

Coxsackieviruses & other Enteroviruses

Fellow's curriculum conference
Hunter Ratliff
12/01/2025





Overview

- Classification, virology, transmission, and epidemiology
- Clinical manifestations
 - Boring viral illness
 - Dermatologic
 - Neurologic
 - Respiratory
 - Cardiac / muscular
 - And more
- Management
 - Diagnosis
 - Treatment
 - Prevention

Classification & virology

- Taxonomy
 - ...and why it doesn't matter
- Virology with a focus on pathogenesis
- Modes of transmission
- Epidemiology

Taxonomy & classification

Historically, there were 4 species in the *Enterovirus* genus

- Enterovirus A: **Coxsackievirus A2**, CV-A2, etc
- Enterovirus B: **Coxsackievirus B1**, CV-B2, etc
- Enterovirus C: **Polioviruses** 1-3 (but also CV-A1..?)
- Enterovirus D: EV-D68

Virus classification 	
(unranked):	Virus
Realm:	<i>Riboviria</i>
Kingdom:	<i>Orthornavirae</i>
Phylum:	<i>Pisuviricota</i>
Class:	<i>Pisoniviricetes</i>
Order:	<i>Picornavirales</i>
Family:	<i>Picornaviridae</i>
Subfamily:	<i>Ensavirinae</i>
Genus:	<i>Enterovirus</i>

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- Enterovirus D: EV-D68

Then they discovered more... over 100 more

- Started changing the classification scheme around
- Wanted to move polio out of the genus

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The classification we care about

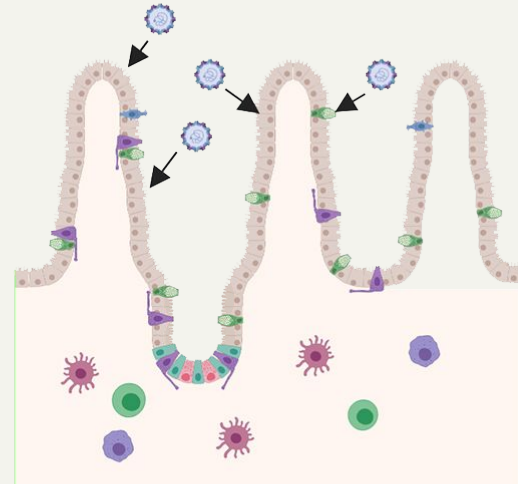
Now, we refer to them by serotypes

- **Group A coxsackievirus** (CV-A)
- **Group B coxsackievirus** (CV-B)
- **Polioviruses** (PV) - Not covered today
- **Numbered enteroviruses** (EV-D68, EV-D70, AV-A71)
- **Echoviruses** (E)
 - Parechovirus is still separate genus
 - Present clinically similarly to echoviruses

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Enteroviruses: Virology

- Small (30 nm), non-enveloped (important for prevention)
- Single-stranded, positive sense RNA
- Bind to cellular attachment factors to allow for intracellular replication
 - A variety of **attachment factors** are **shared across serotypes**
 - This might be why so many different serotypes can cause similar syndromes

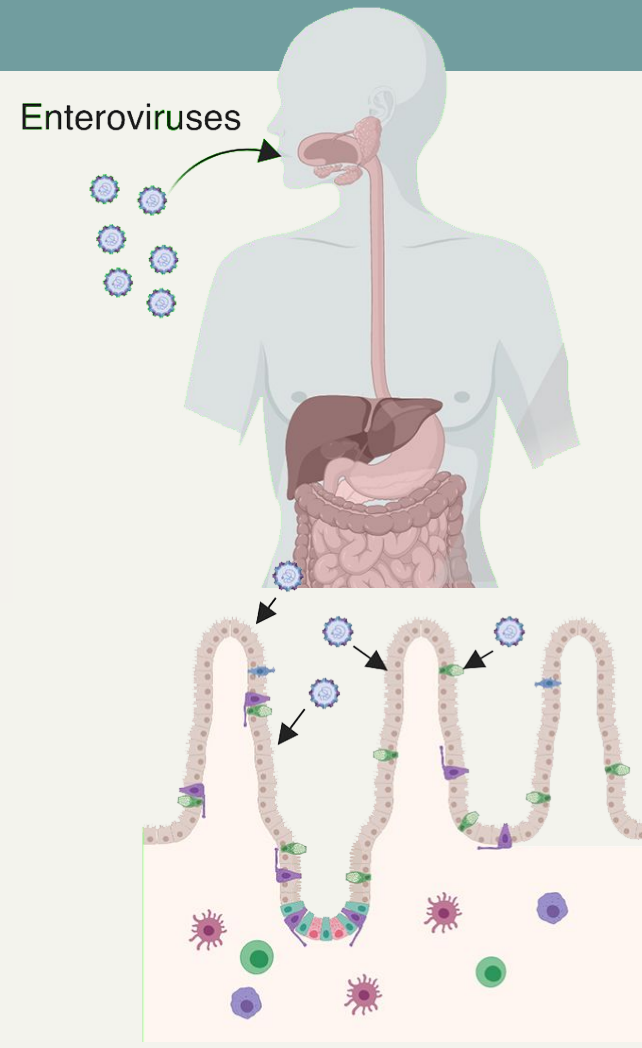


Enteroviruses: Pathogenesis

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Viral uptake & initial replication occurs in **pharynx and terminal ileum**

- Has a transient viremia → hematogenous spread → target organs
- Are relatively **resistant to acid** → allows for fecal oral transmission



Enteroviruses: Transmission



- Predominantly spread via **fecal oral transmission**
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 - Coxsackievirus A21: Severe respiratory illness, seen in military recruits
 - Enterovirus D68: also can cause severe respiratory illness + acute flaccid myelitis
- EV-70 (causes acute hemorrhagic conjunctivitis) is **shed in tears** and can be spread via fingers

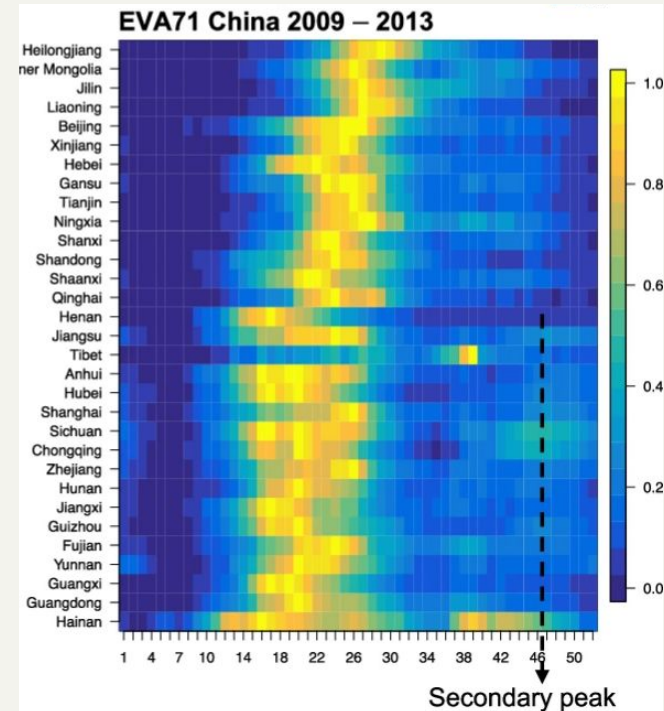
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- **Vertical transmission** can cause spread to infant, especially if infected in the peripartum period

Enteroviruses: Epidemiology

- Seasonal trends, but commonly higher in the **summer and fall**
- Highest rates are in those **under one year old**

Figure 1C of [Baker et al](#) (2024).
Weekly cases of EV-A71 by Chinese province, ordered from north (top) to south (bottom)



Enteroviruses: Epidemiology

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Some serotypes follow **multi-year cycles** (with different periodicities) following a pattern

Large # of kids infected → they are immune (for now) → waning immunity → reaches a critical mass of susceptible kids → sustained transmission → Large # of kids infected

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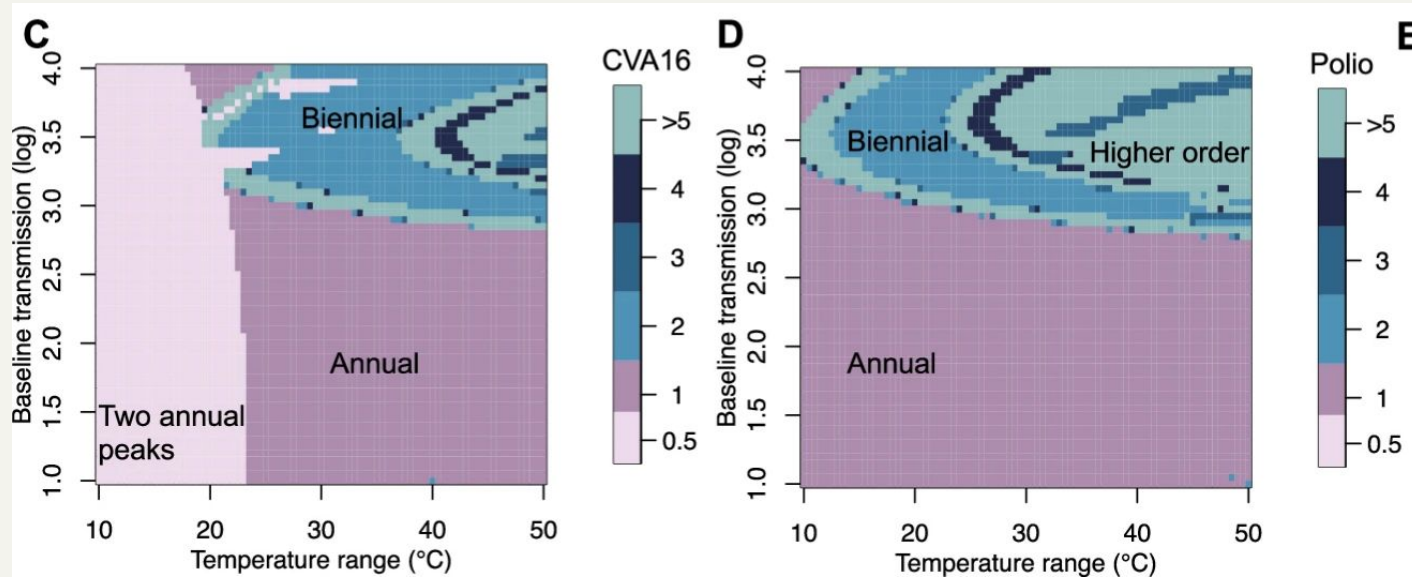


