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Primary meningococcal conjunctivitis: Summary of evidence for the clinical and public health management of cases and close contacts

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SUMMARY

Background: *Neisseria meningitidis* is a rare cause of acute bacterial conjunctivitis but can progress to invasive meningococcal disease (IMD) in the case and their close contacts. There is, however, a lack of consensus on the clinical and public health management of primary meningococcal conjunctivitis (PMC).
Methods: We searched Ovid MEDLINE via PubMed, EMBASE and NHS evidence (up to June 2019) for all publications relating to meningococcal conjunctivitis to provide an evidence-base for developing guidelines for the management of PMC cases and their close contacts.
Results: The review identified a 10–29% risk of IMD among PMC cases within two days of onset of eye infection (range: 3 h to 4 days). In one study, the risk of IMD in PMC cases treated with systemic antibiotics was 19 times lower than topical antibiotics alone ($p = 0.001$). IMD among close contacts of PMC cases is uncommon but potentially fatal. Whether meningococcal vaccination for PMC cases or close contacts provides any additional benefit is unclear.
Conclusions: Systemic antibiotic treatment significantly reduces the risk of invasive disease in PMC cases, while antibiotic chemoprophylaxis for close contacts will reduce their risk of secondary IMD. These findings need to be highlighted in relevant clinical and public health guidelines.

Key points

In patients with primary meningococcal conjunctivitis, systemic antibiotic treatment significantly reduces the risk of invasive meningococcal disease compared to topical antibiotics alone, while antibiotic chemoprophylaxis for close contacts reduces their risk of developing secondary invasive disease.

Introduction

Neisseria meningitidis is a Gram-negative diplococcus that frequently colonises the upper respiratory tract of adolescents and young adults. Rarely, the pathogen will cause serious invasive infection, including meningitis and septicaemia, which are both associated with high morbidity and mortality. Acute conjunctivitis is the most common disorder of the eye, especially in children. In neonates, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the main causes of ophthalmia neonatorum, while *Haemophilus influenzae, Streptococcus pneumoniae* and adenoviruses are the most important pathogens in older infants; *Staphylococcus aureus* is a common cause at any age. Bacterial conjunctivitis is rarely caused by *N. meningitidis*, although the true incidence is most likely underestimated because most cases of conjunctivitis are treated empirically, without adequate microbiological investigations, and recover without complications.[1]

Primary meningococcal conjunctivitis (PMC) refers to infection of the conjunctiva, which may or may not progress to systemic disease, while secondary meningococcal conjunctivitis is an unusual complication of systemic meningococcal disease. PMC occurs after direct inoculation of the meningococcus into the conjunctival sac through direct contact or the airborne route. In neonates, this is often acquired vertically from the mother's genitourinary tract.[2] Most cases of PMC recover with appropriate treatment, although complications such as corneal ulcers, keratitis, sub-conjunctival

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hemorrhage and iritis have been reported.[3] Some studies have suggested PMC to be responsible for around 2% of all bacterial conjunctivitis, but larger studies have estimated the incidence to be well below 1%.[4–6]

There is currently no consensus on the management of individuals with PMC or their close contacts. In the United Kingdom and Australia for example, guidelines for the public health management of meningococcal disease state that PMC cases are at an increased risk of developing invasive meningococcal disease (IMD),[7,8] while US guidance attributes no additional risk of IMD to PMC cases.[9] At the same time, neither the UK National Institute for Health and Care Excellence (NICE) clinical guidelines for Bacterial Meningitis and Meningococcal Septicaemia, which aims to reduce deaths and disability by promoting early recognition of symptoms and timely effective management, nor the UK's College of Optometrists' clinical guidelines for Bacterial Conjunctivitis[10] mentions meningococcal conjunctivitis as a potential precursor of IMD.[11] Similarly, the British National Formulary (BNF), which provides best practice guidance on the drug treatment of medical conditions does not provide any specific recommendations for the treatment PMC in its "Antibacterials for eye infections" section.[12]

In addition to the clinical management of PMC cases, there is also a lack of consensus on the public health management of close contacts of PMC cases. Again, both the UK[13] and Australian[8] public health management guidelines state that close contacts of PMC cases are at an increased risk of IMD and, therefore, recommend antibiotic chemoprophylaxis for them in order to prevent secondary IMD, whereas the US guidance does not acknowledge any increased risk and, therefore, does not make any recommendations for antibiotic chemoprophylaxis for close contacts.[9] There are also conflicting recommendations for meningococcal vaccination; the UK guidelines recommend no vaccination for PMC cases or their close contacts, while the Australian guidelines recommend meningococcal vaccination if the responsible strain belongs to serogroups A, C, W or Y.[13,14] Clinical and public health guidelines for meningococcal disease from most other countries do not make any specific recommendations for PMC cases or their close contacts.[14] We, therefore, performed a review of the literature in order to provide a robust evidence base to support recommendations for clinical and public health management of PMC cases and their close contacts.

