Dengue Shock Syndrome: Its Similarity with Anaphylaxis and with the Homeopathic Medicine *Apis mellifica* (European Honeybee)

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Abstract

Dengue, with four viral serotypes, causes epidemics in tropical and sub-tropical regions. Allopathic antiviral therapies and a vaccine of general use are lacking. The homeopathic medicine *Apis mellifica,* advised in anaphylaxis from honeybee sting, is proposed to address the life-threatening dengue shock syndrome, which develops from dengue hemorrhagic fever and has features of anaphylaxis. In both dengue and anaphylaxis, immunoglobulin E activates, and released vasoactive mediators (importantly histamine, tryptase and platelet-activating factor) cause, a vascular permeability enabling shock. In dengue, another mechanism, namely antibody-dependent enhancement, due to secondary infection with a heterologous dengue serotype, is associated with release of vasoactive mediators. The homeopathic medicine *Apis mellifica* indicates plasma leak, shock, and the serous effusion that is noted in dengue patients, and is a suggested prophylactic and therapeutic medicine for dengue shock syndrome.

Keywords
- dengue shock syndrome
- anaphylaxis
- homeopathy
- *Apis mellifica*

Introduction

The mosquito-transmitted tropical and sub-tropical viral disease of dengue causes an estimated 96 million apparent infections annually, mainly in Asia. Patients with severe illness can develop the potentially deadly dengue shock syndrome.[1] *Aedes aegypti* and *Aedes albopictus* are important vectors.[2,3] The severe form of dengue, namely dengue hemorrhagic fever, which can escalate to the shock syndrome, mostly affects the young.[2] Children and young adults are targeted; risk factors also include female gender[4] and obesity.[4–6] An established vaccine, of general public use, does not exist,[7] and allopathic treatment for arthropod-borne viral diseases is merely supportive.[4]

The alternative/complementary medicine of homeopathy has treated and prevented dengue ("breakbone" fever). Classical homeopathy, selecting single medicines according to the patient's signs and symptoms, has yielded encouraging results,[8,9] while single or combination homeopathic medicines matched to the commonly observed symptoms of dengue epidemics have acted preventively and therapeutically.[3,10] Other studies have used combinations constituting several remedies known to address dengue symptoms.[11,12]

This article proposes the homeopathic remedy *Apis mellifica* (syn.: *Apis mellifera,* European honeybee) for the prevention and treatment of dengue shock syndrome. The remedy's indications and dengue hemorrhagic fever escalating to the shock syndrome are similar and, specifically, both are known as having features of anaphylaxis.

Disease Progression in Dengue

Dengue is considered to have three forms. Dengue fever is the influenza-like initial illness,[13,14] which, in some cases, triggers thrombocytopenia and some bleeding phenomena.[2,8,15] After defervescence, approximately 5% of patients enter a critical phase and progress to true dengue hemorrhagic fever marked by plasma leak from blood vessels and potential escalation to dengue shock syndrome. Severe hemorrhages may occur.[14]

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The incubation period for dengue spans 3 to 14 days. Acute dengue fever lasts 3 to 7 days. Initially, fever with sudden onset reaching approximately 40°C, frontal headache and retro-orbital pain, body aches, joint aches, nausea, vomiting, and facial flush are noted, with possibly a sore throat, injected conjunctivae and a relative bradycardia. Lymphadenopathy is usually seen. After a few days, a remission of 12 to 24 hours may occur; the temperature rises again, then drops to normal or below normal. Between illness days 2 to 6, a rash lasting about 2 to 3 days may appear on the torso, face and limbs, ranging in manifestation from scarlatiniform to maculopapular or producing an erythema with interspersed spots of normal skin. Pruritus and peeling may be noted. Convalescence may last weeks and be accompanied by weakness and depression.[2]