Figure 2
Simulated data for
CV-A16 and polio

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This was seen post-COVID:

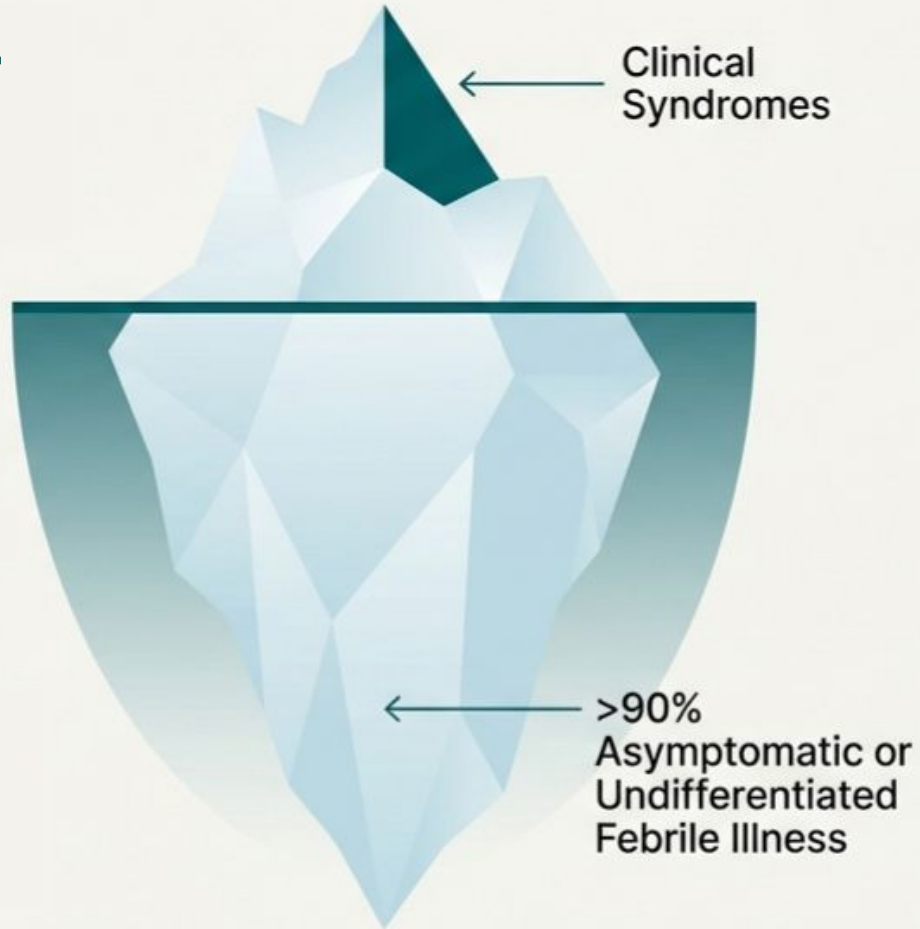
↑ masking ⇒ ↓ immunity ⇒ no more masks ⇒ ↑ older kids infected



Clinical syndromes

- Boring viral illness
- Dermatologic
- Neurologic
- Respiratory
- Cardiac / muscular
- More

Isolated fever



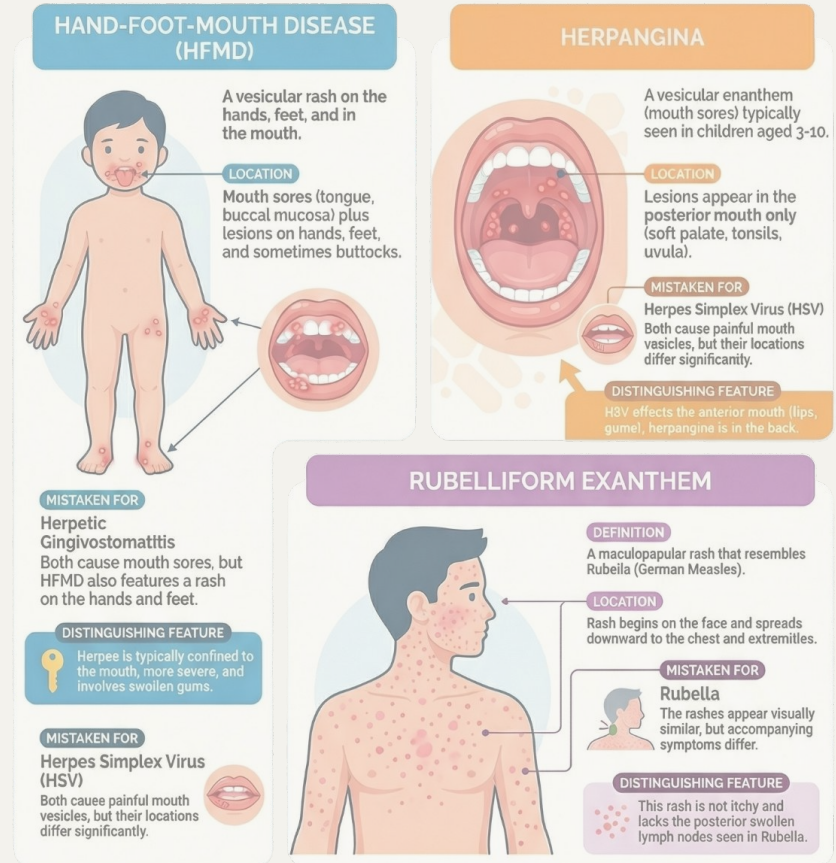
Exanthems & enanthems

Dermatologic manifestations

- Herpetiform exanthems:
 - Hand-foot-mouth disease
 - Herpangina
- Other exanthems:
 - Rubelliform
 - Roseoliform
 - Petechial/purpuric

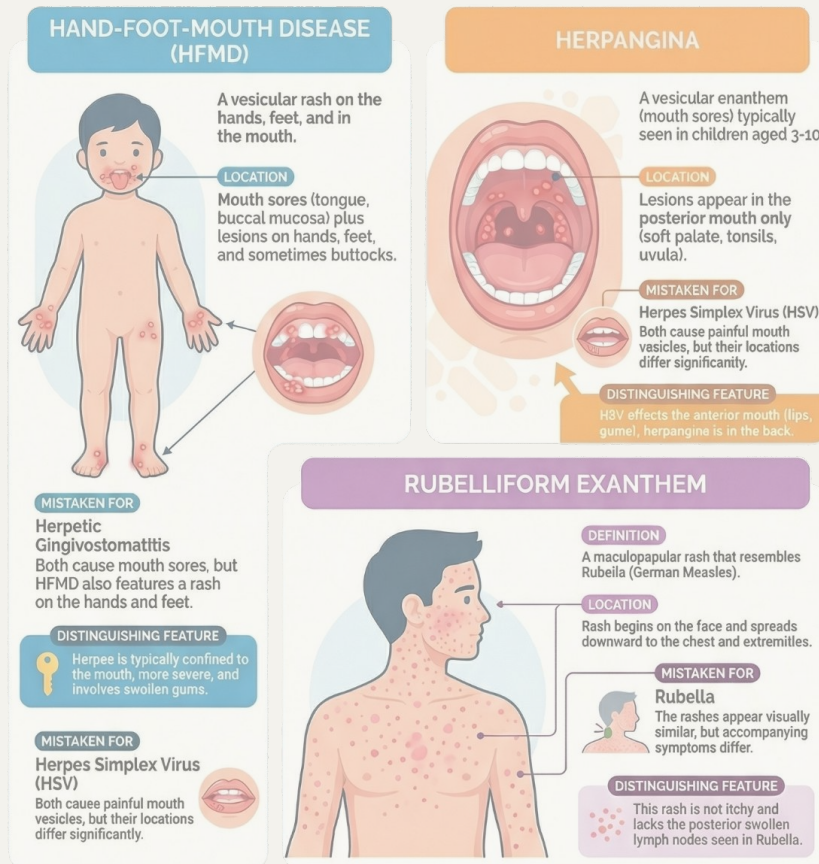
Enteroviruses: Exanthems

- Wide spectrum of presentation
 - Aside from hand-foot-mouth disease (HFMD), these are generally not specific enough to make a diagnosis of an enterovirus infection on exam alone
 - **Substantial overlap** among the exanthems



Enteroviruses: Exanthems

- Wide spectrum of presentation
 - Aside from hand-foot-mouth disease (HFMD), these are generally not specific enough to make a diagnosis of an enterovirus infection on exam alone
 - **Substantial overlap** among the exanthems
- Exanthems themselves **cause little morbidity**, but can be **mistaken for other** more worrisome **infectious conditions**
- Unclear if result of direct skin invasion by the virus or immune mediated



