (CPS, 2015). They propose a screening and treatment strategy as an alternative to required prophylaxis that includes these recommendations:

- Screen *all* pregnant people for gonorrhea and chlamydia at their first prenatal visit.
- Positive test results require treatment with antibiotics during pregnancy and a re-test in the third trimester (or, failing that, at the time of birth with the most rapid tests available); partners should also be treated.
- Negative test results require repeat screening in the third trimester or at the time of birth if the mother was at high risk of getting the infection during the pregnancy.
- If the mother tests positive for gonorrhea at the time of birth, then the newborn should be treated with injectable antibiotics without waiting for test results and should be further evaluated if unwell in any way. This recommendation includes babies born by Cesarean.
- If the mother tests positive for chlamydia at the time of birth, then the newborn should be closely watched for symptoms of pink eye and treated only if the infection occurs.

In response, the Canadian Association of Pediatric Ophthalmology and Strabismus express concern with the new recommendations and urge provincial/territorial committees to keep the required eye ointment (Mulholland & Gardiner, 2015). They argue that there is no evidence to show that screening is a more effective prevention strategy than eye ointment prophylaxis. They also discuss several ways that a screening-only approach could fail. For example, they mention that there could be false-positive tests, false-negative tests, lack of prenatal care or follow-up, bacterial resistance to treatment for prenatal infections, and possible medication side effects.

It's important to realize that public health guidelines are best tailored to specific populations. The CPS's recommendation is for Canadian people who receive care from a mostly single-payer health system (national health insurance). In Canada, there is less variation in healthcare access and use compared

to a country like the U.S., where a person's ability to access healthcare varies by insurance status. A screen-and-treat strategy would be less effective in a country with large numbers of people unable to access timely medical care (Personal correspondence, Dr. Arbeter, 2017). A plan similar to the CPS recommendation might work in the U.S., but would need to be studied after going into effect to see if cases of ON (from gonorrhea, chlamydia, or other bacteria) increase or decrease compared to required eye ointment prophylaxis.

Another option is to wait and see if a newborn develops ON.

This wait-and-see approach is currently used in the United Kingdom, where they don't regularly screen all pregnant people for gonorrhea and chlamydia. If a newborn did not receive eye ointment and develops pink eye, the most important factor that a physician or midwife will consider is the potential for the mother to have been infected with gonorrhea or chlamydia at the time of the birth. If it is unlikely that the newborn was exposed to an untreated infection, then minor pink eye is common and can be closely watched and treated as needed. However, if the pink eye develops into pus-containing discharge, then the infant should be hospitalized immediately so that samples can be tested for gonorrhea. Treatment with injectable antibiotics should begin while waiting for test results (NICE, 2012).

The disadvantage of this approach is that it relies on quick access to injectable antibiotics. If parents don't seek immediate medical care for a newborn with pus-containing pink eye – either because they don't recognize the potential seriousness of the infection or because they lack access to care – then pink eye from gonorrhea can start to cause eye damage within 24 hours.

Another option is Povidone-iodine

Povidone-iodine eye drops are becoming popular in developing countries because they are less expensive than erythromycin. This disinfectant does not increase the risk of antibiotic resistance and it is just as effective as erythromycin and silver nitrate at preventing gonorrheal ON. Povidone-iodone is also thought to be more effective than silver nitrate and equally effective as erythromycin at preventing chlamydial ON. Another advantage is that the newborn's eye turns temporarily brown after putting in the drops, which helps the provider know whether full coverage was achieved.

Some U.S. doctors use 5% povidone-iodine ophthalmic drops off-label (http://bit.ly/2vydCdK) for adenoviral pink eye; however, newborn eye drops made out of povidone-iodine are not yet available in the U.S. We would need a 2.5% or 1.25% solution for ON prophylaxis. A recent study suggests that the lower concentration may be just as effective (Khan et al. 2016).

Another option is colostrum, or the first breast milk after the birth.

Three randomized trials have looked to see if applying drops of the mother's first breast milk into the newborn's eyes can help to lower the risk of ON from non-chlamydial, non-gonorrheal bacteria. All three trials found that drops of the mother's first milk can lower the risk of ON from non-sexually transmitted bacteria better than no prophylactic treatment. The findings disagree, however, with regard to how colostrum compares to antibiotic prophylaxis – one trial found colostrum to be more effective than the antibiotic and another found it to be less.

Earlier, we mentioned a 2014 study from Iran that randomly assigned 300 newborns who were not exposed to chlamydia or gonorrhea to one of three groups: two drops of colostrum, erythromycin, or nothing (Ghaemi et al. 2014). They found that ON from staph bacteria was most common in the infants

that did not receive any prophylactic treatment (33%), followed by the group receiving colostrum drops (24%) and the group receiving erythromycin (16%).

