Fifteen-minute consultation: Enterovirus meningitis and encephalitis: When can we stop the antibiotics?

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Abstract

Enterovirus (EV) is the most common cause of aseptic meningitis and has a benign course, unlike EV encephalitis which can result in long term neurological sequelae. There are no active treatments or prophylactic agents and management is purely supportive. Obtaining an EV positive cerebrospinal fluid (CSF) result usually allows antimicrobial treatment to be stopped. This review will answer some of the common questions surrounding EV meningitis/encephalitis.

Case Vignette 1: A 2-month old girl with enterovirus meningitis

An otherwise healthy 2-month old girl presented with fever of 39^{o}C and irritability. Further history was unremarkable except for an older sibling with an upper respiratory tract infection. She was commenced on intravenous cefotaxime and amoxicillin after blood, urine and cerebrospinal fluid (CSF) samples were sent. The CSF showed 203 white cells/mm^3 (30% polymorphs, 70% lymphocytes) with 3 red blood cells/mm^3 and a normal protein and glucose. The CRP was 23 mg/L. Two days later a CSF reverse transcriptase polymerase chain reaction (RT-PCR) result was positive for enterovirus (EV). Bacterial culture results were negative and antibiotics were stopped once this result was known. She made an uneventful recovery.

Case Vignette 2: An 8-day old with enterovirus meningitis and myocardial involvement

An 8-day old boy was admitted with decreased feeding and drowsiness. His mother had had a mild febrile illness in the perinatal period. He was treated with cefotaxime and amoxicillin. The CSF had 366 white cells/mm^3 (65% polymorphs, 35% lymphocytes), protein 1.8 g/L and glucose 1.8 mmol/L. The blood glucose was 3.7 mmol/L and the CSF to blood ratio was 0.49. After 24 hours he developed seizures and required paediatric intensive care unit (PICU) admission. MRI demonstrated brain-stem and basal ganglia infarcts. He also had ST depression on ECG and an echocardiogram demonstrated a dyskinetic left ventricle with mural thrombus. RT-PCR on CSF from day 5 of his illness demonstrated EV. He required prolonged hospitalisation but was discharged after three weeks and has made a good recovery.

Case Vignette 3: An 14-month old girl with enterovirus encephalitis and slow but complete recovery

A previously well 14-month old developed progressive lethargy and weakness with difficulty walking following fever and coryza for a week. She had a widespread erythematous maculopapular rash and bilateral conjunctivitis. She was unable to sit unaided and had a new onset intermittent squint. The CRP was 18 mg/L and blood white cell count normal. An MRI demonstrated bilateral changes in the cerebellum dentate nuclei. The CSF had 36 white cells/mm^3 (100% lymphocytes) with normal protein and glucose. She was initially commenced on ceftriaxone, amoxicillin and acyclovir. RT-PCR on CSF from day 4 of illness was positive for EV, subsequently confirmed as Coxsackie B and antimicrobials were discontinued. She received 2g/kg intravenous immunoglobulin, gradually improved and was discharged on day 8. She

improved slowly over the following months and by a year had complete resolution of her squint and normal mobility.

What are the presenting features of enterovirus meningitis and encephalitis?

The Enterovirus genus within the family Picornoviridae includes a diverse group of human enteroviruses, coxsackieviruses, echoviruses and polioviruses many of which can cause CNS infection. Non-polio enterovirus (EV) infections result in a wide range of clinical syndromes (Box 1). Polioviruses will not be discussed further in this article.

Box 1: Clinical syndromes typically associated with EV infection

- asymptomatic infection
- upper respiratory tract infection
- gastroenteritis
- hand-foot-and-mouth disease and other exanthems (maculopapular, petechial, vesicular)
- acute flaccid paralysis
- meningitis/encephalitis
- neonatal severe sepsis-like syndrome
- myocarditis

Whilst for any specific serotype there is the potential to cause a wide range of clinical syndromes, some are specifically associated with particular clinical manifestations.

EV meningitis in neonates and young infants usually presents with non-specific signs and symptoms, for example fever with no clear focus, irritability, lethargy and reduced feeding. EV meningitis is often clinically indistinguishable from bacterial meningitis. In older children more specific signs of meningitis such as headache, photophobia and neck stiffness may be present [1]. In EV encephalitis seizures, focal neurological signs and altered mental status reflect inflammation of the brain parenchyma.