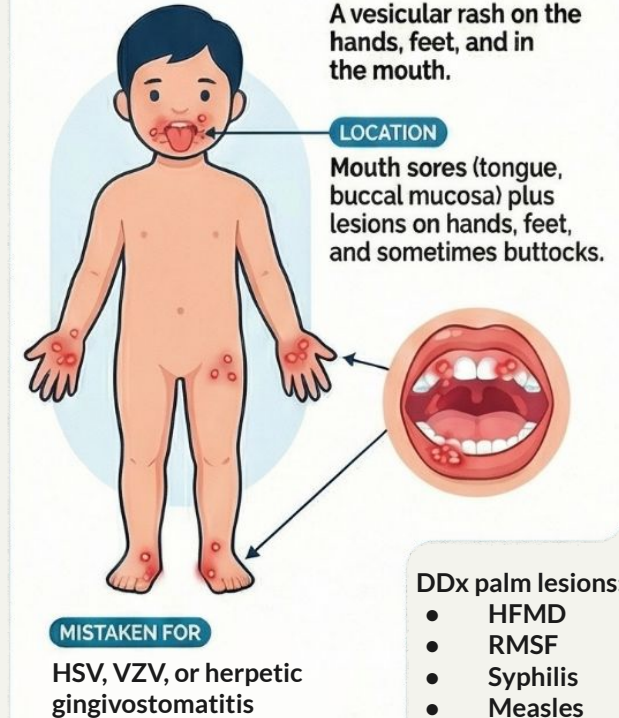
Hand-Foot-Mouth disease

- Enanthem: **Vesicular stomatitis** (painful oral lesions)
 - Mainly buccal mucosa and tongue
 - Accompanied by 1-2 days of low fevers (42%)
- Exanthem: **Vesicles**/papules on palms of hands & feet (occurs in 75% of patients)
 - May also involve the buttocks or genitals
 - May or may not be tender



Mandell Figure 178.1

HAND-FOOT-MOUTH DISEASE (HFMD)



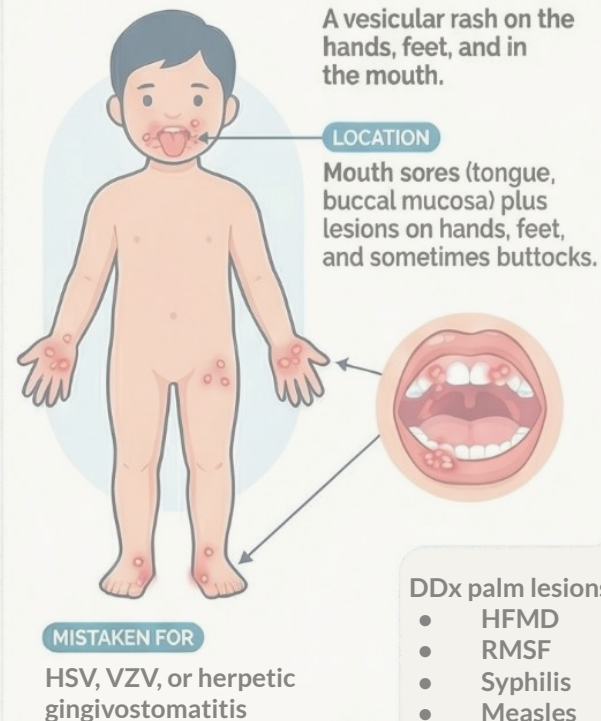
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Atypical HFMD (novel CV-A6) - Basically everything is worse

- Wider distribution of lesions (more like VZV)
- Higher fever
- Lasts longer (12 days on average)
- May have **fingernails fall off** 1-2 months later

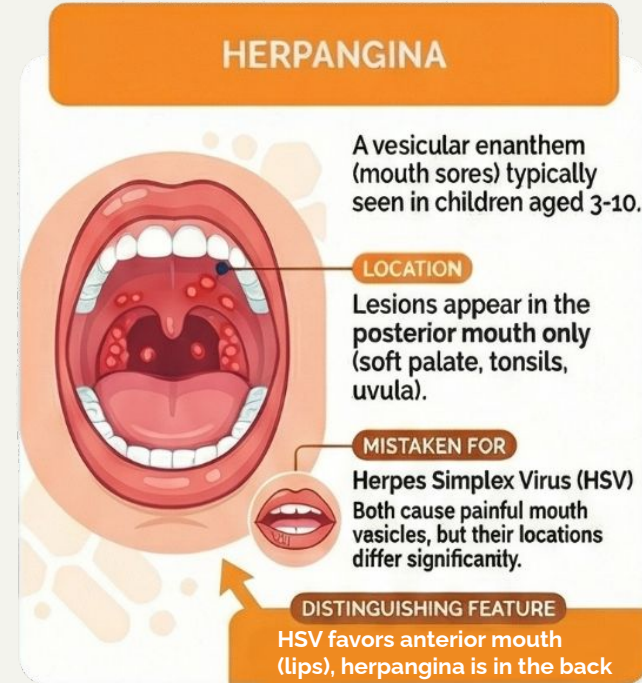
HAND-FOOT-MOUTH DISEASE (HFMD)



Herpangina

- Enanthem: Abrupt, painful **vesicles of posterior oropharynx** (soft palate, tonsils, anterior pillars)
 - Sore throat & odynophagia
 - Unlike HFMD, **fevers are high** (102 - 104 F / 39 - 40 C)
- Exanthem: **No rash** (generally no other symptoms)

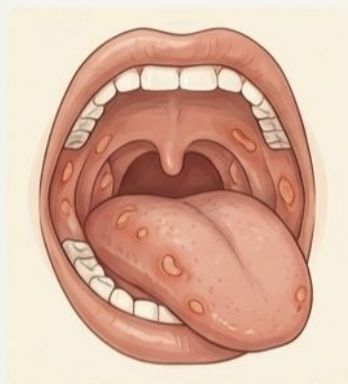
Mainly reported in children (very few adults)



Comparing the herpetiform exanthems

Herpetetic exanthems

- **Coxsackie A group**
 - CV-A9: atypical HFMD
- EV-A71 (also causes other stuff too)



Hand, Foot, and Mouth Disease



Description

Vesicular stomatitis with an exanthem. Patients present with sore mouth/throat.



Key Pathogens

Coxsackievirus A16 (CV-A16) and Enterovirus A71 (EV-A71) are the most common causes.

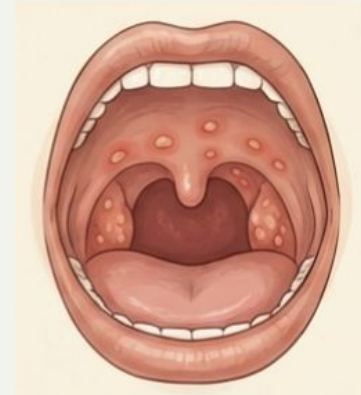
Age

Mostly kids, but adults can get it too



Rash

In 75% of cases



Herpangina



Description

A vesicular enanthem of the fauces accompanied by abrupt onset of fever, sore throat, and odynophagia.



Key Pathogens

Primarily Coxsackievirus A group (CV-A1 to CV-A10).

Rash

None

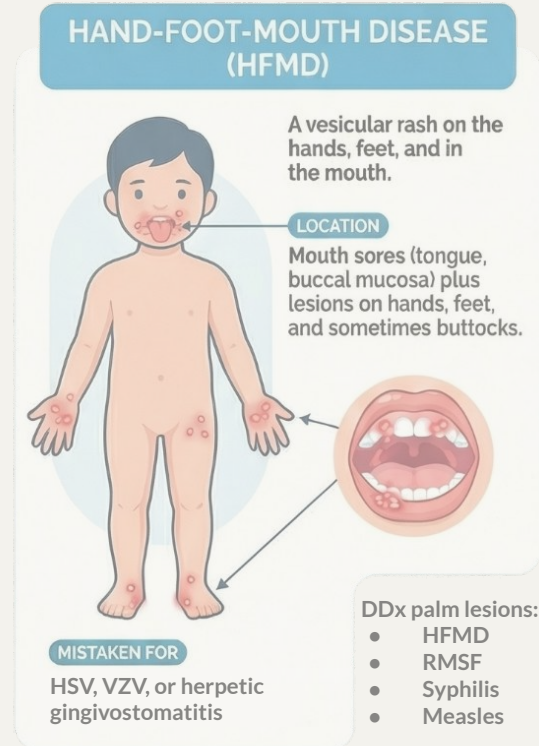
Age

Almost **only kids**

DDx: Herpetiform exanthems

Chickenpox?	HFMD	VZV
Widespread rash + fevers	✓	✓
Involves palms	✓	✗
Oral lesions	+/-	✗

And **don't forget MPox** (mistaken for atypical HFMD)



DDx: Herpetiform exanthems

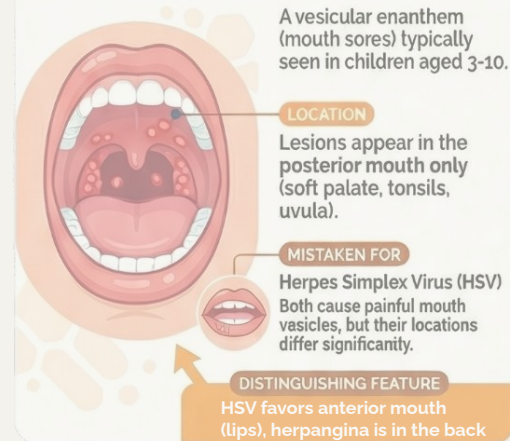
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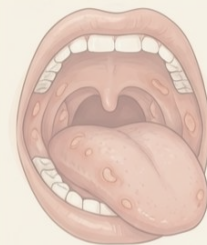
Herpetic gingivostomatitis?

