Risk Factors for Critical Disease and Death from Hand, Foot, and Mouth Disease
Immunosuppressants and Immunostimulants – What Works?
Chongqing Province, China, 2011

Yilin He
Chinese FETP 10th cohort
Email: heyilin001@126.com

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Critical Hand Foot and Mouth Disease (HFMD) and Death

• Characterized by:
  – Brainstem encephalitis
  – Pulmonary edema
HMFD in China

- 1414 children died from HMFD in 2010-2011

- Chongqing Province, western China, has highest case fatality rates:
  - The 3rd (0.13%) in 2010
  - The 1st (0.14%) in 2011

Chongqing

30 million population, 40 counties
Objectives

- To identify risk factors for critical and fatal HFMD
- To provide scientific evidence for prevention of critical and fatal HFMD
Critical case-patient

- Clinically diagnosed HFMD
- Onset from Jan 1, 2010 to Nov 30 2011, in Chongqing
- With ≥1 of the following:
  - Muscle weakness or paralysis
  - Repeated convulsion
  - Needed mechanical ventilation or tracheal intubation
  - Stupor or coma
  - Death
Control-patient

- Randomly selected HFMD inpatients who did not meet critical case definition
- From eligible patients selected individually matched (1:1) by:
  - Same county of residence
  - Age within 24 months
  - Onset of HFMD: 3 months before or after onset month of case-patient
Laboratory confirmed cases and controls

- Identification of enterovirus 71 or other enterovirus by PCR
Participation of case- and control-patients

- **68 (76%) of 89 case-patients**
  - 4 lost to follow-up
  - 4 refused investigation
  - 13 did not fit critical case definition

- **68 (85%) of 80 control-patients**
  - 2 lost to follow-up
  - 1 refused investigation
  - 9 did not fit control definition
Data collection

- Interviewed care-givers of patients
  - Onset of symptoms
  - Healthcare seeking behaviors
  - Self-medications
  - Medical history

- Reviewed medical records
  - Medications used
  - Clinical manifestations
  - Vital signs
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
<th>Cases (n=68)</th>
<th>Controls (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>Median</td>
<td>22</td>
<td>33</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>4-66</td>
<td>8-66</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>%</td>
<td>38</td>
<td>35</td>
<td>0.43</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>Mean</td>
<td>3.2</td>
<td>3.2</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.44</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Congenital Diseases</td>
<td>%</td>
<td>2.9</td>
<td>0</td>
<td>0.24</td>
</tr>
</tbody>
</table>
The first treatment of case- and control-patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Statistic</th>
<th>Cases (n=68)</th>
<th>Controls (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C) at first clinic visit</td>
<td>Median</td>
<td>39.0</td>
<td>38.0</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>37.7-42.0</td>
<td>36.4-40.3</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>%</td>
<td>93</td>
<td>91</td>
<td>0.50</td>
</tr>
<tr>
<td>Days from onset to first clinic visit</td>
<td>Median</td>
<td>1</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-4</td>
<td>0-7</td>
<td></td>
</tr>
<tr>
<td>Village clinics or township hospitals</td>
<td>%</td>
<td>74</td>
<td>56</td>
<td>0.05</td>
</tr>
</tbody>
</table>
### Percent of case and control patients
### Detection of enterovirus nucleotides

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cases % (n=68)</th>
<th>Controls % (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus 71</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>Coxsackie A16</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Enterovirus untyped</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unsampled</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

*P=0.12  2X5 exact test*
Time of exposures to drugs

Case-patient:
- Onset date
- First exposure
- Diagnosed as critical
- Exposure period

Control:
- Onset date
- First exposure
- Imputed critical onset
- Exposure period
### Univariate conditional logistic regression of drug exposure before development of critical disease