In dengue hemorrhagic fever, laboratory values, importantly rising hematocrit (from plasma leakage due to the increased vascular permeability) and thrombocytopenia, help confirm the diagnosis.[2,16] The thrombocytopenia reaches $\leq$100,000/mm^3. Hepatomegaly may be present. Petechiae are common, but hemorrhages may progress to include purpuric or large ecchymotic lesions, less often nasal, gingival, gastrointestinal bleeding, or hematuria. There may be evidence of disseminated intravascular coagulation. In the brain, edema and hemorrhage may occur. Post-mortem, diffuse petechial hemorrhages of most organs were found.[2] In some cases of dengue fever (the milder illness), thrombocytopenia values of $\leq$100,000/mm^3 are also reached;[2,8] hemorrhagic manifestations include petechiae, epistaxis, gastrointestinal bleeding, menorrhagia,[2] non-menstrual vaginal bleeding,[15] and bleeding in spots from the oral mucosa.[8]

In dengue hemorrhagic fever, the skin may be cool and may appear congested and blotchy; the pulse is weak and rapid. The hemorrhages, plasma leak and associated circulatory disturbances lead to hypovolemia and hypotension, enabling shock. In this illness, shock is more commonly caused by plasma leak than blood loss. Effects of plasma leak include hypoproteinemia and, as a post-mortem finding, serous effusion (pericardial, pleural and peritoneal). Volume replacement therapy is crucial in the prevention of death and can lower the fatality rate to $\leq$1%.[2]

Patients may suffer acute abdominal pain and restlessness prior to the onset of shock. When in profound shock, they have undetectable pulse and blood pressure and may succumb within 8 to 24 hours. Children often display facial petechiae, perioral cyanosis and sleepiness.[2]

Complications in dengue unrelated to the shock syndrome can involve major organs,[17,18] and the glandular[19,20] and musculoskeletal systems.[20]

Antibody-Dependent Enhancement and Immunoglobulin E (IgE)-Mediated Effects in Dengue

The virus has four antigenically distinct serotypes known to cause epidemic disease in humans.[2,16,21] Initial infection with a serotype causes the pertaining immunity, yet the other serotypes remain virulent and, in a secondary infection, dengue shock syndrome facilitated by "antibody-dependent enhancement" may occur.[2,14,21–23] On day 2 of the dengue illness, a patient's immunoglobulin G/immunoglobulin M (IgG/IgM) ratio of $\geq$1.10 differentiates secondary from primary infection.[24]

The process of antibody-dependent enhancement, supported by evidence, indicates involvement of IgG.[14] It was described hypothetically in a review of 1998: the antibody, which formed in response to the primary dengue infection, recognizes the newly incoming dengue virus of a different serotype and forms an antigen-antibody complex without being able to neutralize the attacking virus. Immunoglobulin Fc receptors on the cell membrane of leukocytes, particularly macrophages, bind to and internalize this complex. The virus multiplies within the macrophage and other mononuclear cells. The cells react by producing and secreting vasoactive mediators, which enhance vascular permeability, allowing for hypovolemia and shock.[2]

A review of 2018 considered mast cells and macrophages (both extravascular) and monocytes (intravascular) as the three important cells responsive to dengue virus infection. All three induce processes affecting vascular permeability; all have surface Fc receptors rendering them key players in the antibody-dependent enhancement.[21]

Studies, first in 1999,[25] also researched the involvement of IgE in dengue.[13,25] The possibility of "anaphylatoxin" (C3a or C5a, fragments of the complement system) affecting mast cells was indicated previously, and this mechanism was suggested as involved in the production of urinary histamine levels in dengue hemorrhagic fever patients, in a study of 1977.[26]