	HFMD	Herpangina	HSV
Painful oral ulcers + fevers	✓	✓	✓
Involves palms	✓	✗	✗
Hand lesions	✓	✗	+/-
Bilateral skin lesions	✓	✗	✗
Posterior oral lesions	+/-	✓	✗

HERPANGINA



HAND-FOOT-MOUTH DISEASE (HFMD)



Rubelliform and Morbilliform Exanthems

Enteroviruses account for about **5% of acute morbilliform exanthems** (in populations with high MMR immunity)

Summer **echovirus epidemics** (E-9) produce a rash very similar to Rubella

- Rash begins at same time as fevers
- Spreads down from the face
- But not itchy (✗ Rubella)

RUBELLIFORM EXANTHEM



DEFINITION
A maculopapular rash that resembles Rubella (German Measles).

LOCATION
Rash begins on the face and spreads downward to the chest and extremities.

MISTAKEN FOR
Rubella
The rashes appear visually similar, but accompanying symptoms differ.

DISTINGUISHING FEATURE
This rash is not itchy and lacks the posterior swollen lymph nodes seen in Rubella.

Rubelliform and Morbilliform Exanthems

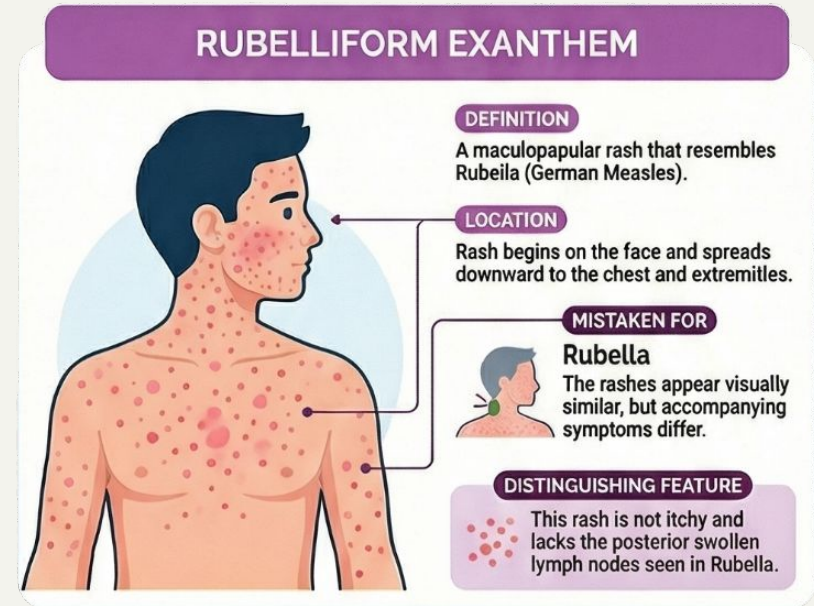
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Rare cases where an enanthem resembles **Koplik spots**

- Absence of coryza and conjunctivitis
 - ✗ measles



Other Exanthems

ROSEOLIFORM EXANTHEM



DEFINITION

A rash notable for its timing, similar to classic Roseola.

LOCATION

Pink macules and papules appear on the face and upper chest.

MISTAKEN FOR

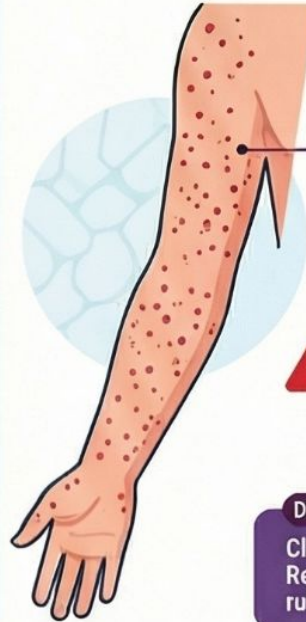
Roseola Infantum (HHV-6)

Fever ———— Rash
Both conditions are defined by the same unique clinical course.

DISTINGUISHING FEATURE

The key is timing: the rash characteristically appears after the fever breaks.

PETECHIAL EXANTHEM



DEFINITION

A hemorrhagic rash of small, non-blanching spots (petechiae).

LOCATION

Mandell & UTD did not say where the rash occurs

MISTAKEN FOR

Meningococcal Disease

This is a dangerous mimic of a life-threatening bacterial infection.



DISTINGUISHING FEATURE

Clinically indistinguishable. Requires urgent evaluation to rule out bacterial meningitis.

Seen with **CV-A9 & echovirus 9**, which also causes encephalitis

Neurologic manifestations

- Aseptic meningitis
- Encephalitis (EV-A71)
- Acute flaccid myelitis (AFM)
 - EV-A71 & EV-A68

Viral/aseptic meningitis

The enterovirus genus is the **leading cause of aseptic meningitis** in adults & kids

- Mainly the EV-B species (coxsackievirus B & most echoviruses)
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- 1/3rd of adults have signs of meningeal irritation
- Often have pharyngitis / URI symptoms
- **Encephalitis** may develop in **5-10%** of cases

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Diagnosis can still be challenging

- 18-30% of infants have no pleocytosis
- Glucose can be low in up to 1 in 3 cases

Encephalitis

General Enteroviral Encephalitis

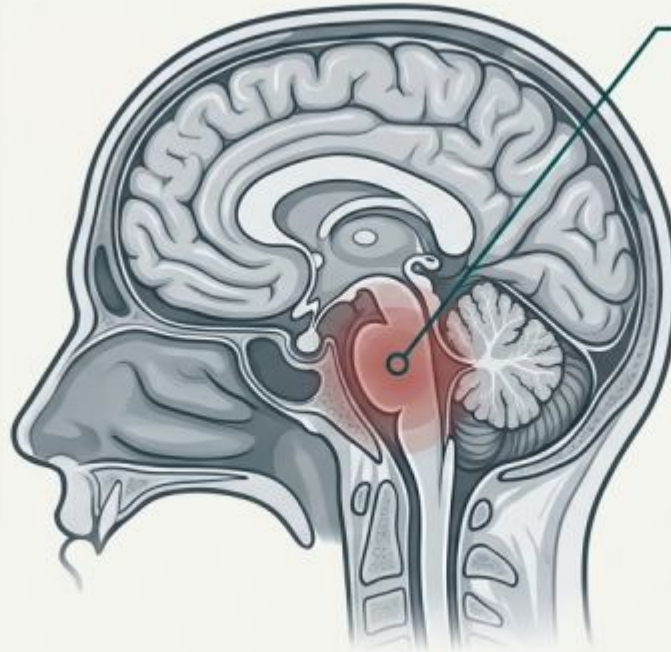
- Occurs in 5-10% of meningitis patients.
- EVs account for 10-22% of all proven viral encephalitis cases.
- Presentation varies from mild encephalopathy to severe disease with seizures, paresis, and coma.

Still good prognosis
unless...

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RED FLAG: EV-A71 Rhombencephalitis

- A severe, often fatal brainstem encephalitis unambiguously linked to **Enterovirus A71**.
- **Population:** Primarily affects infants and young children, often following HFMD or herpangina.
- **Clinical Signs:**
 - Rapid neurologic deterioration.
 - Myoclonus is a frequent and characteristic feature.
 - Leads to secondary noncardiogenic pulmonary edema and cardiovascular collapse.



Detour: Enterovirus A71

1. Hand-Foot-Mouth Disease (HFMD) & Herpangina



- EV-A71 is a common cause of **HFMD**, alongside **CV-A16**.
- Also associated with **Herpangina**.
- Large **outbreaks** involving **thousands** reported in Asia-Pacific region.

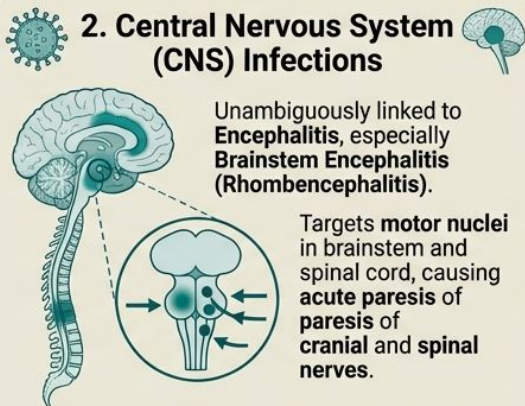


4. Epidemiology

Strikingly high prevalence of EV-A71 encephalitis in countries of the **Asia-Pacific Rim**.

Multiple large outbreaks have occurred.

2. Central Nervous System (CNS) Infections



Unambiguously linked to **Encephalitis**, especially **Brainstem Encephalitis (Rhombencephalitis)**.

Targets **motor nuclei** in brainstem and spinal cord, causing **acute paresis** of **cranial and spinal nerves**.

- Severe, often **fatal**, particularly in **infants & toddlers**.

→ Often preceded by **HFMD** or **Herpangina**.

→ High **mortality rate**.

- Fatal outcomes linked to secondary **Cardiopulmonary Manifestations: Noncardiogenic Pulmonary Edema and Rapid Cardiovascular Collapse**.



3. Acute Flaccid Paralysis (AFP)



- Unique among nonpolio enteroviruses as a cause of **Epidemic AFP**.
- Associated with **Polio-like Paralysis/Myelitis**.
- Outbreaks reported in **Russia, Eastern Europe, Thailand, and Taiwan**.

