

1 Title

Fact Sheet on Infection Control for Enteroviral Infection in Hospitals

2 Causative Agents and Epidemiology

- 2.1 Enteroviruses (EV) refer to a group of small, non-enveloped RNA viruses comprise four species, namely Polioviruses (3 serotypes), Coxsackieviruses A (23 serotypes, Coxsackieviruses B (6 serotypes), Echoviruses (31 serotypes) and Enteroviruses (4 serotypes, namely type 68-71).
- 2.2 In Hong Kong, enteroviral infections peak in May to July with epidemic occurring every two to three years. Young children are its main target and reservoir, but adults can also be infected.
- 2.3 EV71 infection has become a statutory notifiable disease in Hong Kong since March 2009. As of 31 May, 2010, among patients with notified EV71 infection, there were 4 cases with severe complication and no fatal case. (Refer to appendix II)
- 2.4 EV 71 is more often associated with severe complications such as encephalitis, poliomyelitis-like paralysis and even death.
- 2.5 In Singapore, the annual incidence rate per 100,000 population increases from 125.5 in 2001 to 435.9 in 2007. The predominating circulating virus was Coxsackievirus A14 in the 2002, 2005 and 2007 epidemics, and EV71 in the 2006 epidemic. [1]
- 2.6 In Taiwan, EV71 was the most common circulating serotype in 1998, 2000 and 2001 and Coxsackievirus A2 was the predominant serotype in 2008 outbreaks. Compared with those infected by EV71, the children with Cox A2 infection mostly presented with herpangina, had fewer central nervous system complications, and had better overall outcome. [2, 3]
- 2.7 The incubation period for HFMD is 3 to 7 days.
- 2.8 The infectious period starts from several days before the appearance of symptoms and peaks within one week of disease onset. The virus may be excreted in the stools for 6-8 weeks and in respiratory secretion for 1 week
- 2.9 HFMD is mainly transmitted by the faecal-oral route and respiratory droplets. Direct contact with open and weeping skin vesicles or contaminated objects may also transmit the virus.

3 Clinical Manifestations [4, 5, 6, 7, 8, 9, 10]

- 3.1 Enteroviral infections are mostly subclinical or presented as non-specific febrile illness. The same virus can cause several different clinical syndromes. Conversely, the same clinical picture can be caused by different enteroviruses.

Syndrome/Disease	Predominant virus	Clinical features
Nonspecific febrile illness	All types	Fever with upper respiratory and/or gastrointestinal symptoms
Meningoencephalitis	Echoviruses, Enterovirus 71, Coxsackieviruses A & B	Fever, meningeal signs, change in mental status, seizure

Herpangina	Coxsackieviruses A & B	Fever, painful oral vesicles and/or ulcers on tonsils and posterior pharynx
Hand, foot and mouth disease	Coxsackievirus A16, A9 Enterovirus 71	Fever, vesicles and/or ulcers on buccal mucosa and tongue and on interdigital surfaces of hands and feet
Non specific exanthem	Echoviruses	Variable rash +/- fever
Myocarditis/pericarditis	Coxsackieviruses B	Uncommon, myocarditis/pericarditis may present as heart failure or dysrhythmia
Acute haemorrhagic conjunctivitis	Enterovirus 70 Coxsackieviruses A (Adenoviruses)	Epidemic cause of conjunctivitis with lid swelling, subconjunctival haemorrhage and eye pain without systemic symptoms
Neonatal disease	Coxsackieviruses B Echoviruses	Sepsis like picture, meningo-encephalitis, hepatitis, myocarditis
Pleurodynia	Coxsackievirus B3, B5	Uncommon, epidemic, fever and severe muscle pain of chest and abdomen
Acute flaccid paralysis	Coxsackievirus A7, Echoviruses, Enterovirus 71	Fever followed by sudden asymmetric flaccid paralysis

3.2 EV71 infection should be suspected in patients presenting with fever, papulovesicular rash involving the distal extremities, buttocks and extensor surfaces of the knees, and oropharyngeal ulcers. The classical clinical features of HFMD, however, are not necessarily always present together, even in patients with severe EV71 infection. The combination of presenting features can be variable. Scanty papular skin rash without vesicular eruption, absent or minimal oropharyngeal ulcers, absence of fever or just fever without cutaneous or mucosal lesions at presentation have all been documented, even in fatal cases.