An earlier trial, also in Iran, randomly assigned newborns to one of two groups: eye drops of colostrum/breast milk prior to each breast feeding for the first ten days of life (327 newborns) or prophylactic treatment with an antibiotic (238 newborns). (The article is not in English and it is not clear which antibiotic was used.) Pink eye occurred in 9% of the babies receiving breast milk drops and 26% of the babies receiving the antibiotic. The most common cause of ON in both groups was Staphylococcus bacteria (Pishva et al. 1998).

In 1982, Indian researchers at a New Delhi hospital swabbed the eyes of newborns within 12 hours of birth (Singh et al. 1982). The newborns who had negative bacteria cultures were randomly assigned to a drop of their mothers' colostrum in both eyes, three times per day for three days in a row (51 newborns), or to nothing (72 newborns). Pink eye or a more mild condition called "sticky eyes" was observed in 35% of the infants who received no prophylactic treatment versus 6% of the infants who received colostrum drops. The most common bacteria isolated from both groups was Staphylococcus.

Other research shows that breast milk may be effective at resolving newborn pink eye caused by a tear duct being blocked at birth (Verd, 2007). Researchers in Spain looked at breast milk's ability to resolve newborn pink eye caused by a tear duct being blocked at birth. Researchers randomly assigned 25 patients to treatment with antibiotics and 45 patients to treatment with breast milk. By the 30th day of life, pink eye had resolved in 15% of the infants receiving antibiotics and 57% of the infants receiving breast milk drops. By the 60th day of life, 50% of the infants receiving antibiotics and 90% of the infants receiving breast milk drops were cleared of pink eye. The treatments continued until the 150th day of life, at which point 90% of the antibiotic group was clear compared to 100% of the breast milk group.

Three other studies have looked at breast milk's ability to inhibit, or limit the growth of bacteria in a laboratory setting, called "in vitro" studies. One study compared breast milk to a broad-spectrum antibiotic (polymyxin B sulfate/trimethoprim) or no treatment in the ability to inhibit the growth of nine bacteria capable of causing ON (Baynham et al. 2013). Breast milk was better than no treatment for three of the nine bacteria: Gonorrhea, *Moraxella catarrhalis* and viridans group Streptococcus. Interestingly, breast milk was better than the antibiotic for one particular bacteria: gonorrhea. The antibiotic was better than breast milk for the other eight species of bacteria.

The second in vitro study tested colostrum's ability to inhibit the growth of chlamydia (Ramsey et al. 1998). All 13 samples of colostrum effectively inhibited chlamydial growth in a dose-response manner. On average, colostrum inhibited 88% of the chlamydial growth. They found that colostrum was more effective than mature breast milk and that it started to work against chlamydial growth less than 15 minutes after application.

In the third in vitro study, researchers in Nigeria swabbed the eyes of 22 newborns with ON (Ibhanesebhor & Otobo, 1996). They cultured the bacteria from the eye swabs and exposed it to colostrum, mature milk, and a variety of antibiotics that included erythromycin. Of the positive bacterial cultures, 59% detected *Staphylococcus aureus* and 41% detected coliform bacteria. Coliform bacteria, such as *Escherichia coli*, are present everywhere in the stool of warm-blooded animals. They can be harmless or cause ON, and their presence means that contamination with fecal material has occurred. *Staphylococcus aureus* was found to be 50% inhibited by colostrum and 0% by mature milk. Coliform organisms were 57% inhibited by colostrum and 28% by mature milk. Colostrum was effective for an average of six hours after application and mature milk was effective against coliform organisms for

an average of three hours. By comparison, *Staphylococcus aureus* was 50% inhibited by erythromycin and coliform organisms were 0% inhibited by erythromycin. So, colostrum was just as effective as erythromycin at inhibiting the growth of *Staphylococcus aureus* and more effective than erythromycin at inhibiting the growth of coliform organisms.

In summary

Newborns receive erythromycin eye ointment after birth to prevent pink eye in the first month of life, also called ophthalmia neonatorum (ON). The most common cause of ON is chlamydia, a sexually transmitted infection. A less common but more serious cause of ON and the reason for mandatory eye ointment is gonorrhea, another sexually transmitted infection, that now accounts for less than 1% of reported ON cases in the U.S. A newborn can only get ON from chlamydia or gonorrhea if the mother is infected at the time of the birth. Other bacteria account for 30%-50% of ON infections, which are not considered serious.