5. Vaccines



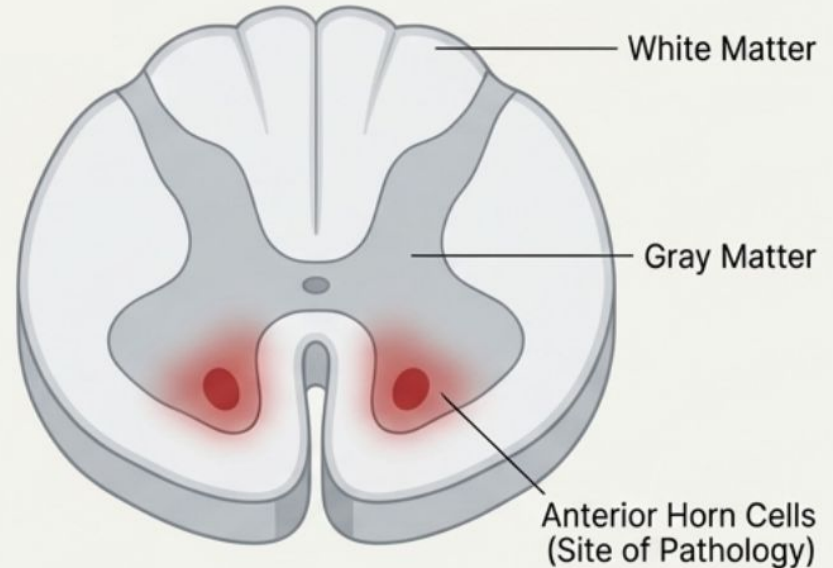
Vaccines for prevention available in Asia (specifically China).

Demonstrated high **efficacy (≥90%)** against **EV-A71 HFMD**.

100% efficacy in preventing neurological complications in HFMD patients.

Acute Flaccid Myelitis/Paralysis

A variety of enteroviruses can cause acute flaccid paralysis/myelitis, but the key ones to know are **poliovirus**, **enterovirus A71** (just discussed), and **enterovirus A68** as their sequelae is most severe



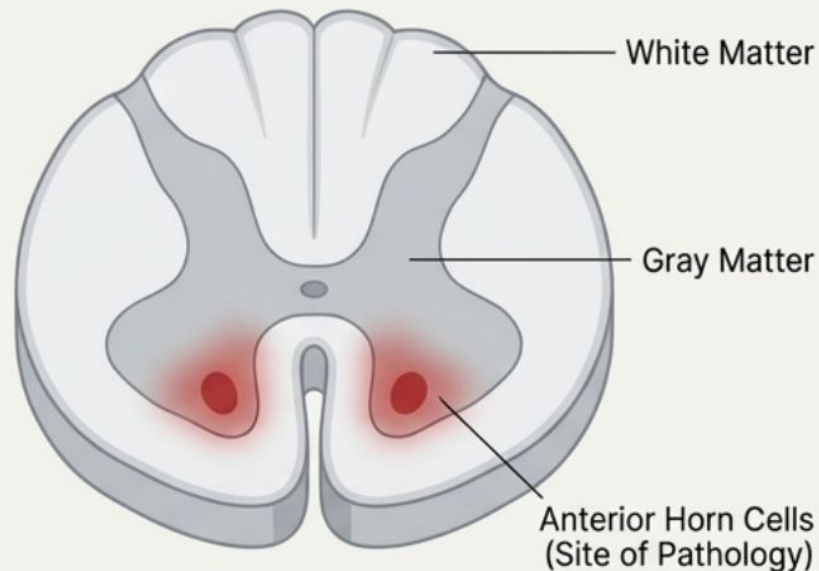
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Clinically, they all look like polio:

- **Biphasic pattern**
- **Abrupt** onset **asymmetric motor deficit**
 - Sensory nerves spared
- May progress to other limbs in 1-3 days
 - +/- cranial nerve involvement

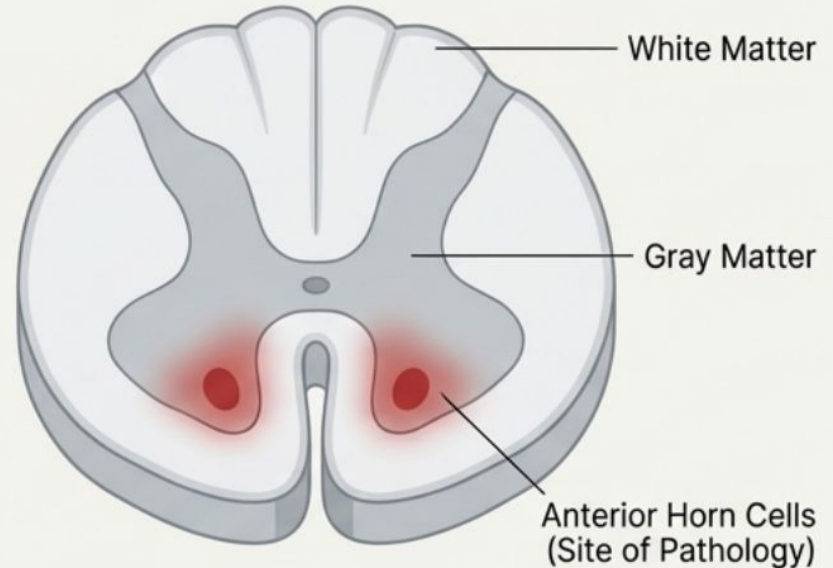
1. Prodromal illness with fever and pharyngitis
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3. Abrupt fever + meningismus + weakness



Acute Flaccid Myelitis/Paralysis

Diagnosis is often indirect

- **CSF:** Pleocytosis, but CSF PCR may be negative
- **MRI:** longitudinally extensive nonenhancing lesions of the gray matter of spinal cord or brainstem

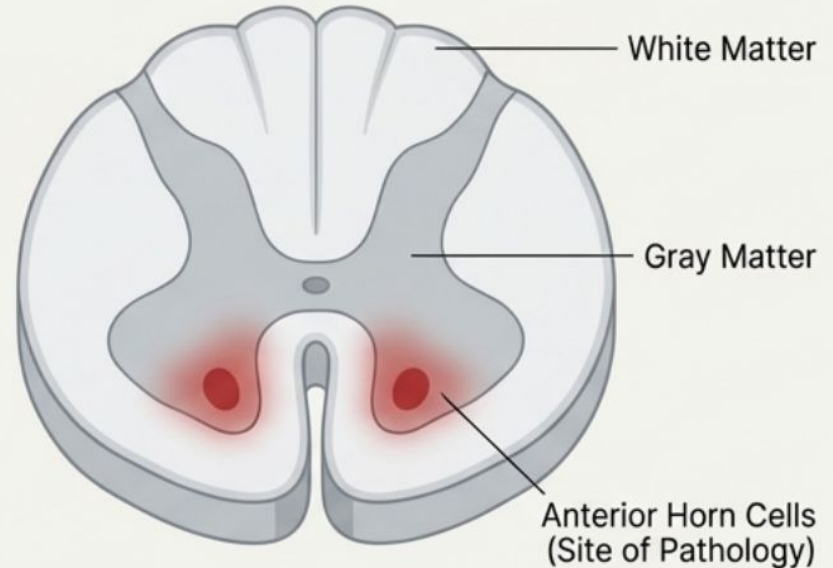


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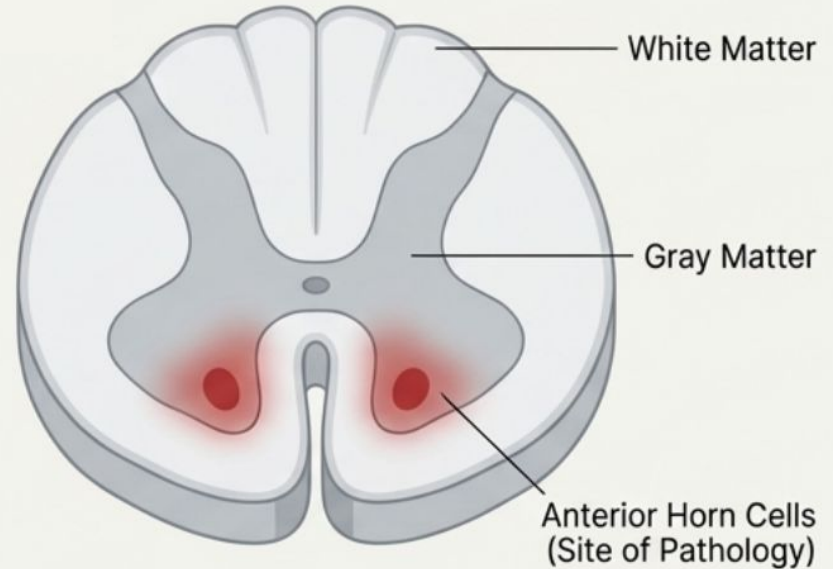
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Fewer than 5% have full recovery



Etiology: Acute Flaccid Myelitis/Paralysis

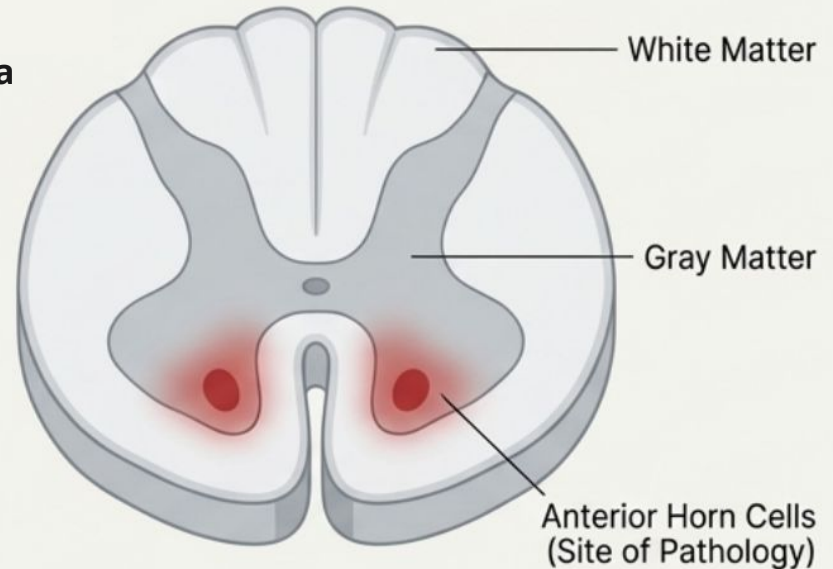
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Etiology: Acute Flaccid Myelitis/Paralysis

