Coxsackievirus Infections

Compiled by Prof E Vardas

Introduction
Enteroviruses are small, single-stranded, positive-sense RNA viruses from the *Enterovirus* genus in the family *Picornaviridae*. They cause disorders with a wide range of clinical manifestations including cutaneous, visceral, and neurological diseases. Human enteroviruses traditionally were classified according to their pathogenicity and cytopathic effects in tissue culture – these subgroups were polioviruses (3 serotypes), coxsackievirus A (23 serotypes), coxsackievirus B (6 serotypes), and echoviruses (28 serotypes). However, because of the limitations of this system, serologically distinct human enteroviruses isolated since 1970 have been designated by serotype numbers, beginning with enterovirus (EV) 68.

Epidemiologically, coxsackieviruses are distributed worldwide and infections occur most frequently during spring and summer. Humans are the only reservoir, and like most enteroviruses spread is through the faecal-oral and respiratory routes with virus present in most body fluids including saliva, tears, faeces, urine. The incubation period is 7–14 days. Coxsackieviruses initially replicate in the upper respiratory tract and distal small bowel. They may be isolated from the respiratory tract for up to 3 weeks, and from faeces up to 8 weeks after initial infection. They replicate in the submucosal lymph tissue and disseminate to the reticuloendothelial system with further dissemination to target organs following a secondary viraemia.

Clinical significance
The majority of coxsackievirus infections (± 90%) are subclinical or present as a mild, non-specific febrile illness. Occasionally severe disease occurs, especially in neonates and immunosuppressed individuals, resulting in serious morbidity and rarely mortality. Organ-specific symptoms, associated viruses, and common presenting symptoms are outlined in Table 1. In general, coxsackie A viruses tend to infect the skin and mucous membranes, causing herpangina, acute haemorrhagic conjunctivitis (AHC), hand-foot-and-mouth disease (HFMD), as well as paralytic CNS disease similar to poliomyelitis. Figure 1 shows a typical HFMD rash and oral lesions, and acute haemorrhagic conjunctivitis. Coxsackie B viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myopericarditis, hepatitis and systemic neonatal disease. Life-long type-specific immunity develops after recovery.