In the past, studies showed that erythromycin eye ointment is around 80% effective against ON from gonorrhea and might also offer some protection against ON from chlamydia. The growing problem of antibacterial resistance means that erythromycin is less effective today—and older studies that provided evidence for eye ointment prophylaxis may no longer be relevant. ON can also be caused by other bacteria in the hospital and home environment, viruses (e.g., herpes), chemicals, and blocked tear ducts. Some evidence suggests that erythromycin may be effective at reducing overall bacteria in the eye and lower the rate of ON from staph bacteria. However, there is little evidence to support the mandatory use of erythromycin for non-gonorrheal, non-chlamydial bacteria; in fact, some strains of these bacteria have become resistant to erythromycin. Drops of breast milk, especially colostrum, have been shown to reduce ON from non-gonorrheal, non-chlamydial bacteria and inhibit the growth of gonorrhea and chlamydia on culture plates in the lab.

ON is treatable in all of its forms, including ON from gonorrhea, as long as antibiotic treatment is started immediately. Strategies to prevent ON include screening for chlamydia and gonorrhea during pregnancy and receiving treatment as needed, using erythromycin eye ointment after birth, a "wait and see" approach in which antibiotics are used only when necessary, using povidone-iodine eye drops after birth (when available), or using drops of the mother's first milk after birth.

Erythromycin eye ointment can be reasonably declined if pregnant people are screened negative during the pregnancy for chlamydia and gonorrhea, if they are in a monogamous relationship with an uninfected partner, and if they are able to get immediate medical care should the newborn develop pus-containing pink eye. It is highly unlikely that a baby born by Cesarean could develop gonorrheal or chlamydial ON as long as the mother's membranes were intact at the time of surgery.

Today, laws in many U.S. states still mandate the use of erythromycin with all newborns even though the erythromycin may not be effective and even though other options are available. Given the fact that other options can be used to safely prevent and treat newborn eye infections, the mandatory nature of these erythromycin state laws should be re-evaluated.

Action Steps

For parents: Take this article to an appointment and discuss it with your care provider! Here are some questions to ask your provider that can help you make an informed decision about whether or not to use erythromycin eye ointment after birth.

- Can we go over my prenatal screening history and discuss my test results for infectious diseases?
- Can we discuss my personal risk status for infection with chlamydia and gonorrhea?
- What will happen if I decide to refuse the erythromycin eye ointment?
- If I decide to consent to the erythromycin eye ointment, could we delay the procedure until after skin-to-skin bonding and the baby's first feed?

For providers: Where do we take this from here? There is an inherent tug-of-war between policy measures intended to protect the vulnerable members of a population and health care consumers who want their care individualized. Based on our literature review, individualized care can be offered in place of mandatory eye ointment. Such care would include a thorough discussion of screening history, risk status, and access to care as well as taking the individuals' values and preferences into account. The following questions are intended to help guide your discussion with clients and enhance the informed consent process around the use of eye ointment prophylaxis.

- **What is their screening status?** Have they been screened for gonorrhea and chlamydia during the current pregnancy (or at the time of birth with a rapid test, if available)? If the test was positive, were they treated with antibiotics along with their partner(s) and re-tested? If the test was negative but the mother is at high-risk for sexually transmitted infections, were they re-tested in the third trimester or at the time of birth?
- **What is their risk status?** Do they claim to be in a monogamous relationship or have multiple sexual partners? How old are they? (Women under 25 years of age are more at risk for gonorrhea and chlamydia.) Do they live or travel to a place where the rate of gonorrhea or chlamydia is high? Did they give birth vaginally or by Cesarean? If the mother gave birth by Cesarean, were her membranes intact at the time of the surgery?
- **If the baby develops pus-containing pink eye, will they receive timely medical care?** It is important to include access to care in your discussion, since a care provider can never be 100% sure of a mother's risk status, and failure to respond quickly to pink eye from gonorrhea can result in eye damage and blindness in as little as 24 hours. Have they been advised to watch for signs of pus-containing pink eye and bring the infant in for medical care immediately if it occurs? Lack of adequate prenatal care, insurance, or permanent housing could be an indication that access to medical care may be a barrier should the infant require treatment for ON.

For more information about erythromycin:

- A lawyer's look at U.S. state laws on mandatory erythromycin in newborns (http://bit.ly/2fmMyaL)
- Official information from the FDA about erythromycin ointment (http://bit.ly/2vIekWe)
- Watch the free EBB video series on Vitamin K and Eye Ointment here (http://bit.ly/2vElJ8x)

Acknowledgment

We would like to extend our gratitude to our expert clinician reviewers for their valuable feedback and critique of this article before publication: Shannon J. Voogt, MD, Board-Certified in Family Medicine; and Allan M. Arbeter, MD, a Pediatric Infectious Disease Specialist in Philadelphia, Pennsylvania. We would also like to thank Cristen Pascucci for her medical editing assistance.

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