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Enterovirus A71: Outbreaks following HFMD (also meningitis/encephalitis). The EV-A71 **vaccine in China** has been **100% effective** in preventing AFM

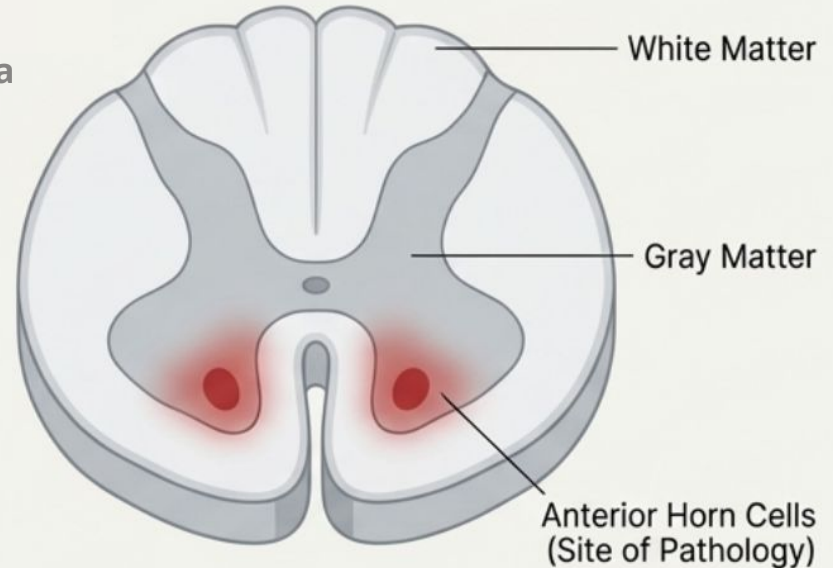


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Enterovirus A68: This one causes *respiratory disease* and is not commonly isolated in the CSF. But there has been inferential links between outbreaks of EV-A68 and increased cases of AFM



Respiratory manifestations

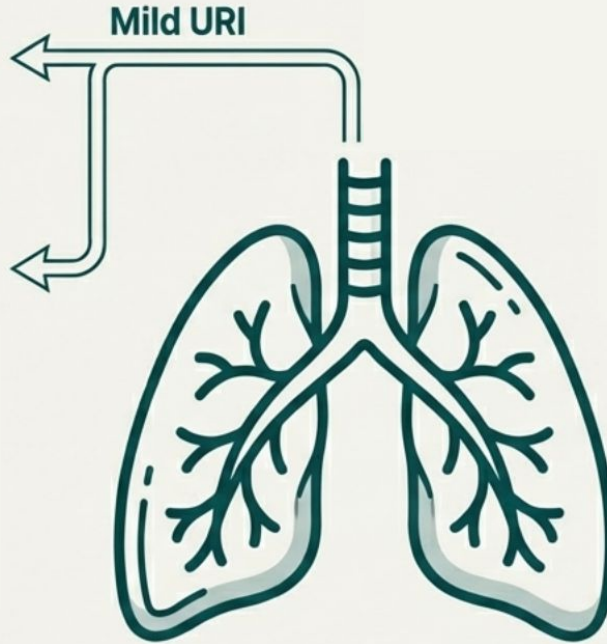
- Mild URI
- Severe respiratory disease
- Acute hemorrhagic conjunctivitis

URIs and lower respiratory infections

Common Upper Respiratory Illness (URI)



NPEVs are a leading cause of undifferentiated febrile illness ("summer gripe") with sore throat, cough, and coryza.



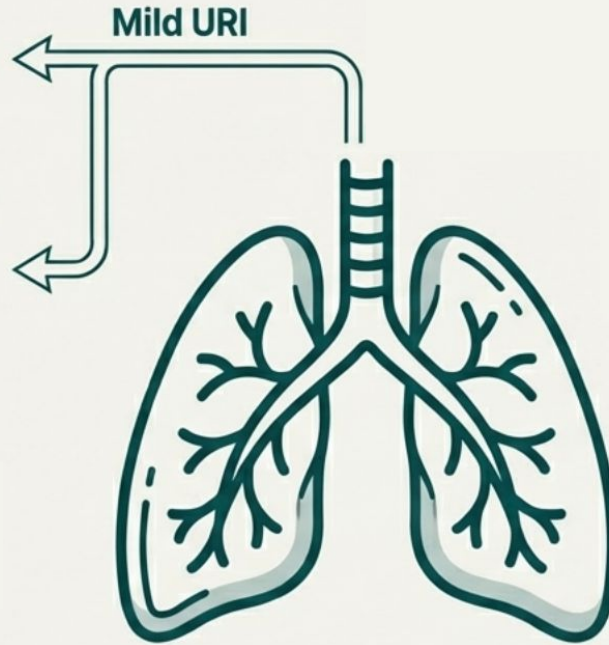
URIs and lower respiratory infections

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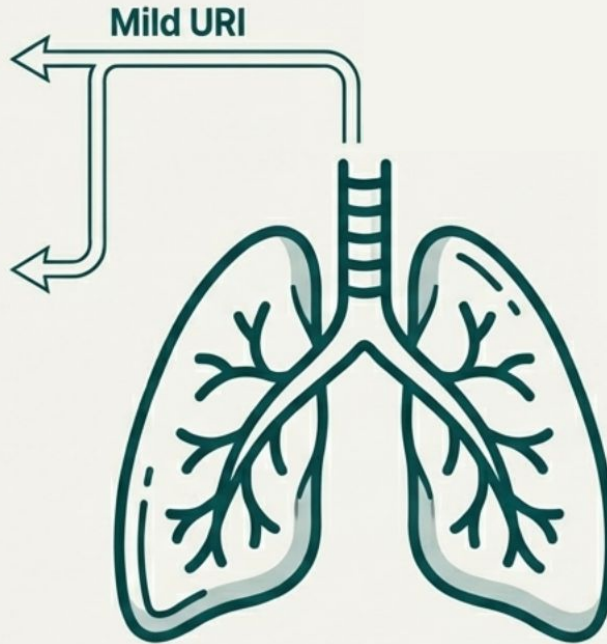
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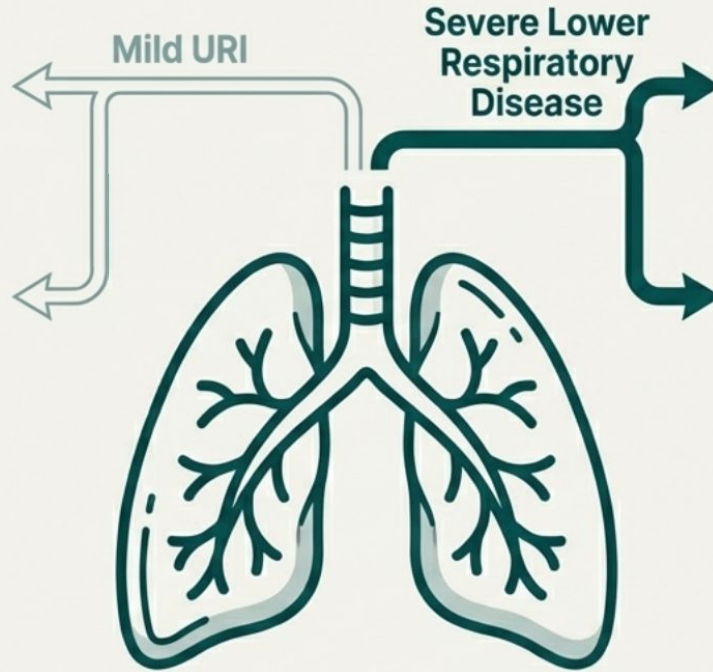
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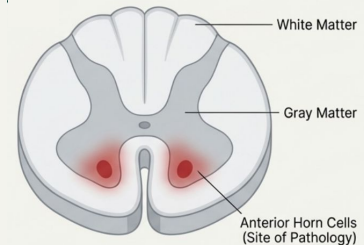
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Severe Respiratory Disease & EV-D68



Enterovirus D68 (EV-D68) has emerged as a cause of periodic, nationwide outbreaks of severe respiratory illness.



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Mild URI

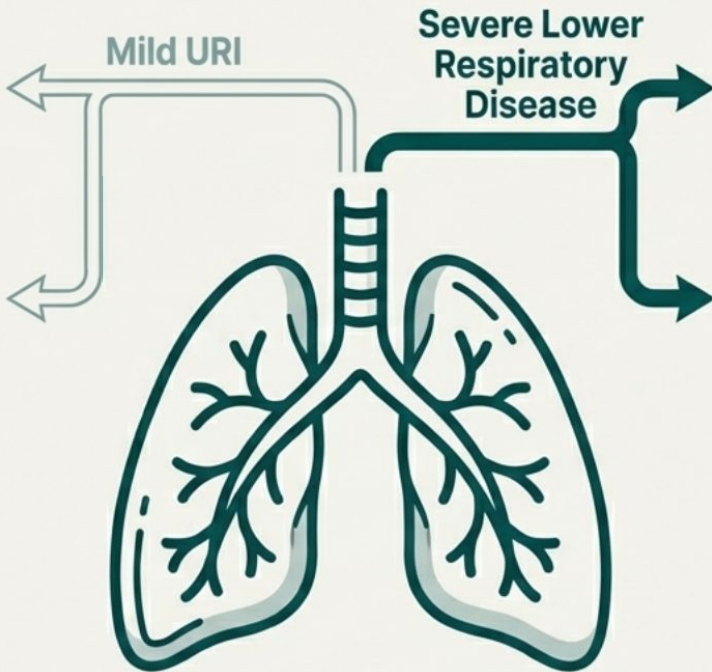
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Severe Respiratory Disease & EV-D68



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- **Population:** Primarily affects children, with a disproportionate impact on those with asthma or a history of wheezing.