3.3 The importance of eliciting a contact history cannot be over-emphasized.

4 Laboratory Diagnosis [11, 12, 13]

4.1 Viral studies for enteroviruses should focus on hospitalised patients with HFMD/ Herpangina/ suspected enterovirus infection with rapid clinical deterioration or severe complications like

- aseptic meningitis / encephalitis
- acute flaccid paralysis
- pulmonary edema/pulmonary hemorrhage/ARDS
- myocarditis

4.2 Specimens should be taken in the early phase of the disease for investigation, including

- rectal specimen, preferably stool rather than rectal swab (shedding continues for a 6-8

- weeks)
 - nasopharyngeal aspirate or throat swab (within the first few days of onset of illness)
 - others as appropriate - vesicular fluid, CSF, eye swab and tissue
- 4.3 Specimens, except CSF, should be put in viral transport medium (T/M) and kept at 4°C during transport to the laboratory. RT-PCR and culture can be performed on the same specimen.
- 4.4 Specimens should be collected from all NDORS notified cases (please refer to 6.1 for reporting criteria) and send to Virology Division, PHLBS, CHP for testing.
 - During non-office hours, arrangement should be made via MCO of CHP-DH.
 - Results are expected to be available in 1-2 days.
- 4.5 RT-PCR on EV would be performed by Virology Division, PHLBS, CHP on cases:
 - in an outbreak; or
 - NDORS notified cases, i.e. suspected EV-71 infection
 - **Severe cases (with or without features of HFMD) suspected to be caused by enterovirus infection**

Please put down clearly the clinical features on the request form.

- 4.6 Viral culture service is available for patients suspected of enterovirus infections,
 - Specimens (refer to 4.2 in the above) should be sent to the Virology Division, PHLBS for processing.
 - **Additional samples may be sent to Virology Laboratory of QMH for RT-PCR testing.**
 - Results are expected to be available in 7 -8 days.
- 4.7 Serologic testing is also available at Virology Division, PHLBS and QMH for retrospective diagnosis of unusual cases. Paired serum samples (acute and convalescent) should be taken at least 14 days apart.

5 Infection Control Measures

- 5.1 Standard Precautions should be strictly observed in healthcare settings.
- 5.2 **Perform hand hygiene by hand washing or follow the WHO Five Moments for Hand Hygiene.**
 - **Hand hygiene can be performed by rubbing hands with alcohol handrub for at least 20 seconds if they are not visibly soiled.**
 - **Based on the currently available scientific evidence, 80% ethanol (i.e. WHO formula I) is the preferred choice of alcohol handrub in caring patients with suspected or confirmed enterovirus infection. [15, 16, 17]**
- 5.3 Contact precautions for duration of illness are indicated for infants and young children or if the patient is incontinent and may contaminate the environment OR patients admitted with confirmed or suspected with EV71 infection associated with severe complications OR for control of institutional outbreaks.
 - Single room isolation is preferred for patients admitted with confirmed or suspected with EV71 infection associated with severe complications. If the number of cases increases, cohorting of patients could be an option.
 - No negative pressure is needed for isolation room
 - Wear gloves and gown once entering the isolation room or cohorting areas. Practice hand hygiene immediately and thoroughly after removing gloves.
 - Use household bleach (1 in 49 diluted) for cleansing contaminated environment.

- Put on personal protection equipments, e.g. mask, faceshield when carrying out procedures that are likely to generate splashes to mucous membranes.
- Restrict the direct contact of patients suffering from HFMD/ enterovirus infection with other patients
- Linen and waste from patients suffering from HFMD should be handled with care, and wash hands after handling.
- Advice to the patients or parents/ caretakers: Pay attention to hand hygiene cleanliness. Do not let children attend nurseries/kindergartens/schools/activities that mix with other children until afebrile and all vesicles have dried up (If enterovirus-71 is confirmed to be the aetiological agent, then take 2 more weeks of sick leave after all vesicles dry up) ; or to follow the advice from CHP if there is an outbreak

5.4 HFMD in Pregnant Women [18]

- Most enterovirus infections during pregnancy cause mild or no illness in the mothers.
- There is no clear evidence that maternal enterovirus infection causes adverse outcomes of pregnancy, such as abortion, stillbirth, or congenital defects.
- Mothers infected shortly before delivery may pass the virus to the newborn. Risk of newborn infection is higher if mothers are having symptoms of enteroviral illness during delivery.
- Most infected newborn have mild illness, but rare severe complications can occur. The risk of developing severe complications is higher during the first 2 weeks of life.
- HCW, including pregnant staff, should strictly observe the Standard and Contact precautions during patient care procedures to protect themselves from contracting any infectious disease, such as enteroviral infection.

6 Reporting of Cases

6.1 General conditions

- All patients regardless of age who present with severe complications clinically compatible with EV71 should be notified and reported to CENO via Notifiable Diseases and Outbreak Reporting System (NDORS) by HA clinicians. Medical Control Officer (MCO) of CHP, DH (pager: 7116 3300 #9179) is the contact person during non-office hour.
- Inform the hospital infection control team on any suspected or confirmed case of Enterovirus infection associated with severe complications. Any hospital-acquired Enterovirus infection should also be reported to hospital ICT for further investigations.

