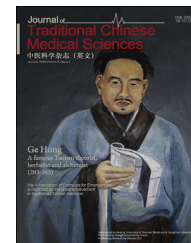


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# Chinese herbal medicine for hand-foot-and-mouth disease in children: An overview of systematic reviews

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## KEYWORDS

Chinese herbal medicine;  
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**Abstract** *Objective:* To summarize the use of Chinese herbal medicines (CHM) for the treatment of hand-foot-and-mouth disease (HFMD) in children and to provide high-level evidence for clinical decision-making.

*Methods:* We conducted an overview of systematic reviews (SRs). Two English-language and four Chinese-language electronic databases were searched from inception to March 31, 2018. Published SRs and meta-analyses evaluating CHM use in children with HFMD and reporting clinically-relevant outcomes such as time to fever resolution were eligible for inclusion in this overview. Reviews were accepted if the intervention featured CHM with or without other treatment. Two authors evaluated the methodological quality of the included SRs by using ASMTAR and ROBIS.

*Results:* Thirty SRs comprising 90 244 children with HFMD were included in this overview of SRs. All SRs were published in Chinese between 2011 and 2017. All intervention arms received CHM with or without conventional treatment and were compared against control arms receiving no treatment, conventional treatment alone, or placebo. All 30 reviews reported the time to fever resolution and results demonstrated that CHM had a greater benefit in reducing fever compared with controls. Twenty-three reviews reported the time to rash resolution which presented similar results. Fourteen SRs reported the time to oral ulcer healing and CHM demonstrated a significantly reduced time to resolution compared to controls. The quality of the included SRs was low to moderate as assessed by the AMSTAR tool.

*Conclusion:* Published reviews demonstrated potential benefits of CHM in children with HFMD.

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Overall, the methodological quality of reviews included in this overview of SRs was low and our findings should be interpreted with caution. We would strongly recommend that future SRs be designed and reported rigorously following PRISMA in order to provide more robust evidence on which to base clinical guidance.

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## Introduction

Hand-foot-and-mouth disease (HFMD) is a common acute infection caused by a group of human enteroviruses, most commonly coxsackievirus A16 (CA16) and enterovirus 71 (EV71).<sup>1</sup> HFMD is most commonly detected in infant and young children below the age of 5, though it can occasionally affect adults. Typical clinical features are fever, sore throat, reduced appetite, feeling unwell, oral ulcers and macules which may develop into a painful vesicular rash on the palmar, plantar and interdigital surfaces of the hands and feet as well as the buttocks.<sup>2</sup> HFMD is usually a minor self-limiting illness and although complications are rare, infections involving EV71 can have serious consequences including viral meningitis, encephalitis, pulmonary edema, myocarditis and even death.

HFMD is one of the most severe epidemic diseases affecting children in the Asia–Pacific region and outbreaks have been documented in China, Malaysia, Japan, Singapore and Vietnam. HFMD has been prevalent in China since 2007. In 2009, an outbreak affected over a million people in China and of these, 13 810 (1.2%) experienced serious complications and 353 (0.03%) died.<sup>1</sup> Although vaccines licensed in China have demonstrated high efficacy against EV71-associated HFMD, children remain vulnerable to non-EV71 HFMD.<sup>3</sup>

Chinese herbal medicine (CHM) is widely used for symptoms of HFMD in China but it is not known how evidence-based guidance is at present on the use of CHM for symptoms of HFMD. Although randomized controlled trials (RCTs) have demonstrated benefits of CHM compared with Western medication for symptoms of HFMD, it is important to summarize all available evidence on the potential benefits and harms of CHM in HFMD. In this study, we conducted an overview of systematic reviews (SRs) with the aim of summarizing the most effective interventions and provide high-level evidence on benefits and harms to inform clinical decision-making.<sup>4</sup>

## Methods

### Criteria for considering SRs for inclusion

#### Study design

In this overview of SRs, all SRs were eligible if they contained at least one RCT that evaluated the use of CHM for HFMD. Inclusion criteria of participants, interventions, comparisons, outcomes reported in the SRs were as follows:

**Participants:** Patients diagnosed with HFMD by diagnostic criteria.

**Intervention & comparison:** SRs were accepted if they evaluated treatment groups using CHM with or without conventional treatment. Acceptable control groups included no treatment, placebo and conventional treatment.

**Outcomes:** According to the guideline for HFMD,<sup>1</sup> the primary outcomes were time to fever resolution, time to rash resolution and safety assessment. Secondary outcomes were time to oral ulcer healing, course of disease and effectiveness rate.

#### Search methods for identification of SRs

We searched two English-language electronic databases (PubMed, Cochrane Library) and four Chinese-language electronic databases (China Network Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (VIP), Wanfang Data, Chinese Biomedicine (CBM)) from inception to March 31, 2018. We used subject searches in CNKI, VIP and Wanfang, CBM databases, and an abstract/title search in PubMed and the Cochrane Library. The search strategy was as follows: (“traditional Chinese medicine” (*Zhongyi*) or “herbal medicine” (*Zhongyao*) or “Chinese patent medicine” (*Zhongchengyao*)) AND (“Hand-Foot-Mouth” (*Shouzukou*) or “HFMD”) AND (“Systematic review” (*Xitongzongshu* or *Xitongpingjia*) or “meta-analysis” or “SR”).

We also manually searched the reference lists of all full-text papers for additional relevant reports. No language restrictions were imposed.

#### Study screening and study selection

Only SRs that assessed the use of CHM for treating HFMD were included in this overview of reviews. Two authors (RHW and SGL) independently screened the literature for eligibility of SRs, according to the criteria above. Any disagreements regarding eligibility were resolved by a third reviewer (JPL).

#### Data extraction

Two authors (RHW and SGL) independently extracted study information such as study characteristics including publication year, sample size, details of interventions, primary outcome, secondary outcomes and safety assessment.

#### Assessment of methodological quality

Two authors (RHW and JS) evaluated the methodological quality of the included SRs using two assessment tools: “assessment of multiple systematic reviews” (AMSTAR) and

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