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Figure 1. Some common coxsackievirus infections
Vesicular exanthem on the skin (A) and oral mucosa (B) associated with HFMD commonly caused by coxsackieviruses A6, A10, A16 and EV71. Haemorrhagic conjunctivitis (C) is commonly due to coxsackievirus A24 and EV70.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Virus</th>
<th>Presenting Symptoms</th>
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<tr>
<td>Aseptic meningitis</td>
<td>Both A and B</td>
<td>Fever and chills, nausea and vomiting, malaise, headache, meningeal, light sensitivity, and upper respiratory tract symptoms. Seizures, lethargy, and movement disorders occur early in 5 – 10% of patients. No long-term neurologic deficits in infants. Adults may have a more prolonged period of fever and headache than children.</td>
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<td>Meningoencephalitis</td>
<td>A9, B2, B5, EV71</td>
<td>Encephalitis is unusual but can sometimes accompany aseptic meningitis. Enteroviruses account for approximately 5% of all cases of encephalitis. In rare cases, enterovirus encephalitis mimics herpes simplex virus encephalitis.</td>
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<td>Other Neurologic Complications</td>
<td>Both A and B, EV71, Enterovirus D68</td>
<td>Sporadic cases of acute flaccid paralysis that mimics poliovirus infection. Guillain-Barré syndrome, acute cerebral ataxia, transverse myelitis, polyradiculoneuritis. NOTE: acute flaccid paralysis is a notifiable condition.</td>
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<tr>
<td>Acute Haemorrhagic Conjunctivitis</td>
<td>A24, EV70</td>
<td>Highly contagious. Pain, oedema of the eyelids together with subconjunctival haemorrhage. Patients may report photophobia, foreign body sensation, fever, malaise, and headache. Spontaneously resolves in approximately 1 week. Rare complications include keratitis and motor paralysis.</td>
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<tr>
<td>Myopericarditis</td>
<td>Mainly B</td>
<td>Enteroviruses accounts for 50% of all cases of acute viral myopericarditis. Can occur at any age, males &gt; females and frequently in young adults. Clinical presentation ranges from minimal symptoms to heart failure and death. Commonly presenting features include dyspnoea, chest pain, fever, and malaise; often preceded by an upper respiratory infection in the previous 7 – 14 days. Signs: pericardial friction rub, gallop rhythm, and cardiomegaly and/or pericardial effusion on CXR. ECG: varying degrees of heart block and ST/T changes. Decreased ejection fraction and left ventricular wall abnormalities on echo. Elevated serum myocardial enzymes. Mortality rate is low, and prognosis good, better in children than in adults. Complications: pericardial effusion, arrhythmia, heart block, valvular dysfunction and dilated cardiomyopathy.</td>
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| Exanthems                         | A6, A10, A16, EV71 and other group A | Two distinct rashes occur:  
- HFMD which most often affects children and spreads easily to other family members. Usually present with sore throat and mouth; vesicles on buccal mucosa and tongue. Vesicles can coalesce, form bullae, and ulcerate. Peripheral cutaneous lesions occur in 75% of cases. Severe HFMD is associated with coxsackievirus A6 and EV71.  
- Herpangina: a vesicular enanthem of the posterior oropharynx with fever, sore throat, occasional throat exudate, odynophagia, and dysphagia. Typically quick recovery. |
| Epidemic pleurodynia (Bornholm disease) | Mainly B                  | Direct viral inflammatory infection of intercostal muscles. Present with fever and sharp, paroxysmal, spasmodic pain in the chest and upper abdomen. Complete recovery after 1 week. |
Diagnosis
Tests for routine diagnosis of coxsackievirus infections comprise antibody detection, and molecular detection by PCR.

Molecular detection by PCR is the method of choice for identifying coxsackieviruses in clinical samples such as CSF, throat swabs and faeces samples. The main disadvantage of PCR tests is that it detects conserved genes that are common to the entire enterovirus group, and so cannot easily and cost effectively provide type-specific information. Due to the sensitivity of molecular testing, a positive enterovirus PCR result may represent either a recent or a current infection. PCR testing of blood samples for enteroviruses is NOT recommended as coxsackievirus viraemia is short-lived.

Serological tests for coxsackievirus include antibody neutralisation tests, immunofluorescent assays (IFA) or immunoassays (ELISA). Antibody neutralisation tests detect only neutralising antibodies, and can be problematic due to cross-reactivity between different coxsackievirus serotypes. Furthermore neutralisation tests require live virus and cell culture systems, and therefore take more than 48 hours for results to be available. These tests are difficult to standardise between different laboratories, labour intensive and suffer from significant inter- and intra-observer variability.

Currently, the serological diagnostic method of choice for coxsackievirus infections is IFA, which provides a rapid, standardised, and automated platform for the identification of antibodies to a range of coxsackievirus serotypes. The IFA test used by Lancet Laboratories uses cells infected with coxsackieviruses A7, A9, A16, A24, and B1 - B6, which allow detection of both IgG and IgM antibodies against these specific coxsackieviruses.

IgM antibodies become detectable a few days after the onset of disease, and titres remain high during the acute illness. Acute or very recent coxsackievirus infection can be confirmed with a positive IgM result, or with a significant increase in IgG titre between acute and convalescent samples taken at least 2 weeks apart.

Treatment
There are currently no antiviral agents for treatment of coxsackievirus infection, nor is there a preventative vaccine. Patients should be treated symptomatically and reassured that this is a self-limiting infection. Antibiotic treatment is only required if there is a proven secondary bacterial infection. Standard precautions, including basic hand hygiene and careful disposal of potentially infected faeces and respiratory secretions should be sufficient to prevent spread.

References