6.2 Sick Leave Reporting for health-care staff

- Those developing any symptoms of Enterovirus infection (e.g. fever, rash, vesicular lesions, ect) AND with known contact history should seek medical advice and must be off from work for the duration of illness.
- He or she can only resume duty after all symptoms have subsided, e.g. fever has been down and all vesicular lesions have dried up.
- Supervisor of the concerned staff should notify hospital ICT on the incident and report via Staff Early Sickness Alert Systems (SESAS).

7 Patient Management [19, 20, 21, 22, 23, 24, 25]

- 7.1** Most cases of HFMD and herpangina are mild and do not warrant hospitalization. Prompt recognition and management of patients with severe complications is of paramount importance.
- 7.2** Secondary cases from household contact may be more severe (inoculum effect or initial high viral load due to prolonged close contact) and require closer observation.
- 7.3** Supportive treatment, (including prompt fluid balance avoiding fluid overload and dehydration, ventilator support in case of respiratory failure or CNS suppression) remain the mainstay.
- 7.4** There is no definite antiviral therapy. The efficacy of intravenous immunoglobulin (IVIG) therapy in severe EV71 infection remains to be proven. The Centre for Disease Control of Taiwan does not recommend its use in children >5 years of age.
The indications for IVIG therapy proposed by Taiwan CDC include:
- children with HFMD / herpangina or
 - children who are close contacts of confirmed HFMD / herpangina cases (i.e. only an epidemiologic link in the absence of clinical features of either condition) **and** who develop the following signs during the course of illness:
 - myoclonic jerks plus unexplained tachycardia (HR >150/min)
 - acute flaccid paralysis
 - acute encephalitis, especially if accompanied by specific features of focal brainstem dysfunction such as ataxia, cross hemiplegia, cranial nerve palsy or brainstem dysautonomia
 - acute respiratory failure (acute pulmonary oedema, pulmonary haemorrhage, ARDS)
 - heart failure
 - sepsis syndrome (not recommended if complicated by multiorgan failure)
 - When IVIG is considered, the regimen recommended by Taiwan CDC is 1 g/kg infused over 12 hours for once only.
- 7.5** There is no preventive vaccine against enteroviral infection.

Reference:

1. Ang LW, Koh BK, Chan KP, Chua LT, James L, Goh KT. Epidemiology and Control of Hand, Foot and Mouth Disease in Singapore, 2001-2007. *Ann Acad Med Singapore* 2009 Feb; 38 (2): 106-112
2. Chen SP, Huang YC, Li WC, Chiu CH, Huang CG, Tsao KC, Lin TY. Comparison of Clinical Features Between Coxsackievirus A2 and Enterovirus 71 During the Enterovirus Outbreaks in Taiwan, 2008: A Children's Hospital Experience. *J Microbiol Immunol Infect* 2010 Apr; 43 (2): 99-104
3. Chang LY. Enterovirus 71 in Taiwan. *Pediatr Neonatol.* 2008 Aug; 49 (4): 103-112
4. Alexander JP Jr, Baden L, Pallansch MA, Anderson LJ. Enterovirus 71 infection and neurologic disease—United States, 1977–1991. *J Infect Dis* 1994; 169: 905–8.
5. Chang LY, Huang YC, Lin TY. Fulminant neurogenic pulmonary oedema with HFMD. *Lancet* 1998; 352: 367.
6. Chang LY, Lin TY, Hsu KH, Huang YC et al. Clinical features and risk factors of pulmonary oedema after enterovirus-71-related hand, foot, and mouth disease *Lancet* 1999; 354: 1682–86
7. Huang CC, Liu CC, Chang YC, Chen CY et al. Neurologic Complications in Children with Enterovirus 71 Infection. *N Engl J Med* 1999; 341: 936-942
8. Ho M, Chen ER, Hsu KH, Twu SJ et al. An Epidemic of Enterovirus 71 Infection in Taiwan. *N Engl J Med* 1999; 341: 929-935
9. AbuBakar S, Chan YF, Lam SK et al. Outbreaks of Enterovirus 71 Infection. *N Engl J Med* 2000; 342: 355-356
10. Pérez-Vélez CM, Anderson MS, Robinson CC et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge *Clin Infect Dis.* 2007 15; 45(8):950-7.
11. Sawyer MH, Holland D, Aintablian N, Connor JD et al. Diagnosis of enteroviral central nervous system infection by polymerase chain reaction during a large community outbreak *Pediatr Infect Dis J* 1994; 13(3):177-82.
12. Rotbart HA, Ahmed A, Hickey S, Dagan R et al. Diagnosis of enterovirus infection by polymerase chain reaction of multiple specimen types. *Pediatr Infect Dis J* 1997; 16(4):409-11.
13. Nolte FS. Case studies in cost effectiveness of molecular diagnostics for infectious diseases: pulmonary tuberculosis, enteroviral meningitis, and BK virus nephropathy *Clin Infect Dis.* 2006 1; 43(11):1463-7.
14. Gilbert GL. Infections in pregnant women. *Med J Aust.* 2002 Mar 4; 176 (5): 229-236
15. J.B. Kurtz ET AL. The action of alcohol on rotavirus, astrovirus and enterovirus. *J Hosp Infect.*