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cases % (n=68)</th>
<th>Controls % (n=68)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids(GC)</td>
<td>37</td>
<td>5.9</td>
<td>20</td>
<td>2.7-149</td>
</tr>
<tr>
<td>Chinese Traditional Medicine</td>
<td>46</td>
<td>31</td>
<td>1.8</td>
<td>0.91-3.7</td>
</tr>
<tr>
<td>Antipyretic</td>
<td>63</td>
<td>49</td>
<td>1.7</td>
<td>0.89-3.3</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>69</td>
<td>65</td>
<td>1.2</td>
<td>0.61-2.3</td>
</tr>
<tr>
<td>Antiviral</td>
<td>63</td>
<td>88</td>
<td>0.19</td>
<td>0.07-0.56</td>
</tr>
<tr>
<td>Andrographolide(AG)</td>
<td>16</td>
<td>57</td>
<td>0.13</td>
<td>0.04-0.35</td>
</tr>
<tr>
<td>Interferon</td>
<td>5.9</td>
<td>19</td>
<td>0.18</td>
<td>0.04-0.82</td>
</tr>
<tr>
<td>Each additional three months age</td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.44-0.75</td>
</tr>
</tbody>
</table>
Andrographolide

• From east and south Asian plant
• Effective in treatment of upper respiratory infections
• Immunostimulant that increases lymphocyte activity
## Multivariable conditional logistic regression of drug exposure before development of critical disease

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<tr>
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<td>24</td>
<td>1.2-463</td>
</tr>
<tr>
<td>Andrographolide (AG)</td>
<td>16</td>
<td>57</td>
<td>0.22</td>
<td>0.52-0.92</td>
</tr>
<tr>
<td>GC and AG</td>
<td>7.4</td>
<td>1.5</td>
<td>4.3</td>
<td>0.03-552</td>
</tr>
<tr>
<td>Interferon</td>
<td>5.9</td>
<td>19</td>
<td>0.06</td>
<td>0.00-6.1</td>
</tr>
<tr>
<td>Each additional three months</td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.51-0.89</td>
</tr>
</tbody>
</table>
### Multivariable conditional logistic regression of drug exposure during 48h after onset

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cases % (n=68)</th>
<th>Controls % (n=68)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids (GC)</td>
<td>25</td>
<td>4.4</td>
<td>6.8</td>
<td>1.1-43</td>
</tr>
<tr>
<td>Andrographolide (AG)</td>
<td>22</td>
<td>46</td>
<td>0.27</td>
<td>0.08-0.98</td>
</tr>
<tr>
<td>GC and AG</td>
<td>5.9</td>
<td>1.5</td>
<td>2.3</td>
<td>0.02-295</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>37</td>
<td>53</td>
<td>0.86</td>
<td>0.20-3.7</td>
</tr>
<tr>
<td>Interferon</td>
<td>2.9</td>
<td>15</td>
<td>0.27</td>
<td>0.02-3.7</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>18</td>
<td>4.4</td>
<td>3.5</td>
<td>0.49-25</td>
</tr>
<tr>
<td>Each additional three months age</td>
<td></td>
<td></td>
<td><strong>0.65</strong></td>
<td><strong>0.49-0.87</strong></td>
</tr>
</tbody>
</table>
Summary of Findings

- Glucocorticoids: Associated with critical diseases of HFMD
  - No other drugs had similar association
  - Reinforces findings of other observational studies

- Andrographolide: Associated with a protective effect

- Effects seen after giving either drug:
  - Giving drug before onset of critical findings
  - During first 48 hours of mild (HFMD) disease
Main Limitations

- This was not a prospective study or clinical trial and thus subject to potential selection biases.
- Case-control study was hospital-based and does not assess many mild cases.
- Many patients received multiple drugs the effect of which cannot be reliably assessed.
Conclusion

- Glucocorticoids, immunosuppressants, are a risk factor for development of critical and fatal HFMD
- Andrographolide, a known immunostimulant, appears to have a protective effect
Recommendations

- Glucocorticoids should not be used for mild HFMD
- Glucocorticoids have no proven effectiveness in severe or critical EV 71 infections and should also not be used
- Andrographolides should undergo clinical trials for enterovirus 71 infections
Acknowledgement