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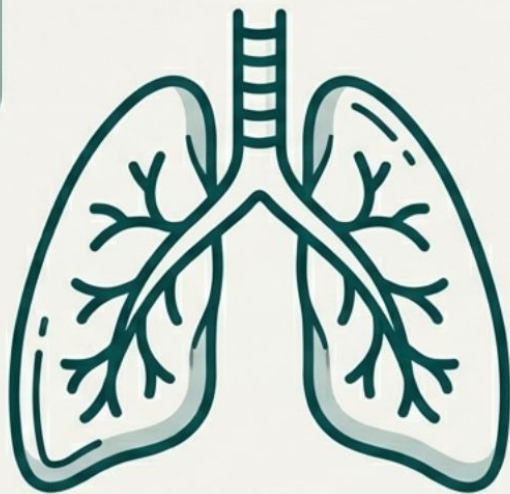
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- **Population:** Primarily affects children, with a disproportionate impact on those with asthma or a history of wheezing.
- **Syndromes:** Bronchiolitis, bronchitis, and pneumonia.
- **Clinical Signs:** Low-grade fever, cough, significant wheezing, dyspnea, and hypoxia, often requiring ICU admission.



Acute hemorrhagic conjunctivitis

Highly contagious, but generally self-limiting conjunctivitis; often from **EV-D70** or **CV-A24**

- Unlike other EV infections, spreads from **fingers or fomites directly to the eye**
- Often associated with **outbreaks**, most commonly in poor sanitary conditions & crowding

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Abrupt onset of symptoms (**peaks within 24h**, unlike adenovirus)

- Most often burning, ocular pain, photophobia, eyelid swelling, and watery discharge
- ~1 in 5 have constitutional symptoms
- Hallmark is **subconjunctival hemorrhage**

Generally resolves within a week



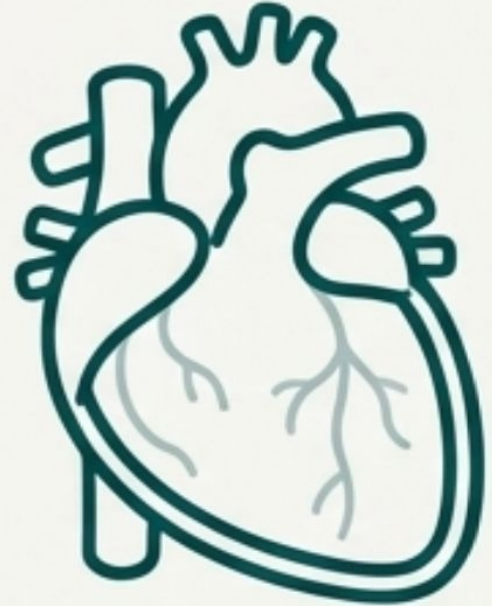
Other clinical manifestations

- Cardiac: Myopericarditis
- Muscular: Pleurodynia
- Diabetes..??

Myopericarditis

Common cause of acute viral myopericarditis, mainly from **Coxsackie B**

- Accounted for $\geq \frac{1}{3}$ **cases** (before COVID)
- Tends to happen in physically active **adolescents & young adults**



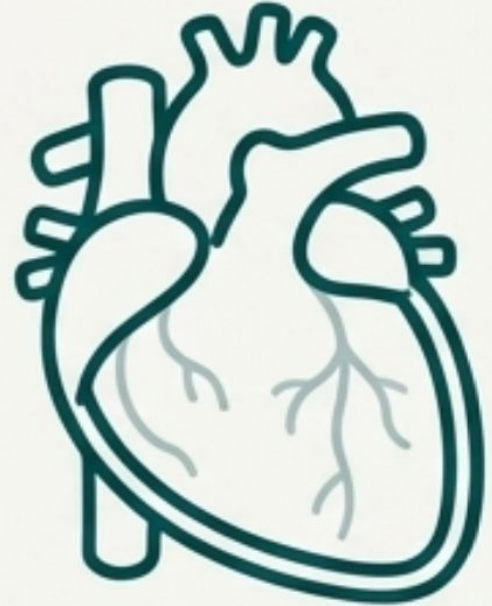
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Presentation: Typically (2/3rd) have **preceding URI** in past 1-2 weeks

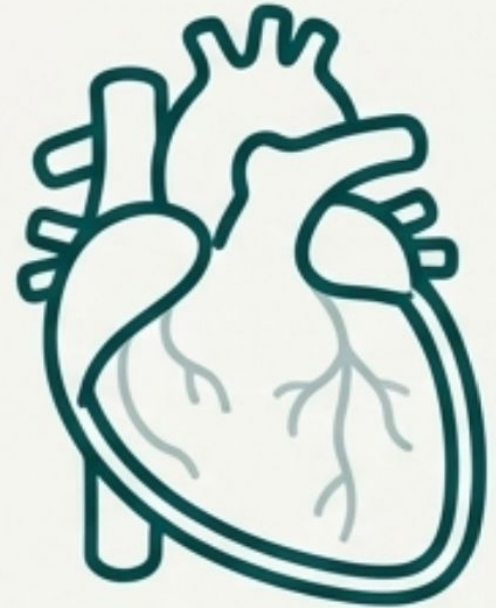
- Followed by typical pericarditis &/or CHF symptoms
- Ranges from **asymptomatic** to **florid heart failure** with complete heart block (may need ECMO)



Myopericarditis

Diagnosis: Often is **circumstantial** (e.g. pericarditis + biofire positive), but *can* be isolated from tissue

- But it depends on which test you are using (recall, over 100 types of EVs)



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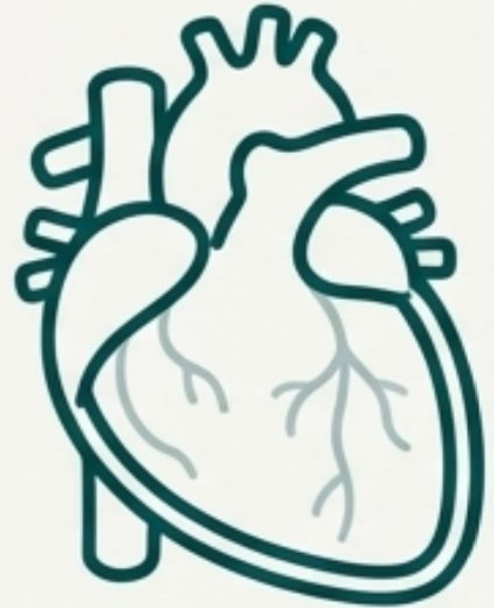
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Treatment:

- **Largely supportive** (up to and including LVAD)
- Has been interest in therapy (e.g. IVIG, steroids) but inconclusive results

Prognosis: About **1/3rd** have **long term damage**



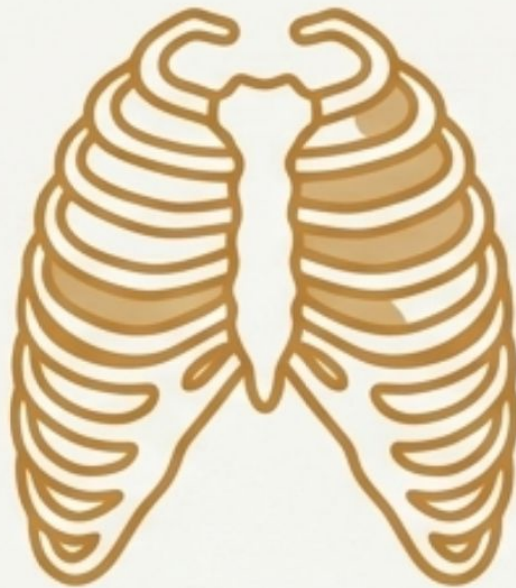
Pleurodynia (“Devil’s Grippe”)

- Acute infection of skeletal muscle, classically from **Coxsackie B**
 - Tends to affect older kids & adults
 - Observed in infrequent outbreaks (10-20 year intervals)
- **Spasmodic** and **paroxysmal pain** (hallmark) **with fever**
 - Often in the chest or upper part of the abdomen
 - Mimics ACS, PE, acute abdomen
- Is not a whole body myositis
 - Tends to be localized to a body area (but not a focal point)



