Epidemic enteroviral infections – clinical presentation, complications and management

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Human enteroviruses

>90 serotypes of non-enveloped small RNA viruses of Picornaviridae family

- Coxsackieviruses A (23 serotypes)
- Coxsackieviruses B (6 serotypes)
- Echoviruses (31 serotypes)
- Polioviruses (3 serotypes: 1, 2, 3)
- Enteroviruses (4 serotypes: 68, 69, 70, 71)
- Unclassified enteroviruses (>30 serotypes)

Human enteroviruses

- ubiquitous, worldwide distribution
- humans are the only known natural hosts
- increased activity and transmission mainly during summer and early autumn months in temperate climates (peaks in May to July in HK) while prevalent year-round in tropical climates
- young children are its main target and reservoir but adults can also be infected
- routes of transmission
 - faecal-oral (infants in diapers appear as to be the most efficient transmitters)
 - oral-oral (sharing of eating utensils foodborne, waterborne)
 - direct contact (faeces, saliva, respiratory secretions, vesicular fluid)
 - fomites
 - droplets (when there is an associated respiratory illness)
 - vertical (rare)



Immunity

- immunity to enteroviral infection is serotype specific
- humoral immune response plays a dominant role in acute infection and protection against reinfection
- secretory IgA, which appears in mucosal secretions and colostrum 2-4 weeks after infection, provides relative protection against infection
- infants retain transplacental immunity for the first 4-6 months of life



HAIDC Risk profile among different age groups

Age	Immunity	Risk	Reasons
0-5 years old	_	++++	No previous exposure Immature immunity
6 years old	++	+++	Fair personal hygiene Contract the virus while in kindergarten
7-12 years old	+++	++	School
Adult	++++	+	Stress



disease (HFMD)

Non-specific exanthem

Myocarditis/pericarditis

Acute haemorrhagic

Neonatal disease

Acute flaccid paralysis

conjunctivitis

Pleurodynia

Enteroviral infections are mostly subclinical Same virus can cause several different clinical syndromes Same clinical picture can be caused by different enteroviruses

and tongue, papulovesicular rash on hands,

Uncommon, myocarditis / pericarditis may

present as heart failure or arrhythmia

eye pain without systemic symptoms

Epidemic cause of conjunctivitis with lid swelling, subconjunctival haemorrhage and

Sepsis-like picture, meningoencepahalitis, hepatitis, myocarditis, pancreatitis, DIC

Uncommon, epidemic, fever and pain of

chest and abdomen, costochondritis

flaccid paralysis or monoplegia

Fever followed by sudden asymmetric

feet, knees and buttocks

Variable rash +/- fever

Syndrome	Predominant virus	Clinical features
Non-specific 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 on tonsils and

Non-specific febrile illness	All types	gastrointestinal symptoms
Meningoencephalitis	Echoviruses, Enterovirus 71 Coxsackieviruses A & B	Fever, meningeal signs, change in mental status, seizure
Herpangina	Coxsackieviruses A & B Enterovirus 71	Fever, painful oral vesicles on tonsils and posterior pharynx
Hand, foot and mouth	Coxsackieviruses A16, A9	Fever, vesicles / ulcers on buccal mucosa

Enterovirus 71

Echoviruses

Coxsackievirus B

Enterovirus 70, Coxsackieviruses A

Coxsackieviruses B, Echoviruses

Coxsackieviruses A7, Echoviruses

Coxsackieviruses B3, B5

Enterovirus 71

Epidemic enteroviral infections

Epidemic HFMD – Coxsackie A16, EV71

 Epidemic acute haemorrhagic conjunctivitis – EV70, Coxsackie A

Case scenario

- 4-year-old girl with fever for 2 days, sore throat, refusal to feed and drooling of saliva for 1 day
- non-itchy slightly tender rash noted on distal extremities, knees and buttocks on day of clinic visit
- no respiratory or gastrointestinal symptoms
- several classmates had recently been absent from the kindergarten due to similar illness