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- Prof. Guang Zeng
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- Dr T. Shen
- Dr. Lijie Zhang
- Prof. Guoqing Shi

Chongqing CDC
- Yulin Wang
- Qin Li
- Jiang Long
- Qingliang Jia
- Bangzhong Xiao
Thank you
Extra slides
### Multivariable conditional logistic regression of drug exposure during 72h after onset

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cases % (n=68)</th>
<th>Controls % (n=68)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids (GC)</td>
<td>27</td>
<td>5.9</td>
<td>13</td>
<td>1.03-172</td>
</tr>
<tr>
<td>Andrographolide (AG)</td>
<td>13</td>
<td>56</td>
<td>0.16</td>
<td>0.04-0.71</td>
</tr>
<tr>
<td>GC and AG</td>
<td>5.9</td>
<td>1.5</td>
<td>0.15</td>
<td>0.00-43</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>40</td>
<td>59</td>
<td>0.33</td>
<td>0.04-2.5</td>
</tr>
<tr>
<td>Interferon</td>
<td>4.4</td>
<td>19</td>
<td>0.18</td>
<td>0.01-3.6</td>
</tr>
<tr>
<td>Each additional three months age</td>
<td></td>
<td></td>
<td>0.66</td>
<td>0.50-0.88</td>
</tr>
</tbody>
</table>
Clinical manifestations of 68 critical cases before discharged or died

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>94</td>
</tr>
<tr>
<td>Fever $\geq 38.5^\circ\text{C}$</td>
<td>84</td>
</tr>
<tr>
<td>Repeated convulsion</td>
<td>68</td>
</tr>
<tr>
<td>Needed mechanical ventilation or tracheal intubation</td>
<td>59</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>57</td>
</tr>
<tr>
<td>Repeated vomits</td>
<td>49</td>
</tr>
<tr>
<td>Cough</td>
<td>48</td>
</tr>
<tr>
<td>Stupor or coma</td>
<td>41</td>
</tr>
<tr>
<td>Irritable</td>
<td>29</td>
</tr>
<tr>
<td>Paralysis</td>
<td>19</td>
</tr>
<tr>
<td>Sore throat</td>
<td>16</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
</tr>
</tbody>
</table>
Subjects were investigated among 21 counties of Chongqing province.
Exposure timing of andrographolide (AG) and glucocorticoids (GC)

Onset date AG exposure

Case-patient

- Onset date
- AG exposure
- 24h
- 48h
- 72h
- 96h
- GC exposure
- Diagnosed as critical

Control

- Onset date
- AG exposure
- 24h
- 48h
- 72h
- 96h
- GC exposure
- Imputed critical onset

Exposure period
AG exposure frequency in different time among cases
GC exposure frequency in different time among cases

Before critical GC exposure cases

GC exposure cases

24h 48h 72h Before critical
The exposure rates of androg and glucocorticoids at different time among 68 groups

<table>
<thead>
<tr>
<th>Exposure time</th>
<th>Statistic</th>
<th>Androg</th>
<th>Glucocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=68)</td>
<td>(n=68)</td>
</tr>
<tr>
<td>48 hours</td>
<td>%</td>
<td>12</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>0.27(0.08-0.98)</td>
<td>6.8 (1.1-43)</td>
</tr>
<tr>
<td>72 hours</td>
<td>%</td>
<td>13</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>0.16 (0.04-0.71)</td>
<td>13 (1.03-172)</td>
</tr>
<tr>
<td>Before critical</td>
<td>%</td>
<td>16</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>0.22(0.52-0.92)</td>
<td>24 (1.2-463)</td>
</tr>
</tbody>
</table>
### PCR results of throat swabs among 68 groups

<table>
<thead>
<tr>
<th>Objects</th>
<th>EV71</th>
<th>Cox A16</th>
<th>EV</th>
<th>Negative</th>
<th>Unsampled</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>34</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Dead</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>18</td>
<td>40</td>
</tr>
</tbody>
</table>