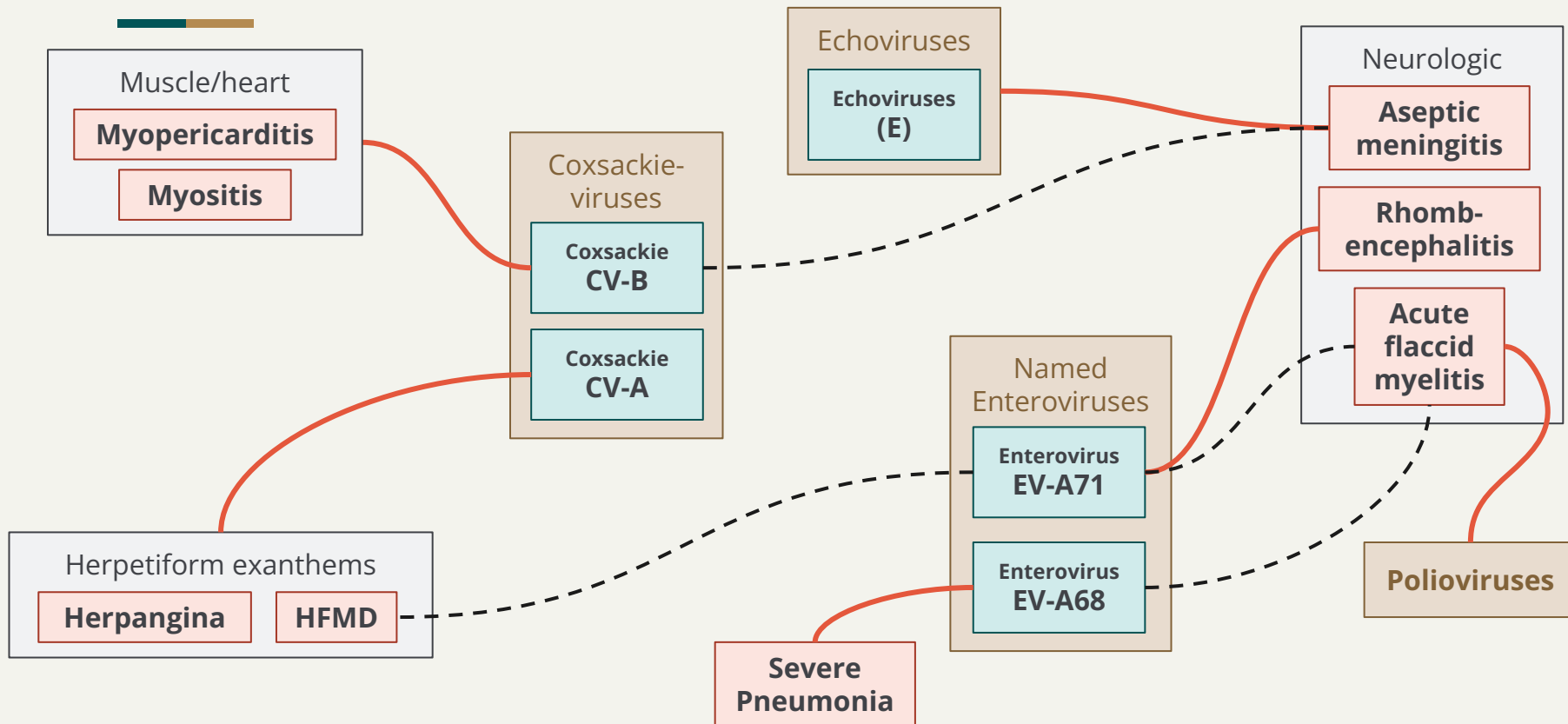
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- Is not a whole body myositis
 - Tends to be localized to a body area (but not a focal point)
- First paroxysm is most severe (4-6 days)
 - May be confined to bed
- **One in four** will have a **recurrence of pain**
 - Sometimes days later (in rare cases, months later)
 - Half of the time, pain is at another site



Who does what?

 = Strongest association with that disease/condition



Diabetes?

There are temporal & geographic associations with between **enterovirus infections** and **onset of type 1 diabetes**

One meta-analysis of 26 case-control studies found that EV infection was associated with development of

- Islet cell autoimmunity: OR 3.7 (2.1 - 6.8)
- Type 1 diabetes: OR 9.8 (5.5 - 17.4)

Exact mechanism still not clear

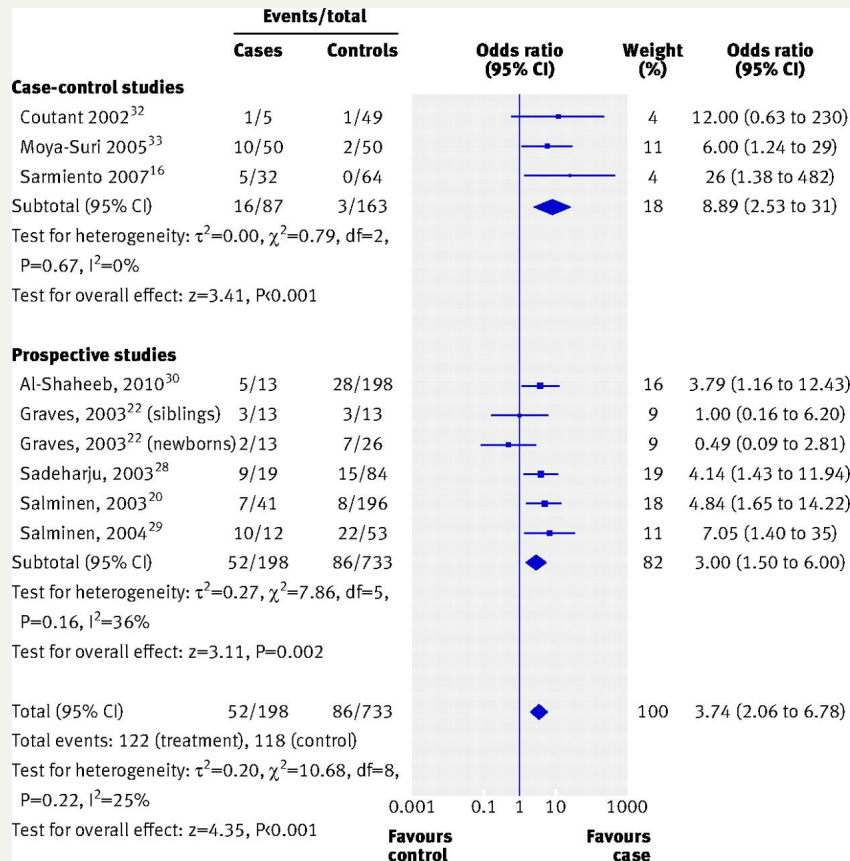


Figure 1 of [Yeung et al \(2011\)](#)



Management

- Diagnosis
- Treatment
- Prevention

Diagnosis & Treatment



Diagnosis

Laboratory diagnosis is **generally not needed** (clinical dx, self-limited disease). When it is, **RT-PCR is king**

- Shares same 5' nontranslated region with *rhinovirus* (hard to distinguish the two)

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Generally, do a PCR the organ that is involved

- Conjunctivitis often has negative resp PCR
- CSF pretty good for meningitis
 - Not great for encephalitis
- AFM and myopericarditis are more challenging

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Treatment

Symptomatic & supportive care

In life-threatening cases, there are no evidence-based therapies, but some have tried IVIG and select capsid inhibitors

Prevention



Vaccination

China has a few vaccines for **EV-A71**

- **>90%** protective of HFMD (from EV-A71)
- **100%** for preventing neurologic complications
- Suggestive it might protect from other genotypes

Not available outside of China

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Isolation: Generally **standard precautions**

- **Contact** if incontinent (or diapers)
- During outbreaks of **EV-D68** (the one that causes a bad pneumonia), **contact + droplet**
- Pregnant patients should avoid contact with those who have EV infections

Learning points & take aways

THE CLINICAL SPECTRUM OF ENTEROVIRUS INFECTIONS

Will AI replace me?

Prompt: “Describe the clinical manifestations of enterovirus infections”. No additional feedback given (zero touch deployment)

Model: Nano Banana (Gemini 2.5 Flash Image) via NotebookLM (11/24/25)

Sources: **Three PDFs** (chapter 178 of Mandell & two UpToDate articles)

Fever, oral vesicles, pharyngeal inflammation, tongue, tender rash on hands, feet, buttocks. Cossackievirus A16 and EV-A71 are most common.

ATYPICAL HFMD

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VIRAL (ASEPTIC) MENINGITIS

Most common CNS manifestation. Infants: fever, irritability. Older children/adults: fever, headache, photophobia, stiff neck.

ENCEPHALITIS

Less common, serious brain inflammation; encephalopathy, seizures, focal neurologic symptoms. EV-A71 is notably linked to severe, sometimes fatal, brainstem encephalitis (rhombencephalitis).

ACUTE FLACCID MYELITIS (AFM)

Polio-like syndrome, acute motor neuron weakness. EV-D68 and EV-A71 key causes, often after respiratory/febrile illness, leading to asymmetric limb weakness and paralysis.

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PLEURODYNIA (BORNHOLM DISEASE)

Acute skeletal muscle infection; fever, sharp, spasmodic chest/upper abdomen pain. Group B coxsackieviruses most important cause.

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NEONATES

Uniquely susceptible to fulminant, often fatal, systemic disease acquired perinatally. Manifestations: myocarditis (Group B coxsackieviruses) or fulminant hepatitis with multi-organ failure (Echovirus 11).

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Individuals with B-cell defects (e.g., agammaglobulinemia) at risk for persistent, severe, and often fatal chronic meningoencephalitis due to inability to clear virus.

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Aside from labeling the stomach as the lungs, the **highlighted** (typographic) errors are all easily edited out in Adobe Acrobat (took <15 mins)

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Sources

- Chapter 178 of Mandell (Coxsackieviruses, Echoviruses, and Numbered Enteroviruses [EV-D68, EV-D70, EV-A71]), 10th edition
- UpToDate: Hand, foot, and mouth disease and herpangina (accessed 11/24/25)
- UpToDate: Enterovirus and parechovirus infections: Epidemiology and pathogenesis (accessed 11/24/25)
- UpToDate: Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention (accessed 11/24/25)

Access the NotebookLM I used [here](#) (I still confirmed all of the written text that I used in these slides with the primary material, but it's not like the AI made many mistakes)

Slides available on hunteratliff1.com/talk/