Control and Management of EV 71 Associated HFMD

Amr Ismail

MBBCh, MSc, MD, MACP , FISQua , FABAM , CHPI

Consultant Dermatologist

Objectives

- To overview EV 71 associated HFMD outbreaks.
- To describe prevention and control measures of EV71 associated HFMD including vaccines.

Introduction

- HFMD is one of the most recognizable common febrile viral disease in children.
- HFMD is caused most frequently by Coxsackie virus A16 and EV71.
- HFMD is usually a mild illness.
- EV71 associated HFMD outbreaks show high incidence of severe neurological complications like brainstem encephalitis and acute flaccid paralysis.
- Fatalities have been reported esp. in child < 5 years.
- EV71 associated HFMD is a serious public health threat and burden to health care systems.

Enterovirus 71 (EV71)

- EVs are nonenveloped, single-stranded, positive-sense viruses in the *Picornaviridae* ("small RNA virus") family.
- EV71 is non-Poliovirus belongs to Human enterovirus A.
- EV71 was 1st discovered in California 1969 (20/1/A).
- EV71 Genotypes A,B(B1~B5),and C(C1~C5).
- EV71 Genotypes D (India), E and F (Africa)and rare subgenotypes Bo , Co and C2 like have been identified.
- EV71 outbreaks occur in a cyclical pattern every 2-3 years, predominantly caused by strains that are distinct from previous outbreaks.

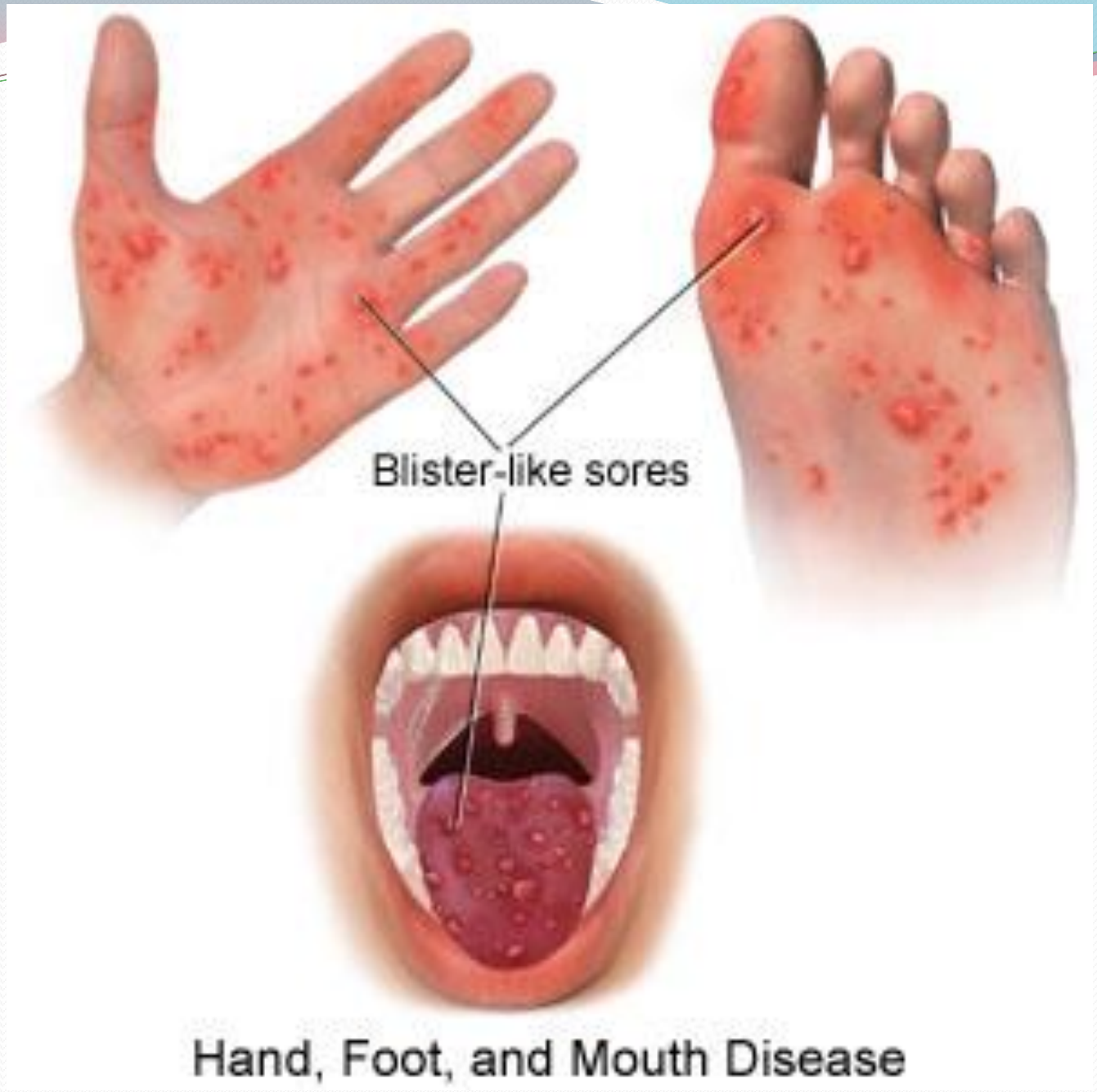
EV 71 associated HFMD Major Outbreaks World Wide