### PCR results of feces samples or anal swabs among 68 groups

<table>
<thead>
<tr>
<th>Objects</th>
<th>EV71</th>
<th>Cox A16</th>
<th>EV</th>
<th>Negative</th>
<th>Unsampled</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>24</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>35</td>
<td>68</td>
</tr>
<tr>
<td>Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>survival</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>dead</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>
Andrographolides (Androg)

- Androg *paniculata extract* stimulate the cytotoxic T lymphocyte (CTL) production through enhanced secretion of IL-2 and IFN-γ by T cells and thereby inhibit the tumor growth. (K. Sheeja and G. Kuttan. *Immunopharmacology and Immunotoxicology*, 29:81–93, 2007)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>cases % (n=68)</th>
<th>Control % (n=68)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>25</td>
<td>4.4</td>
<td>5.7</td>
<td>1.7-19</td>
</tr>
<tr>
<td>Antipyretics</td>
<td>62</td>
<td>38</td>
<td>3.0</td>
<td>1.4-6.7</td>
</tr>
<tr>
<td>Paracetamols</td>
<td>18</td>
<td>4.4</td>
<td>4.0</td>
<td>1.1-14</td>
</tr>
<tr>
<td>Diclofenac methyl ester</td>
<td>5.9</td>
<td>2.9</td>
<td>2.0</td>
<td>0.37-11</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>7.4</td>
<td>1.5</td>
<td>5.0</td>
<td>0.58-43</td>
</tr>
<tr>
<td>Pyrazolones</td>
<td>10</td>
<td>5.9</td>
<td>2.5</td>
<td>0.49-13</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5.9</td>
<td>4.4</td>
<td>1.3</td>
<td>0.30-6.0</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>29</td>
<td>27</td>
<td>1.2</td>
<td>0.55-2.4</td>
</tr>
<tr>
<td>Traditional Chinese Medicines</td>
<td>35</td>
<td>25</td>
<td>1.5</td>
<td>0.77-3.1</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>57</td>
<td>54</td>
<td>1.1</td>
<td>0.57-2.3</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>46</td>
<td>38</td>
<td>1.3</td>
<td>0.69-2.5</td>
</tr>
<tr>
<td>Penicillins</td>
<td>26</td>
<td>26</td>
<td>1.0</td>
<td>0.45-2.3</td>
</tr>
<tr>
<td>Antivirals</td>
<td>49</td>
<td>74</td>
<td>0.29</td>
<td>0.25-1.1</td>
</tr>
<tr>
<td>Androg</td>
<td>12</td>
<td>46</td>
<td>0.18</td>
<td>0.07-0.46</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>37</td>
<td>53</td>
<td>0.45</td>
<td>0.21-0.99</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>15</td>
<td>16</td>
<td>0.88</td>
<td>0.32-2.4</td>
</tr>
<tr>
<td>Interferon</td>
<td>2.9</td>
<td>15</td>
<td>0.11</td>
<td>0.14-0.88</td>
</tr>
<tr>
<td>Each additional 3 months old</td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.44-0.75</td>
</tr>
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### Univariate conditional logistic regression in 72h after onset

<table>
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<tr>
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<th>Control % (n=68)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
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<td>29</td>
<td>5.9</td>
<td>38</td>
<td>5.2-277</td>
</tr>
<tr>
<td>Antipyretics</td>
<td>60</td>
<td>47</td>
<td>1.6</td>
<td>0.85-3.2</td>
</tr>
<tr>
<td>Diclofenac methyl ester</td>
<td>5.9</td>
<td>2.9</td>
<td>3.0</td>
<td>0.31-29</td>
</tr>
<tr>
<td>Paracetamols</td>
<td>18</td>
<td>5.9</td>
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<td>Control % (n=68)</td>
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<td>95% CI</td>
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Univariate conditional logistic regression of drugs and age in 37 EV71 infected groups before diagnosed as critical

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<th>95% CI</th>
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Multivariable conditional logistic regression of drugs and age in 37 EV71-infected groups before diagnosed as critical

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### Exposure rates of Pyrazolones in different time after onset

<table>
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<th>Controls % (n=68)</th>
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