Risk factors for EV CNS infection include young age and immunodeficiency, especially hypogammaglobulinaemia.

How common is EV meningitis and encephalitis?

EV infections occur throughout the year but are most common in the summer and autumn months [2]. The incidence of viral meningitis in developed countries has been reported between 7-26/100,000 in children less than 14 years old, with the highest incidence in infants less than one year old [3] and EV accounts for most of these infections [4]. A recent UK study identified 70 children admitted to hospital with a final diagnosis of meningitis. Of these 39 had a proven aetiology (13 bacterial and 26 viral) with 20/26 (77%) viral cases being due to EV infections [5]. EV is the most common pathogen causing meningitis in children [6]. EV encephalitis is much rarer accounting for 13% of neonates and children with EV CNS infections in one case series [7].

Does it matter which EV serotype causes disease?

Although some serotypes, for example EV-71 and EV-68, have been associated with more severe CNS disease or worse outcomes [8], clinical management does not alter depending on the serotype detected. EV serotyping is usually only available in regional reference laboratories and is rarely carried out, except in the setting of an outbreak.

Are the CRP or blood WCC abnormal in EV meningitis/encephalitis?

Most studies commenting on WCC and CRP in EV meningitis also include those with non-EV aseptic meningitis. In one study the median (interquartile range) WCC was 9.4 (7.3-14.4) $x10^9$/L [9] and in another 10.8 (8-13.8) $x10^9$/L [10]. In a third study [3] the WCC was normal (less than or equal to $15x10^9$/L) in 72% and raised (greater than $15x10^9$/L) in 28%. Only 18% had a predominance of lymphocytes. Studies investigating blood CRP have found a median (interquartile) range of 17 (7-26) mg/L [10] and 6 (4-13) mg/L [11] and a mean (standard deviation) of 10.8 (27) mg/L [12]. The study by Sormunen et al [13] found 93% of infants had a CRP than 20 mg/L and the maximum CRP was 40 mg/L and in the study by Michos et al [3] the CRP was less than 20 mg/L in 84% of patients (note units in the referenced published article were stated as mg/dL due to a typographical error). A CRP greater than 50 mg/L is unusual in EV meningitis.

What CSF findings are typical for EV meningitis/encephalitis?

The CSF WCC findings demonstrate wide variation in infants with EV meningitis (Table 1). The earlier a lumbar puncture is performed in the illness the more likely the absence of a raised CSF WCC. The WCC differential often shows an early

(within the first 1-2 days) predominance of neutrophils with an increasing proportion of lymphocytes as time progresses. This process is highly variable [4]. In neonates CSF protein levels are frequently raised and glucose levels may be normal or reduced, thus potentially causing confusion with bacterial meningitis [14]. In older infants and children CSF protein and glucose levels are usually normal [15].

Table 1 summarises the typical CSF findings in EV meningitis.

Table 1: Typical CSF findings in EV meningitis [14–20].

	Age of infant/child	
CSF parameter	Less than 90 days	90 days to 16 years
Total white cell count (WCC)	• Median of 79 WCC/mm^3 • Range: 0-4608 WCC/mm^3 (90% of infants have less than 1000 WCC/mm^3) • Up to 33% have a normal WCC	• Median of 82 WCC/mm^3 • Range: 0-1290 WCC/mm^3 • Greater than 90% have an abnormal WCC
Neutrophils	• Very variable (0-98% of total WCC) • In 33% of infants greater than 50% of the total WCC is neutrophils	• Very variable (0-98% of total WCC) • Median of 51% of the total WCC is neutrophils
Protein	Normal or raised	Normal
Glucose	Normal or reduced	Normal

How do I test for EV meningitis/encephalitis?