Hand, foot and mouth disease









Courtesy of Paediatric Infectious Disease Unit, HA Infectious Disease Centre



















Index of suspicion

During an epidemic, EV71 or Coxsackie A16 infection should be suspected if

- fever
- papulovesicular rash involving the distal extremities, buttocks and extensor surface of the knees
- oropharyngeal vesicles / ulcers
- a positive contact history (most contributory)



Hand, foot and mouth disease

- epidemics in May to July are caused by Coxsackievirus A16 and Enterovirus 71
- major route of transmission is faecal-oral, also spread by respiratory droplets and direct contact with objects contaminated by faeces, respiratory secretions, saliva and vesicular fluid from infected persons
- enteroviruses can survive for days on fomites at room temperature
- incubation period 3-7 days
- infectious several days before symptom onset but most infectious in first week of illness
- virus shed in respiratory secretions for 1 week and in stool for 6-8 weeks

Transmission rates of EV71

Household contacts (overall) 52%

siblings84%

cousins83%

parents41%

grandparents28%

uncles and aunts26%

Intra-familial and kindergarten transmission as major mode of transmission (both in Taiwan & Singapore)



Clinical spectrum of EV71 infection

Household survey	Children (n=183)	Adults (n=87)
Asymptomatic	6%	53%
Uncomplicated HFMD	73%	8%
Herpangina or non- specific febrile illness		39%
Complicated by CNS or cardiopulmonary manifestations	21%	Nil

Herpangina



Hand, foot and mouth disease

- oral lesions may be more extensive in EV71 infection
- skin rash may be absent, scanty or atypical in EV71
- EV71 is more neurovirulent than Coxsackie A16
- in cases with CNS involvement, a brief febrile illness may sometimes be followed by a period of relative well being, and then a recrudescence of fever with neurological manifestations a few days later (biphasic pattern not universal in severe disease)
- 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
- fatalities from EV71 occur in children <5 years of age but rare – overall mortality 0.06% during previous epidemics in Taiwan and Singapore











The classical clinical features of HFMD are not necessarily always present together even in patients with severe EV71 disease





Nail shedding in HFMD (rare phenomenon during convalescence)



Complications of EV71 infection

Severe disease and mortality can occasionally occur in previously healthy or immunocompetent subjects with HFMD, herpangina or undifferentiated fever – EV71 is neurotropic and neurovirulent

- aseptic meningitis
- encephalitis (in particular, brain stem encephalitis or rhombencephalitis)
- encephalomyelitis
- poliomyelitis-like acute flaccid paralysis (typically monoplegia)
- neurogenic pulmonary oedema +/- pulmonary haemorrhage



Rarer complications caused by EV71

interstitial pneumonia

myocarditis

intrauterine infection

neonatal hepatic necrosis

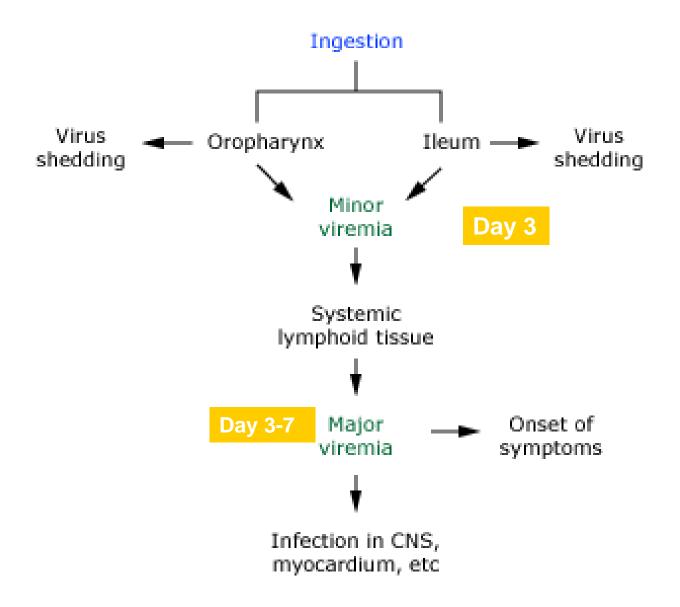
Complications of Coxsackie A16 infection

aseptic meningitis

myocarditis

interstitial pneumonia

Cell entry, replication and dissemination





Outpatient management

- most cases are self-limiting and do not warrant hospitalization
- apart from symptomatic and supportive measures (antipyretics, analgesics, ensure adequate hydration), no specific therapy is required
- beware of increased severity in secondary cases from household contact
- immunocompromised hosts and children <3 years of age are at higher risk of mortality or serious morbidity