Year	Country	Clinical findings	CASES/Fatalities
1975	Bulgaria	Aseptic meningitis Bulbar encephalitis	705 /68
1978	Hungary	Aseptic meningitis Bulbar encephalitis	1550/45
1997	Malaysia	Cardiopulmonary failure	5999/>35
1998	Taiwan	HFMD /HA with Encephalitis	129106/78
2008 - 2012	China - mainland	HFMD – encephalitis Pulmonary edema	7.2 million/2457
2009	Korea	HFMD Encephalitis	91/2

EV71 associated HFMD

Year	Country	Clinical findings
2009-2013	Denmark	HFMD with ND N=63 HFMD N= 6
2012	France	Neonatal fever and meningitis N=4
2012-2013	Sydney	Severe disease N=119 Classic HFMD N=28

EV71 Subgenotypes	Country (Year)
C4	Austria , Germany (2004) , China(2008-2011), France(2004 and 2012) and Denmark (2012).
B5	Malaysia(1999) , Japan (2003), Denmark (2007), Taiwan (2008 and 2012) and France (2013).


Blister-like sores
Hand, Foot, and Mouth Disease

Clinical Grading HFMD

Grade	Clinically
I	Uncomplicated Fever Vesicles/papules – oral mucosa Hand , foot and buttocks
II	Central Nervous System (Myoclonus – fingers)
III	Autonomic Nervous Disease
IV	Cardiopulmonary Failure

EV71 Complications

- Acute severe with high mortality.
  - Pulmonary hemorrhage.
  - Brain stem encephalitis.
  - Aseptic meningitis.
  - Flaccid paralysis.

Prevention and Control Measures

1. **Surveillance**:

   1.1 The data used to tackle a disease of significant public health importance and to provide EV71 disease activity in the community.

   1.2 The importance of formation of International network for Enterovirus surveillance.

2. **Strategies can effectively control and prevent spread and diffusion of HFMD**

2.1. **To reduce transmission rate** :

A. Popularize healthcare education and teaching good hygiene practices : Frequent hand washing before and after eating and after going to the toilet. Avoiding thumb-sucking and nail-chewing. Putting on a face mask when feeling unwell.

B. Strengthen hospital infection control practices to avoid nosocomial cross infection.

2.2. **To increase recovery rate** of non hospitalized cases and clinical case management in timely fashion.

3. Others: School closures (no evidence of effectiveness).

Treatment : Antiviral Strategies

- Effective antivirals against EV71 are still not available due to high frequency of mutation and recombination in EV71.