Methods

We searched PubMed with the terms "Meningococcal", "Conjunctivitis", "primary meningococcal conjunctivitis" and any combination of "transmission" or "invasive disease". Publication dates and languages were not limited. We searched Ovid MEDLINE via PubMed, EMBASE and NHS evidence (up to December 2018 week 3). The advanced search mode was used including the terms "Meningococcal", "Conjunctivitis", "primary meningococcal conjunctivitis" and any combination of "transmission" or "invasive disease" or "contacts" or "management" or "treatment". Publication dates and languages were not limited. Case series and review articles that summarised previous publications on PMC were prioritised; the individual publications cited in such studies were not retrieved for additional review.

Results

Primary Meningococcal Conjunctivitis

PMC may present as acute or hyperacute purulent conjunctivitis which is clinically indistinguishable from conjunctivitis caused by *N.gonorrhoeae*.[15] Published studies have reported 10–29% of PMC cases may lead to IMD (Table 1), with systemic symptoms occurring within two days of onset of eye infection (*range*: 3 h to 4 days).[3,16–19] Systemic antibiotic therapy for PMC is more effective than topical antibiotic therapy alone in prevention of systemic disease.[3,15–17,20–26] In one study, the risk of developing IMD when PMC cases were treated with topical antibiotics alone was 19 times greater ($p = 0.001$) than if combined with systemic antibiotic treatment.[3]

Antibiotic chemoprophylaxis for close contacts

Patients with PMC may also transmit the meningococcus to close contacts, who may then go on to develop systemic disease. In several studies, screening of household and close contacts of PMC cases found them to be carrying identical strains to the one responsible for the conjunctivitis.[27–29] This suggests that meningococcal strains causing PMC can circulate among the household and close contacts, potentially putting them at risk of invasive disease. This risk, however, has not been quantified and there are very few such instances reported in the literature,[16,30] although at least three deaths from IMD following close contact with a case of PMC have been reported.[16,17,30]

Discussion and clinical implications

Neisseria meningitidis is a rare cause of acute bacterial conjunctivitis in any age group but it is important to identify this pathogen as the cause because of an increased risk of invasive meningococcal disease among both the PMC cases themselves and their close contacts.[31] It is also important to distinguish between meningococcal and gonococcal infection when Gram-negative diplococci are identified on microscopy or culture of an eye swab. This is because treatment, contact tracing and outcomes are different for the two aetiologies. Reassuringly, empiric treatment for gonococcal conjunctivitis already includes systemic antibiotics,[31] which will also treat PMC. Based on the current literature, patients with PMC should be treated as early as possible with systemic antibiotics in addition to topical antibiotics to reduce the risk of developing IMD. Antibiotic chemoprophylaxis should also be offered to household and close contacts of PMC cases because of a small, unquantified but potentially fatal risk of IMD.

The recommendation to treat PMC cases with systemic antibiotics in addition to topical antibiotics raises three important questions:

(i) *Unless a Gram stain of the conjunctival swab is performed quickly, the culture results of the bacterial eye swab may take at least 48 h to be reported. Therefore, should PMC cases initially treated with topical antibiotics alone be recalled for systemic antibiotics?*

Among the published cases, Gram-negative diplococci were usually identified on a Gram stain performed on the initial conjunctival swab and, therefore, systemic antibiotics were initiated relatively quickly. However, given the continuing risk of invasive disease up to 4 days after onset of conjunctivitis, it would be prudent to initiate systemic antibiotics as soon as PMC is diagnosed, even if the patient is systemically well.

(ii) *Can children with PMC be treated with oral antibiotics when N. meningitidis is confirmed as the cause of the conjunctivitis?*

Both intravenous[3,16,17] and oral[15,30] antibiotics have been used successfully to treat PMC cases and prevent progression to systemic disease, suggesting that a treatment course of oral antibiotics should be adequate in otherwise well children with PMC alone and no systemic symptoms. In neonates with conjunctivitis, it may be prudent to initiate treatment with an intravenous cephalosporin

Table 1
Summary of publications relating to primary meningococcal conjunctivitis (PMC).