When to consider hospital admission

• Children (especially \leq 5 years of age) with HFMD / herpangina

or

- Close contacts of known cases of HFMD / herpangina
- With the following warning signs within 7 days of onset of illness:
 - 1. High fever (>39°C)
 - 2. Persistent fever (>3 days)
 - 3. Neurological features

irritability, lethargy, sleepiness, frequent sleep interruption, drowsiness, difficulty to arouse, fluctuating consciousness, persistent headache, repeated vomiting, bulging anterior fontanelle in infants, neck pain or neck stiffness, abnormal posturing, generalized hypotonia or rigidity, myoclonic jerks, unsteady gait, ataxia, limb weakness, visual or auditory hallucinations, diplopia, photophobia, abnormal eye movements (sustained upward gaze, nystagmus, opsoclonus), squint, cranial nerve palsy

When to consider hospital admission

4. Autonomic disturbance (increased sympathetic tone)

agitation, insomnia, increased startle reflex, panic attacks, pallor, cold sweating, tremor, tachycardia out of proportion to the degree of fever, hypertension, abdominal distension (paralytic ileus), urinary retention (atonic neurogenic bladder), hyperglycaemia, leukocytosis

5. Cardiopulmonary features

pallor, cyanosis, tachypnoea, shortness of breath, hypotension, cold extremities, poor peripheral circulation, delayed capillary refill, tachycardia, bradycardia, irregular pulse rhythm

6. Others

poor feeding, decreased urine output

10 important questions to ask

- 1. Any unexplained panic attacks?
- Any persistent tachycardia?
- 3. Any unusual somnolence?
- 4. Any insomnia?
- 5. Any diplopia or conjugate ocular disturbance?
- 6. Any squint?
- 7. Any intension tremor inability to hold things?
- 8. Any ataxia cannot walk or sit?
- 9. Any myoclonic jerks?
- 10. Any monoplegia / hemiplegia?



3 most important warning signs of severe EV71 disease (Taiwan CDC)

- persistent sleepiness / drowsiness
- repeated vomiting
- frequent myoclonic jerks (see videos)
 - occurring several times or more in an hour
 - distinguish from sleep jerks





Pathogenesis of pulmonary oedema in EV71 infection

 EV71-related pulmonary oedema is believed to be neurogenic in origin and not due to myocarditis:

Brainstem encephalitis (rhombencephalitis)

- → destruction of medial, ventral and caudal medulla (vasomotor centre)
- → autonomic dysregulation / brainstem dysautonomia (sympathetic overdrive)
- → surges of catecholamines activity
- → intense generalised vasoconstriction (an initial phase of hypertension may be noted)
- → high systemic vascular resistance
- → increased afterload to the heart
- → left ventricular failure
- → passive pulmonary volume overload
- → catastrophic pulmonary oedema / haemorrhage
- immunopathologic mechanisms in the pathogenesis of pulmonary oedema has also been suggested (e.g. hypercytokinemia or cytokine storm triggered by overwhelming viral sepsis results in severe systemic inflammatory response with increased permeability of alveolar microvasculature)