Previously viral culture was used to detect EV in the CSF. This has been superseded by the use of real-time reverse transcriptase polymerase chain reaction (RT-PCR). RT-PCR has a very high sensitivity and specificity (greater than 95%) although it does vary at different times after the onset of symptoms [21–23]. If the collection of CSF is delayed by more than two days after symptom onset, then a negative CSF EV PCR does not reliably rule out EV meningitis [22]. EV may be detected in the blood in children with CNS infection by RT-PCR [24]. The detection of EV in stool or respiratory secretions is of less value in investigating the aetiology of CNS infection given the frequency of uncomplicated respiratory and gastrointestinal infections with this virus. However, a negative CSF and stool EV PCR result makes a CNS EV infection unlikely [22]. EV serology is possible but rarely has a role in clinical practice.

Is the EV viral load in CSF important?

A study that measured the EV CSF viral load in 21 children less than one year old with a clinical diagnosis of meningitis/encephalitis found it ranged from 241 - 22,468 copies/μL [25]. A higher viral load was not associated with more severe disease [25]. Younger children may have higher viral loads than older children [25]. The CSF EV viral load currently has no clinical utility.

What is the treatment for EV meningitis/encephalitis?

Most cases of EV meningitis only require supportive care, as it is generally a self-limiting illness without any long term sequelae. There are currently no specific therapies for EV infections with a proven benefit. For infants and children with severe CNS infections there are limited data suggesting intravenous immunoglobulin (IVIG) may be beneficial [26]. The only randomised clinical trial of IVIG for the treatment of EV infections in neonates demonstrated some very minor improvements in clinical and laboratory parameters in those infants who received IVIG, however, only 16 infants were included in the trial [27]. In older children there are conflicting reports on the benefit of IVIG in EV CNS infection. A clinical trial (The IgNiTE Study, http://trials.ovg.ox.ac.uk/trials/immunoglobulin-treatment-encephalitis) is currently underway to assess the role of IVIG in all cause encephalitis, including EV encephalitis, in children 6 weeks to 16 years old. There is currently insufficient evidence to recommend the routine use of IVIG for infants and children with EV CNS infection.

Pleconaril, a capsid inhibitor, has *in vitro* activity against EV, however, clinical trials have been underpowered to be able to demonstrate any benefit in neonates and infants with severe EV CNS infection or sepsis [28,29]. It is not licensed for use in the UK or USA and is no longer available even for compassionate use in the UK. Another antiviral for the treatment of severe EV infections, pocapivir, has been used safely in a neonate [30], however, it is still in development and has not been evaluated in a clinical trial.

When is it safe to stop antibiotics in children with proven EV meningitis/encephalitis?

Almost all children who present with signs and symptoms suggestive of CNS infection will have been started on antibiotics empirically pending microbiological results. Antibiotics can be stopped once a positive EV CSF result is obtained if the clinical and laboratory features make bacterial meningitis unlikely (low CRP and blood WCC, negative CSF bacterial cultures). Whilst bacterial and EV co-infection are reported [31–33], the small number of reports and clinical experience suggest this is rare [34]. When CSF has been obtained after antibiotics have been given a negative bacterial culture cannot exclude co-existent bacterial infection and decision making is then more challenging especially where the CSF shows a neutrophil predominance. However, if the clinical picture and laboratory findings make bacterial meningitis unlikely (i.e. CSF absolute neutrophil count less than 1000 cells/mm^3, CSF protein less than 0.8 g/L, peripheral blood absolute neutrophil count less than 10,000 cells/mm^3 and no history of seizures before or at presentation) antibiotics can be discontinued.

A positive EV CSF result is associated with a reduction in hospital length of stay and length of course of antibiotic treatment compared to children with CSF not tested for EV [3,35,36]. EV CSF RT-PCR testing should, therefore, be carried out in all children with signs and symptoms suggestive of a CNS infection who have required a lumbar puncture and have a pleocytic CSF. For infants less than three months old this should be extended to include those where the CSF WCC is normal as EV infection with no pleocytosis is more common in this age group.

Are there any acute complications of EV meningitis/encephalitis?

Neurological complications (e.g. seizures, intracranial haemorrhage or infarction, hydrocephalus) can occur as a result of direct EV CNS infection, predominantly EV encephalitis. EV infection is also occasionally associated with myocarditis and hepatitis, particularly in neonates, and thus investigations for these complications should be considered if the clinical picture is suggestive.

Is neuroimaging required for EV meningitis/encephalitis?