Reports of invasive meningococcal disease (IMD) in patients with primary meningococcal conjunctivitis (PMC)

Citation (country)	Ref No.	Study type	Key results
Barquet et al., 1990 (Spain)	3	Observational cohort and literature review	*N. meningitidis* found in 2.0% (21/1030) of all acute bacterial conjunctivitis seen in the hospital over 5 years. Six of the 21 (28.6%) PMC cases resulted in systemic disease 63 PMC cases identified in the literature, including 9 (14.3%) reported with systemic disease Among PMC cases with systemic disease ($n = 15$), 2 died (overall CFR, 13.3%) Risk of IMD among PMC cases was 19 times greater among those who received topical antibiotics alone (31.7%) compared to those who received systemic antibiotic therapy (2.38%); $p = 0.001$
Moraga Llop et al., 1996 (Spain)	21	Prospective observational study	34 PMC cases identified over a 10-year period in a single hospital (mean age, 3.5 years) and 10 (29.4%) developed IMD. PMC was bilateral in 7 patients and unilateral in 27 Topical antibiotics only were given to 24 patients and 10 (41.7%) developed IMD compared to none of the 10 who received systemic antibiotics ($p = 0.04$) None of the patients died and none developed ocular sequelae.
Stansfield et al., 1994 (Scotland)	17	Case series	8/53 (15.1%) PMC cases had either concurrent or subsequent IMD. Detailed account of 3/8 PMC cases reported - two were associated with systemic sepsis and one died
Ellis et al., 1992 (UK)	18	Case series	2 cases of perinatally-acquired PMC in neonates which rapidly progressed to IMD at 60 h and 72 h of age, respectively. Both neonates were initially treated with neomycin eye ointment only
Mangiaracine and Pollen, 1944 (USA)	26	Case series	3/10 (30%) PMC cases (age range: 14 weeks to 15 years) went on to develop IMD; all 3 were initially only treated with topical solutions/antibiotics.
Odegaard et al., 1983 (Norway)	16	Case report	Single case in 15-year-old male that progressed to IMD with a fatal outcome; initially treated with only chloramphenicol eye drops; 18 h after the eye swab was taken, meningococcal serogroup B was isolated. Topical antibiotic therapy was not changed to systemic antibiotics
Nussbaum et al., 1978 (USA)	23	Case report	Single case of PMC progressing to IMD in an infant, who was initially treated with ophthalmic solution alone.
Dillman, 1967 (USA)	22	Case report	Single case of PMC that progressed to IMD in a 24-year old male who was initially treated with sulfacetamide ointment only
Reese, 1936 (USA)	19	Case report	Single case of unilateral PMC that progressed to IMD in a nurse who had been on duty with a case from an IMD outbreak

Reports of invasive meningococcal disease (IMD) in close contacts of patients with primary meningococcal conjunctivitis (PMC)

Citation	Ref No.	Study type	Key results
Stansfield et al., 1994 (Scotland)	17	*Case series*	3 PMC cases associated with systemic sepsis reported A 10-year-old boy with bilateral conjunctivitis was prescribed topical chloramphenicol and discharged home; eye swab culture subsequently grew N. meningitidis (C:2b:P1.2), while led to immediate systemic antibiotics for the case and prophylactic rifampicin for close contacts The patient's 5 year-old sister, 5-year-old female developed sepsis with a characteristic petechial and purpuric rash which began on third days after her brother's illness). her blood and throat cultures were taken after she had received rifampicin chemoprophylaxis and no pathogen was identified.
Bigham et al., 2001 (Canada)	30	Case study	A case of PMC in a child with evidence of transmission to the mother, who subsequently died of IMD. Cultures from the child and mother were both positive for *N.meningitidis* serogroup C:2a:P10.2

Reports of identical strains from PMC cases and screening of their household or close contacts in the absence of invasive disease