Drugs	Mode of action	References
Intravenous immunoglobulin (IVIg)	Suppress viral replication Limit organ damage (anti-inflam. activity)	Ooi et al.2007
Ribavirin and type I Interferon	In vitro and in vivo protective effects on EV71	Li etal. 2008 Li et al 2005
Pleocarnil	1.Broad spectrum antiviral against EV71 serotypes. 2. No cytopathic inhibition effects.	Pevear 1999 Chen et al. 2008

Future consideration: EV71 Vaccines

- Development of EV71 vaccines would be the most effective approach to prevent EV71 outbreaks.
- Efficiency data published only 5 years after China made HFMD a notifiable disease on 2008.
- Liang and Wang 2014 summarized the results 3 phase III clinical trials of inactivated EV71 whole virus vaccine in mainland China.
- Two vaccination procedure : od and 28d.
- Voluntary Surveillance for HFMD/HA in one year follow up.

Vaccine Strain	Nucleotide difference	Amino acid difference
C4	97.3% - 99%	98.3% - 99.7%

EV71 associated HFMD Vaccine Efficacy

Manufacturer	Subjects	EV71 Vaccine Efficacy	References
Sinovac	Infants (6-35 months) Vaccine gp= 5044 Placebo gp =5033	97.5% (6M) 94.8 % (12M)	Zhu et al. 2014
Vigoo	Infants (6-35 months) Vaccine gp= 5120 Placebo gp =5125	90.0% (67.1 % – 96.9%)	Zhu et al. 2013
Kunming Institute (K.I.)	Infants (6-35 months) Vaccine gp= 6000 Placebo gp =6000	97.3% (92.6% - 99.0%)	Li et al. 2014

EV71 associated HFMD Vaccine Safety

Manufacturer	Adverse Effects (AE)	Incidence of vaccine AE	Placebo
Sinovac	**Most common** fever less than Grade 3	41.6%	35.2%
Vigoo		35.2%	33.9%
K.I.		34.6%	35.1%
Sinovac	**Severe**	1.2%	1.5%
Vigoo		2.2%	2.6%
K.I.		1.1%	2.1%

- The rate for preventing hospitalization for EV71 associated HFMD (100%).
- 1 year follow up (+ve neutralizing Abs)

Sinovac 99% (>1:8)

Vigoo 92%(>1:16)

Major Key points of EV71 vaccines

Points	Remarks
1. Promoting vaccine application	•How to persuade the public to accept that HFMD is still epidemic even after vaccination. •The urgent need to establish WHO guidelines to accelerate vaccine application.
2. Cross protection	•C4 and B5 two pandemic strains . •C4 vaccine showed good cross neutralization (B4,B5,C2,C5). •B4 vaccine was unable to neutralize C2.
3. Monitoring vaccine safety and effectiveness	•Phase III studies conducted 30.000 infants only. •The need to conduct Phase IV clinical trials on large population size.

Comparison of EV71 vaccines

Vaccines	Tested	Advantages	Disadvantages
Live-attenuated vaccine	*In vitro / in vivo*	Broad spectrum, low cost	Incomplete attenuation
Inactivated vaccine	*In vitro / in vivo / clinical trial*	Inability to replicate	High cost
Subunit vaccine	*In vitro / in vivo*	Safe to use	Low immunogenicity
Synthetic peptides	*In vitro / in vivo*	Small and safe to use	Low immunogenicity, escape mutants
Virus-like particles	*In vitro / in vivo*	Safe to use	Unstable, need purification, high cost
DNA vaccine	*In vitro / in vivo*	Most resemble native virus, fast production, low cost, can be manipulated	Low neutralising effect

Conclusions

- EV71 associated HFMD outbreaks have occurred for decades with severe complications and deaths in children.
- Frequent EV71 mutations have hampered the development of effective antiviral treatment.
- EV71 vaccines are eagerly awaited but there are several challenges to overcome to save lives and ensure health and welfare of children with EV71 associated HFMD.

Thank You

email: amrismailmd@gmail.com