3 risk factors for development of neurogenic pulmonary oedema

- hyperglycaemia (OR = 21.5, 95% CI 3-159)
- leukocytosis
- limb weakness

Lancet 1999;354:1682-6





- prompt recognition of clinical deterioration and timely supportive therapy is the mainstay of management
- early detection of signs of CNS (especially brainstem) involvement, careful monitoring of fluid balance, and accurate assessment of left ventricular function are of critical importance
- patients should be closely monitored (HR, RR, BP, SpO2, neurological signs and symptoms) for clinical evidence of aseptic meningitis, encephalitis, encephalomyelitis, acute flaccid paralysis, and neurogenic pulmonary oedema +/-pulmonary haemorrhage → can be life-threatening or result in severe short-term and long-term morbidity



Lumbar puncture

CSF examination can be deferred (to be performed later when clinical condition is stabilized) in the following situations:

- rapidly deteriorating conscious level
- status epilepticus
- unstable cardiorespiratory status
- evidence of significantly raised intracranial pressure
- presence of focal neurological signs





Neuroimaging

- MRI is indicated in case of persistent or progressive neurological signs with or without accompanying cardiopulmonary collapse or pulmonary oedema, and is the imaging study of choice
- Cranial or spinal CT usually gives negative finding in severe EV71 infection with CNS involvement



- early intubation with mechanical ventilation and prompt institution of neurointensive care if conscious level deteriorates or cardiopulmonary collapse (rapid progression to severe cerebral oedema and fulminant neurogenic pulmonary oedema +/- pulmonary haemorrhage may ensue)
- consider left ventricular failure and perform early echocardiographic assessment if apparent shock or cardiovascular collapse fails to respond to initial fluid resuscitation (e.g. hypotension not corrected after 2-3 bolus infusions of 20 ml/kg of volume expanders in children)
- inotropic support +/- vasodilator therapy and measures to reduce ICP should be instituted when indicated



- laboratory diagnosis
 - viral culture NPA, T/S, rectal swab, stool, vesicular fluid, CSF
 - RT-PCR for rapid diagnosis of EV71
 - paired serology
- vigorous fluid resuscitation may be detrimental by aggravating cerebral oedema and/or pulmonary oedema if the condition is not suspected
- specific antiviral therapy is not available
- ICU admission for signs of organ failure
- consult infectious disease specialist or neurologist for need of IVIG therapy





Rationale for use of IVIG in enteroviral infection

- B-cell deficient patients with chronic or persistent enteroviral meningoencephalitis, on a case by case basis, with mixed results
- non-randomized trials in neonates and children with myocarditis showing improvement in recovery of left ventricular function compared to children who received anti-failure therapy alone
- possible benefits for patients receiving immunosuppressive therapy





IVIG in severe EV 71 disease

- efficacy of IVIG therapy in severe EV71 disease remains to be proven
- Centre for Disease Control of Taiwan does not recommend its use in children >5 years of age
- indications for IVIG therapy proposed by Taiwan CDC include:
 - (1) children with HFMD / herpangina

or

(2) 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)



IVIG in severe EV 71 disease

- when IVIG is considered, the regimen recommended by Taiwan CDC is 1 g/kg infused over 12 hours for once only
- other investigators have used 1g/kg/day infused over 12 hours for 2 consecutive days
- a single dose of 400-500 mg/kg of IVIG ≈ 10 times the daily amount of IgG produced by the body
- critical timing for IVIG therapy is at the earliest sign of autonomic dysregulation prior to deterioration with onset of pulmonary oedema
- IVIG therapy may be too late by the time pulmonary oedema sets in



- no therapeutic endpoints have been established
- sequential sampling of the infected site may be beneficial in documenting elimination of the infecting serotype
- given the limitations of culture-based methods for detection of EV, it would be more advisable to rely on RT-PCR for their detection





Discharge instructions to child carers on enteroviral infection

\$院管理局

製作:醫管局傳染病控制中心 衛生防護中心及醫管局協作小組 頒佈日期: 二〇〇八年五月 Title: Instructions to child carers on enteroviral Infection (Chinese and English version)

照料患腸病毒兒童,家長須知:

貴子女經醫生診斷患腸病毒病感染,請注意以下事項:

- 1. 大多數患腸病毒兒童,於發病後七至十日內會自行痊癒。
- 2. 腸病毒在兒童間的傳播速度是很快的,因此患者應按醫生指示留在家中休息,至退熱, 皮膚水泡乾透及潰瘍痊癒。患病期間應避免與非照料人士接觸,尤其孕婦及新生嬰 兒,以降低腸病毒擴釣機會。
- 患者的口鼻分泌物,以及糞便、皮膚水泡、潰瘍都具傳染力;爲減低疾病的傳播,應注意以下各點:
 - 保持空氣流涌。
 - ii. 照顧有嘔吐、咳嗽的患者,須先戴上口罩。
 - iii. 接觸患者或其他小孩 前、後,都必須洗手
 - 小心處理 患者的糞便及口鼻分泌物。用過的尿布、紙巾應直接棄置入有蓋垃圾箱內,
 - 1.處理完畢須立即洗手。
 - v. 注意環境清潔及消毒,經常觸摸的地方,均須以一份家居漂白水混入四十九份的清水消毒。
 - vi. 患者糞便或口鼻分泌物污染過的布類和衣物,亦應浸泡於稀釋漂白水中三十分鐘或以高於攝氏 60 度或以上熱水浸洗。
 - vii. 不應與他人共用食具。患者用後的食具必須分開處理和消毒。
 - viii. 家人若有出現相同徵狀,需盡早求醫
- 4. 患者可能因爲口腔內潰瘍導致進食困難,注意補充水分,慎防脫水,以免加重病情。 患者的飲食以流質爲佳。
- 患者發熱情况會持續數天,爲患者每隔四小時測量體溫一次。按照醫生指示給兒童服 食退熱藥。
- 6.若發現以下情况,應立即帶兒童回診所或醫院再作診治:
 - ♦ 高熱達攝氏 39 度或以上不退
 - ◆ 呆滯
 - ♦ 肢體軟弱無力
 - ◆ 指令及足少
 - 10000000
 - .lastdasinto'n.l.
 - ▼ 多別別回門
 ◆ 昏睡、不安
 - ◆ 手腳肌肉不自主持續地跳動

Hospital Authority

Prepared by: HA Infectious Disease Centre CHP-HA Collaboration Unit Issue Date: May 2008 Title: Instructions to child carers on enteroviral Infection (Chinese and English version)

Your child has been diagnosed to have enterovirus infection, please take note of the followings:

- In most of affected children, the disease is self-limiting, Symptoms usually resolve in around seven to ten days.
- 2. Since, enterovirus can spread between children rapidly, therefore, the infected child should follow doctor's advice by staying at home until fever comes down, all the blisters have dried up and ulcers have healed. To limit the spread of enterovirus, infected person should avoid contact with other people other than the carers; especially pregnant women and newborn babies.
- 3. Oral or nasal secretion, feces, excretions from blisters and ulcer of infected person could spread the virus. To prevent the spread of the disease, please take notes of the following points:
 - Maintain good ventilation at home.
 - ii. Wear mask when caring for infected children with cough or vomiting.
 - iii. Wash hands before and after caring the infected child and other children.
 - Handle infected child's fecal matter and oral-nasal secretion with care. Dispose of napkins and tissue paper directly into a covered rubbish bin and wash hands immediately afterwards.
 - Use one part of home-use bleach added into 49 part water to disinfect frequently touched areas and toys.
 - Disinfect soiled clothings and linen by soaking them into diluted bleach for 30 minutes or by washing them in >= 60°C hot temperature washing cycle.
 - Do not share eating utensils. Handle and disinfect the used utensils of the infected child separately.
 - If another family member shows similar signs and symptoms of infection, seek early medical advice.
- As the infected child may suffer from oral ulcer and have poor appetite, ensure that the child has adequate fluid intake to prevent dehydration.
- Measure the child's body temperature at four hours' intervals when child has fever. Give antipyretic medication to the child according to doctor's advice.
- 6. Bring back your child to the hospital if he / she has any of the following symptoms:
 - persistent fever higher than 39°C
 - ♦ lethargy
 - ▲ wooknes
 - refusing feeds and passing less urine
 - rapid breathing
 - vomiting
 - drowsiness or irritability
 - repeated jerky limbs movement