Citation	Ref No.	Study type	Key results
Stuart and McWalter, 1948 (Scotland)	27	Case series	Six cases of PMC in children aged 9 weeks to 10 years; 2/6 cases had close contacts with positive postnasal cultures – both were family members of the cases
Mangiaracine and Pollen, 1944 (USA)	26	Case series	Nasopharyngeal swab from the mother of one child with PMC grew an identical strain as the one causing conjunctivitis
Brook et al., 1979 (USA)	4	Case report	Throat swab were taken from a 19-year-old woman with PMC and 7 close contacts; an identical strain was identified from 1/7 contacts; neither the case nor the close contacts were given systemic antibiotics
Lewis and Ferris, 1948 (Australia)	28	Case report	An infant with bilateral PMC was treated with oral penicillin and sulphacetamide drops; both parents of the infant and a visiting uncle carried the same meningococcal strain as the infant
Kahaner and Lanou, 1945 (USA)	29	Case report	An infant with unilateral PMC had the same meningococcal type isolated from nose and throat cultures of the father

such as cefotaxime if Gram-negative diplococci are seen on the eye swab, until the pathogen is identified; subsequent antibiotic treatment can then be optimised accordingly.[32,33]

(iii) *What is the duration of oral antibiotic treatment in an otherwise well child with PMC and no systemic symptoms?*

The current UK guidelines recommend seven days of intravenous ceftriaxone for the treatment of IMD.[11] For PMC, the duration of systemic antibiotic treatment in the literature varied from 5 days of oral penicillin[15] to 10 days of oral cefprozil.[30] Like IMD cases, patients with PMC who are treated with antibiotics other than intravenous cephalosporins should also receive ciprofloxacin

chemoprophylaxis to eradicate carriage and, therefore, interrupt potential transmission to close contacts in the future. The recent EU-wide restrictions precautions on the use of systemic fluoroquinolone antibiotics (including ciprofloxacin) due to very rare reports of serious side-effects does not apply to the single dose of ciprofloxacin recommended for chemoprophylaxis of meningococcal disease.[34]

Chemoprophylaxis and meningococcal vaccination for close contacts

Close contacts of patients with IMD have a 1 in 300 (0.3%) risk of invasive disease when antibiotic chemoprophylaxis is not administered; this is more than 300 times the incidence of sporadic invasive disease in the general population.[35] The rationale behind giving antibiotic prophylaxis to close contacts of IMD is to eliminate carriage of meningococci from the close contact group and thus reduce onward transmission. In doing so, the risk of secondary cases in close contacts is reduced by up to 89%[36]

Although rare, the small but significant risk of severe invasive disease among close contacts of PMC cases with several reported fatalities would justify a recommendation for antibiotic chemoprophylaxis for this group. The serogroups responsible for PMC will depend on the circulating strains in that region, and all the major serogroups have been reported to cause PMC (Table). There have also been reports of PMC caused by non-groupable meningococci, which are generally considered to be less virulent, in immunocompetent individuals and, therefore, unlikely to become invasive in the case or their close contacts. Systemic antibiotic treatment of the PMC case and antibiotic chemoprophylaxis for the close contacts should, however, be initiated as soon as *Neisseria meningitidis* is identified to be responsible for the conjunctivitis.

There is currently no evidence for or against offering meningococcal vaccination to PMC cases or their close contacts. Vaccinating the PMC case and close contacts, however, is unlikely to offer any additional protection because meningococcal transmission should have been interrupted by treating the case with appropriate antibiotics and offering chemoprophylaxis to the close contacts.

Conclusions

Primary meningococcal conjunctivitis is rare, with incidence ranging from <0.08% to 2% of all acute conjunctivitis cases, although the true incidence is likely to be underestimated because microbiological investigations are not routinely performed for uncomplicated conjunctivitis cases. Unlike other causes of conjunctivitis, around 10–29% of PMC patients go on to develop IMD. Those who are treated with systemic antibiotics in addition to topical antibiotics alone, however, are significantly less likely to develop IMD compared to those treated with topical antibiotics alone. Clinicians need to be aware of the need to treat PMC cases with systemic antibiotics. Additionally, close contacts of PMC cases may rarely go on to develop severe and potentially fatal invasive disease which can be prevented through appropriate antibiotic chemoprophylaxis, as currently offered to close contacts of IMD cases. Meningococcal vaccination of the PMC case or close contacts is unlikely to offer any additional protection after appropriate antibiotic treatment and prophylaxis, respectively. These findings specific to PMC cases and their close contacts need to be highlighted in the relevant clinical and public health guidelines for the management of sporadic cases of meningococcal disease.

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Declaration of Competing Interest

SNL performs contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London and Public Health England but receive no personal remuneration. The Immunisation and Countermeasures Department has provided GSK with post-marketing surveillance reports on meningococcal, *Haemophilus influenzae*, and pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. All other authors: no conflict.

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