Neuroimaging (CT or MRI) is not usually undertaken in the setting of suspected EV meningitis. Neuroimaging will, however, usually be undertaken in infants and children with signs and symptoms suggestive of encephalitis to aid diagnosis or to investigate for potential sequelae or differential diagnoses. There are no abnormalities on neuroimaging that are characteristic for EV CNS infection, although white matter changes are common in EV encephalitis [37–39]. Any part of the brain, brainstem and spinal cord can be affected [39].

Is EV infection contagious and can it be prevented?

Enteroviruses are spread via the faeco-oral route and also by respiratory droplets. Neonates, who are the most vulnerable to severe EV infections, often acquire the infection from their mothers (either antenatally, intrapartum or postnatally) [14] but may also acquire it from other contacts. Older children develop EV infection from infected contacts. Ensuring excellent hand hygiene reduces the risk of transmission. In hospital, standard contact precautions should be followed for infection control purposes.

There are currently no prophylactic agents against EV available. Human immunoglobulin has antibodies against some EV serotypes that may help reduce the risk of EV infection [40], however, immunoglobulin should not be routinely used to prevent EV infections. Vaccines for serotypes that have been associated with large outbreaks, for example EV-71, are available in some countries for example China [41]. No EV vaccines are available in the UK.

Is any follow up required after EV meningitis/encephalitis?

Whilst hearing loss is a common sequelae of bacterial meningitis it appears to be rare following EV meningitis where most cases resolve without sequelae [42]. In one Chinese study including 74 children with EV serotype 71 meningitis, at 2-6 months after hospital discharge all had fully recovered and had normal neuropsychological tests [37].

A retrospective study of 103 children found all had normal hearing at 8-10 weeks after EV meningitis [42]. Another study of infants with EV meningitis identified by viral culture, found one of 33 (3%) had sensorineural hearing loss identified at follow up between 2-17 years and this was in an individual with a family history of sensorineural hearing loss [43]. The lack of control data or information on hearing loss preceding meningitis make it unclear whether the hearing loss was caused by the EV infection. From the data available routine hearing screening is not warranted following isolated EV meningitis.

Children with EV encephalitis are much more likely to have long term neurological sequelae. An Australian study including children with EV encephalitis demonstrated eight of 18 (44%) had neurological abnormalities at follow up including epilepsy,

learning disability, behavioural problems, speech problems and physical or motor disability [39]. In the Chinese study [37] mentioned above two (5%) of 40 children with EV encephalitis had abnormal neuropsychological tests at 2-6 months after hospital discharge. Infants and children should be routinely followed up after hospital discharge for EV encephalitis to assess hearing, vision and neurodevelopmental progress.

Should infants and children with parechovirus CSF infections be managed similarly to those with EV CSF infections?

Parechoviruses are genetically closely related to enteroviruses and can also cause CNS infection, particularly in young infants [44]. Parechovirus and EV CNS infections are clinically indistinguishable and have similar associated acute complications, for example neonatal severe sepsis-like-syndrome, myocarditis and hepatitis [45]. EV RT-PCR will not detect parechoviruses for which specific RT-PCR testing is required. Parechovirus CNS infections are managed as for EV CNS infections as outlined above [46]. There is less data on outcome after parechovirus CNS infection than for EV.

Conclusion

EV meningitis infection is relatively common, especially in infants, but EV encephalitis much less so. The diagnosis is based on RT-PCR from CSF as EV infection is indistinguishable from bacterial and other viral causes of meningitis clinically and from inflammatory markers in the blood (WCC and CRP) and CSF (WCC, protein and glucose). There is no active treatment and thus management is

purely supportive. An EV positive CSF RT-PCR result combined with a clinical picture compatible with EV meningitis and negative bacterial cultures should lead to stopping antimicrobials. A positive EV RT-PCR result has been shown to reduce the length of hospital stay and length of antimicrobial treatment in children with signs and symptoms of meningitis. CSF EV RT-PCR should, therefore, be routinely requested in infants and children with presumed CNS infection and a raised CSF WCC and in all infants less than three months old, with suspected meningitis. The vast majority of infants and children with EV meningitis appear to have no long term sequelae, however, long term neurological complications have been reported, especially in infants with EV encephalitis. Parechovirus CNS infections should be managed similarly to those caused by EV.

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