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
- Reinfection with the same serotype → asymptomatic
- 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
<table>
<thead>
<tr>
<th>Age</th>
<th>Immunity</th>
<th>Risk</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years old</td>
<td>−</td>
<td>++++</td>
<td>No previous exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immature immunity</td>
</tr>
<tr>
<td>6 years old</td>
<td>++</td>
<td>+++</td>
<td>Fair personal hygiene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contract the virus while in kindergarten</td>
</tr>
<tr>
<td>7-12 years old</td>
<td>+++</td>
<td>++</td>
<td>School</td>
</tr>
<tr>
<td>Adult</td>
<td>++++</td>
<td>+</td>
<td>Stress</td>
</tr>
</tbody>
</table>
**Enteroviral infections are mostly subclinical**

Same virus can cause several different clinical syndromes

Same clinical picture can be caused by different enteroviruses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Predominant virus</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific febrile illness</td>
<td>All types</td>
<td>Fever with upper respiratory and/or gastrointestinal symptoms</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>Echoviruses, Enterovirus 71</td>
<td>Fever, meningeal signs, change in mental status, seizure</td>
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<tr>
<td></td>
<td>Coxsackieviruses A &amp; B</td>
<td></td>
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<tr>
<td>Herpangina</td>
<td>Coxsackieviruses A &amp; B</td>
<td>Fever, painful oral vesicles on tonsils and posterior pharynx</td>
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<tr>
<td></td>
<td>Enterovirus 71</td>
<td></td>
</tr>
<tr>
<td>Hand, foot and mouth disease (HFMD)</td>
<td>Coxsackieviruses A16, A9</td>
<td>Fever, vesicles / ulcers on buccal mucosa and tongue, papulovesicular rash on hands, feet, knees and buttocks</td>
</tr>
<tr>
<td></td>
<td>Enterovirus 71</td>
<td></td>
</tr>
<tr>
<td>Non-specific exanthem</td>
<td>Echoviruses</td>
<td>Variable rash +/- fever</td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td>Coxsackievirus B</td>
<td>Uncommon, myocarditis / pericarditis may present as heart failure or arrhythmia</td>
</tr>
<tr>
<td>Acute haemorrhagic conjunctivitis</td>
<td>Enterovirus 70, Coxsackieviruses A</td>
<td>Epidemic cause of conjunctivitis with lid swelling, subconjunctival haemorrhage and eye pain without systemic symptoms</td>
</tr>
<tr>
<td>Neonatal disease</td>
<td>Coxsackieviruses B, Echoviruses</td>
<td>Sepsis-like picture, meningoencephalitis, hepatitis, myocarditis, pancreatitis, DIC</td>
</tr>
<tr>
<td>Pleurodynia</td>
<td>Coxsackieviruses B3, B5</td>
<td>Uncommon, epidemic, fever and pain of chest and abdomen, costochondritis</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>Coxsackieviruses A7, Echoviruses Enterovirus 71</td>
<td>Fever followed by sudden asymmetric flaccid paralysis or monoplegia</td>
</tr>
</tbody>
</table>
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)
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%
- siblings 84%
- cousins 83%
- parents 41%
- grandparents 28%
- uncles and aunts 26%

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

### Clinical spectrum of EV71 infection

<table>
<thead>
<tr>
<th>Household survey</th>
<th>Children (n=183)</th>
<th>Adults (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>6%</td>
<td>53%</td>
</tr>
<tr>
<td>Uncomplicated HFMD</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Herpangina or non-specific febrile illness</td>
<td>73%</td>
<td>39%</td>
</tr>
<tr>
<td>Complicated by CNS or cardiopulmonary manifestations</td>
<td>21%</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Herpangina

Courtesy of Paediatric Infectious Disease Unit, HA Infectious Disease Centre
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

- Ingestion
  - Virus shedding
  - Oropharynx
  - Ileum
    - Virus shedding
    - Minor viremia
      - Systemic lymphoid tissue
        - Major viremia
          - Onset of symptoms
            - Infection in CNS, myocardium, etc

Day 3
Day 3-7
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 ≤ 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?
2. 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
Inpatient management

• 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.
Inpatient management

• 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
Inpatient management

- 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
Inpatient management

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
  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)