1980; 1:321-325.

16. Kurtz, J. B. Virucidal effect of alcohol against echovirus 11. *The Lancet*. 1979 March i:496–497.
17. Murray Drulak et al. The relative effectiveness of commonly used disinfectants in inactivation of echovirus 11. *J. Hyg., Camb.* (1978), 81:77-87.
18. US CDC. Fast Facts and Questions and Answers for Hand, Foot, & Mouth Disease (HFMD). <http://www.cdc.gov/ncidod/dvrd/revb/enterovirus/hfmd-ga.htm>
19. Taiwan CDC. Guidelines on clinical management of enterovirus infection and its complications (in Chinese). <http://www.cdc.gov.tw/public/Attachment/951415533871.pdf>
20. Taiwan CDC. Disease Information for Hand, Foot and Mouth Disease (in Chinese). http://www.cdc.gov.tw/sp.asp?xdurl=disease/disease_content.asp&id=1662&mp=1&ctnode=1498#01
21. US CDC. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007. http://www.cdc.gov/ncidod/dhqp/gl_isolation.html
22. Scientific Committee on Enteric Infections and Foodborne Diseases. Strategies for the Prevention and Control of EV71 Infection in Hong Kong. http://www.chp.gov.hk/files/pdf/sas4_ev71_20050927.pdf
23. Centre for Health Protection. Letters to Doctors. Guideline on Hand-foot-mouth Disease (HFMD) Management in health care settings issued on 23 May 2007. http://www.chp.gov.hk/files/pdf/letters_to_doctors_2007052301.pdf
24. Department of Health, Hong Kong. Statistics on on Communicable Disease: Hand, foot and mouth disease. Yearly Enteroviral infections from 1994-2008(Jan-Feb) http://www.chp.gov.hk/data.asp?lang=en&cat=4&dns_sumID=53&id=292&pid=44&p_d=26
25. Centre for Health Protection. Guidelines on prevention of communicable diseases in child care centres / kindergartens / schools. http://www.chp.gov.hk/files/pdf/School_full_eng_20090115.pdf

Appendix I: Notes on diagnostic methods based on specimen types

- ♦ RT-PCR has superior sensitivity compared to cell culture for the identification of enteroviruses in the CSF (up to 86 percent versus 30 percent).
- ♦ Among patients with CNS manifestations and a negative CSF PCR, upper respiratory tract and gastrointestinal tract specimens for enterovirus PCR may be needed to establish a diagnosis of enterovirus infection.
- ♦ Sensitivity of PCR compares favorably to that of culture for respiratory and serum specimens, although urine culture may still be superior to urine PCR. Limitations to PCR include availability and serotyping capabilities.
- ♦ Because the EVs are shed from the oropharynx and gastrointestinal (GI) tract for weeks to months after infection, their detection from these sites must be cautiously interpreted. Their presence at these sites does not establish causality of the syndrome being evaluated.
- ♦ The identification of an EV from the CSF, blood, tissue or urine (if sterilely obtained), is strongly supportive of an invasive infection and carries with it a high probability of being the causal agent of the patient's illness. Samples from these sites represent the ideal sources from which to diagnose EV infections

Appendix II: Yearly Enterovirus infections 2005 - 2010 (As of May 27, 2010)

(Source: Centre for Health Protection, Department of Health, Hong Kong
http://www.chp.gov.hk/en/guideline1_year/29/134/441/502.html)

Year	Number of HFMD institutional outbreaks (persons affected)^	Number of EV71 cases	Number of EV71 cases with severe complication	Number of fatal cases
2005	90 (656)	8	0	0
2006	236 (1743)	16	1	0
2007	157 (1081)	12	0	0
2008	167 (967)	98	8	1
2009	103 (727)	31	3	1
2010	211	33	3	0

^Statistics on HFMD also includes herpangina

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