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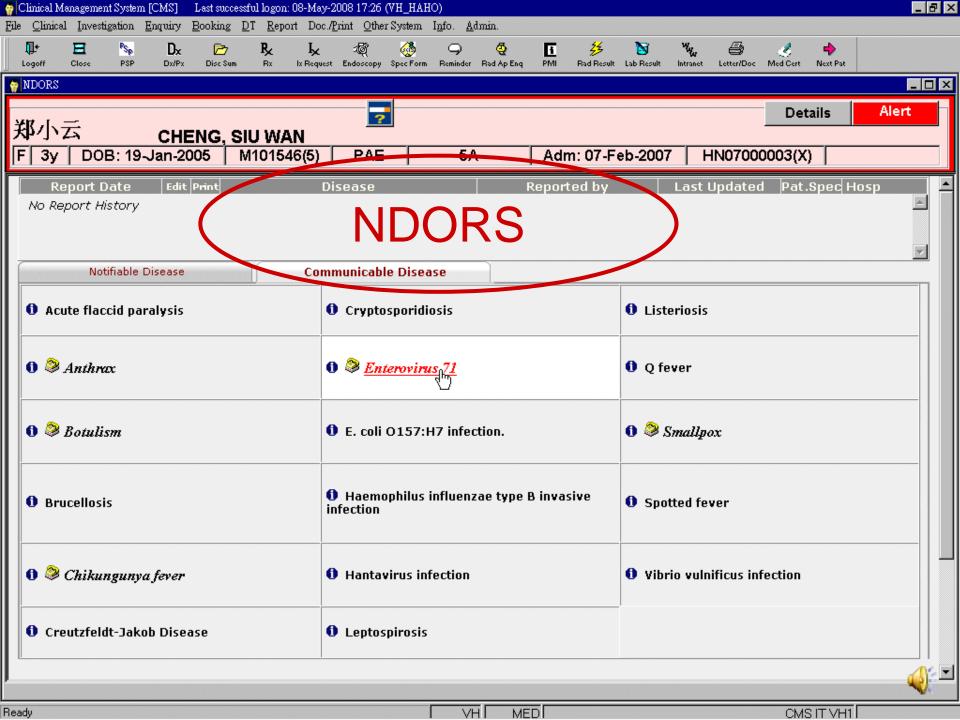
Summary of the 1998 EV71 epidemic in Taiwan

- 129,106 cases of HFMD / herpangina reported by physician-based sentinel surveillance system representing 8.7% of primary physicians in Taiwan
- 405 severe cases
- **78** deaths (0.06%)
- 91% fatalities were ≤5 years of age
- 83% of fatal cases had pulmonary oedema or pulmonary haemorrhage
- EV71 was the cause in 92% of fatal cases from whom a virus was isolated (vs 75% for hospitalized patients and 48.7% for outpatients)

Table. Number of confirmed severe/fatal enterovirus infections and viral isolation results from patients with fatal cases, Taiwan, 1998–2000^a

Case/enterovirus serotype	1998	1999	2000	2001
Severe cases	405	35	291	389
Fatal cases	78	9	41	55
Enterovirus 71	34	1	25	26
Coxsackievirus B3	0	3	1	0
Echovirus 4	0	0	0	3
Other enteroviruses	3	4	12	7
Negative	31	1	3	13
Specimens not available	10	0	0	6

^aData provided by the Center for Disease Control, Ministry of Health, Taiwan (1998–2001).





Case reporting - ePaed

Paediatric Surveillance Programme for Severe Complications Related to HFMD and Influenza (launched 14 May 2008)

- children >1 month and ≤12 years old on date of admission AND
- fever / HFMD / herpangina AND
- with one of the following complications:
 - > severe pneumonia
 - severe sepsis
 - > shock
 - encephalopathy
 - myocarditis
 - acute flaccid paralysis
 - > pulmonary oedema / haemorrhage