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
Inpatient management

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

1. In most of affected children, the disease is self-limiting. Symptoms usually resolve in around seven to ten days.
2. Enterovirus can spread among 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 persons should avoid contact with other people other than the children especially pregnant women and newborn babies.
3. Oral or nasal secretion, feces, excretions from blisters, and stool of infected persons could spread the virus. To prevent the spread of the disease, please take note of the following points:
   a. Maintain good ventilation at home.
   b. Wear mask when caring for infected children with cough or vomiting.
   c. Wash hands before and after caring infected child and other children.
   d. Handle infected child's facial matter and oral nasal secretion with care. Dispose of napkins and tissue paper directly into a covered rubbish bin and wash hands immediately afterwards.
   e. Use one part of household bleach added into 45 part water to disinfect frequently touched areas and toys.
   f. Disinfect soiled clothes and bedding by soaking them into diluted bleach for 30 minutes or boiling them at more than 60°C for 30 minutes. After the baby takes a bath, the water and soap should be disposed of in the sewage system.
   g. Do not share eating utensils. Handle and disinfect the used utensils of the infected child separately.
   h. If another family member shows similar signs and symptoms of infection, seek early medical advice.
4. 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 interval when child has fever. Give antipyretic medication to the child according to doctor's advice.
5. If the infected child has fever, check pyrexia and other signs of infection. If the child's body temperature is 39°C or above, take medical advice immediately.
6. Bring back your child to the hospital if he/she has any of the following symptoms:
   - Persistent fever higher than 39°C
   - Chills
   - Swelling in hands, feet, face, neck, and torso
   - Poor feeding
   - Abdominal pain
   - Drowsiness
   - Rash that spreads from the palms and soles
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)

NEJM 1999;341:929-35
## Table. Number of confirmed severe/fatal enterovirus infections and viral isolation results from patients with fatal cases, Taiwan, 1998–2000

<table>
<thead>
<tr>
<th>Case/enterovirus serotype</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
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</thead>
<tbody>
<tr>
<td>Severe cases</td>
<td>405</td>
<td>35</td>
<td>291</td>
<td>389</td>
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<tr>
<td>Fatal cases</td>
<td>78</td>
<td>9</td>
<td>41</td>
<td>55</td>
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<tr>
<td>Enterovirus 71</td>
<td>34</td>
<td>1</td>
<td>25</td>
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<tr>
<td>Coxsackievirus B3</td>
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<td>Echovirus 4</td>
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<td>3</td>
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<tr>
<td>Other enteroviruses</td>
<td>3</td>
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<tr>
<td>Negative</td>
<td>31</td>
<td>1</td>
<td>3</td>
<td>13</td>
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<tr>
<td>Specimens not available</td>
<td>10</td>
<td>0</td>
<td>0</td>
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aData provided by the Center for Disease Control, Ministry of Health, Taiwan (1998–2001).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Reported by</th>
<th>Last Updated</th>
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<tbody>
<tr>
<td>Acute flaccid paralysis</td>
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<tr>
<td>Anthrax</td>
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<tr>
<td>Botulism</td>
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<tr>
<td>Brucellosis</td>
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<tr>
<td>Chikungunya fever</td>
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<tr>
<td>Creutzfeldt-Jakob Disease</td>
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<td>Cryptosporidiosis</td>
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<td>E. coli O157:H7 infection</td>
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<td>Haemophilus influenzae type B invasive infection</td>
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<td>Hantavirus infection</td>
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<td>Leptospirosis</td>
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<td>Listeriosis</td>
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<td>Q fever</td>
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<td>Spotted fever</td>
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<tr>
<td>Vibrio vulnificus infection</td>
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</tbody>
</table>
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 \textbf{AND}
- fever / HFMD / herpangina \textbf{AND}
- with one of the following complications:
  - severe pneumonia
  - severe sepsis
  - shock
  - encephalopathy
  - myocarditis
  - acute flaccid paralysis
  - pulmonary oedema / haemorrhage
**PATIENT, 588952**

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Serious Clinical Complications</th>
<th>Condition</th>
<th>Ventilated</th>
<th>Last Update</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td>08-May-2006 17:19 (QMH)</td>
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</table>

**Laboratory investigations related to influenza or enteroviral infection within 3 months**

<table>
<thead>
<tr>
<th>Request Hosp. Specimen</th>
<th>Collection Date</th>
<th>Lab. Result Ready Date</th>
<th>Test</th>
<th>Result</th>
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<tr>
<td>NDH NASOPHARYNGEAL ASPIRATE</td>
<td>01-Mar-2008</td>
<td>PWH</td>
<td>02-Mar-2008</td>
<td>Influenza, Antigen</td>
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<tr>
<td>NDH NASOPHARYNGEAL ASPIRATE</td>
<td>01-Mar-2008</td>
<td>PWH</td>
<td>02-Mar-2008</td>
<td>Influenza virus type B</td>
</tr>
</tbody>
</table>

**Presenting Symptoms:**

- **Fever**
  - Onset Date: 08/05/2008

- **Respiratory Symptoms**
  - Cough
  - Sputum

- **Gastrointestinal Symptoms**
  - Diarrhea
  - Abdominal Pain

- **Non-Specific**
  - Headache

- **Others**
  - Hand-foot-mouth vesicles
  - Herpangina

---

*Note: The document contains medical information and symptoms related to a patient named PATIENT, 588952.*
**e-Paed Reporting Criteria**

1. Children > 1 month and \( \leq 12 \) years old on date of admission, **AND**
2. Fever/HFMD/herpangina, **AND** with
   3. One of the following complications:
      (a) Severe pneumonia; **OR**
      (b) Severe sepsis; **OR**
      (c) Shock; **OR**
      (d) Encephalopathy; **OR**
      (e) Myocarditis; **OR**
      (f) Acute flaccid paralysis; **OR**
      (g) Pulmonary edema/hemorrhage