Also, primary infection can cause dengue hemorrhagic fever and dengue shock syndrome,[13] and IgE, triggering mast cells to release vasoactive mediators (e.g., histamine), plays a role in the escalation to shock.[13,14] Serum samples of 168 dengue patients aged 7 months to 14 years (52% female), who had contracted dengue during the 1995 to 1996 dengue epidemic in Indonesia, were examined. Forty-one patients suffered a primary infection, and 127 had a secondary infection: respectively, 29 and 42 patients had dengue fever, 5 and 25 had dengue hemorrhagic fever, and 7 and 60 had dengue shock syndrome. Those patients developing dengue shock syndrome had significantly raised total IgE levels compared with dengue fever and dengue hemorrhagic fever patients; and patients developing dengue hemorrhagic fever and/or dengue shock syndrome had significantly raised dengue virus-specific IgE levels compared with dengue fever patients. Both raised IgE levels were found highest during the day after the onset of acute illness and were suggested as prognostic markers for dengue severity. The authors reviewed studies linking viral infections, such as acute Epstein-Barr infection and hemorrhagic fever infections, with IgE or anaphylactic reactions.[13]

Moreover, in a dengue-endemic region, San Andrés Island, Colombia, 168 evaluated persons with a history of dengue infection had raised total IgE levels compared with persons with no such history, which was suggested to indicate immune memory. Acute primary and secondary dengue infection caused raised IgE levels in infected compared to uninfected persons.[25]

The review by King et al noted vasoactive mediators released from mast cells as being associated with clinical dengue severity and pointed to both antibody-dependent enhancement and IgE as stimulators of mast cells. Studies on the treatment of dengue patients, one using anti-histamines and steroids and one using low-dose targeting of histamine, could demonstrate shortening of the disease course.[14]

Immunological responses seemed to hinder the effectiveness of the first licensed dengue vaccine, a live attenuated vaccine (tetravalent) with a yellow fever vaccine backbone (CYD-TDV), named Dengvaxia. When given to seronegative subjects, it causes proneness to severe dengue illness starting at 30 months post-vaccination. The initial vaccination would thus act like a silent "primary" infection leading to the risk of a serious "secondary" infection transmitted by a mosquito bite. Therefore, this vaccine is recommended and endorsed only for persons with a laboratory-confirmed previous dengue infection.[7]

IgE and Vasoactive Mediators Have Roles in Both Severe Dengue and Anaphylaxis

In 2003, it was concluded that a dengue patient's pre-existing total IgE levels, released dengue virus-specific IgE antibodies and, particularly, raised IgE levels in dengue hemorrhagic fever/dengue shock syndrome, strongly pointed to IgE responses as contributory in the pathogenesis of dengue or as revealing the underlying immunological pathogenetic processes.[13] Atopic diseases, such as allergic rhinitis or asthma, appear to be a risk factor for severe dengue,[6] which also indicates a relationship between IgE activity and severe dengue. A review of 2020 assessing such a relationship concluded that IgE positivity and dengue severity were associated, which would suggest an increased likelihood of dengue severity for allergic patients.[27]

Primarily foods, drugs or insect venoms are known to carry antigens triggering anaphylaxis.[28] In honeybee envenomation, importantly the allergen phospholipase A_2 induces IgE-mediated anaphylaxis.[29] In most anaphylactic reactions, tissue mast cells and blood basophils release vasoactive mediators within minutes of exposure to the allergen.[28] Vadas et al, examining 10 patients with severe anaphylaxis (grade 3), found consistently elevated levels of platelet-activating factor (a mediator). Of these patients, 100% had elevated platelet-activating factor levels, compared with 70% with elevated histamine levels and 60% with elevated tryptase levels.[28]

Comparably, in patients developing severe dengue, mast cells release heightened amounts of vasoactive mediators correlating with the degree of dengue severity, importantly histamine,[26] tryptase[30] and platelet-activating factor.[15]

Toxic and Anaphylactic Reactions from Honeybee Sting Compared with Dengue Symptoms

To propose the remedy *Apis mellifica* for the treatment of severe dengue, the substance used for preparation of the remedy must cause similar symptoms in the healthy, such as from acute poisoning or from a proving with the attenuated substance. In 1790, this homeopathic law of similars was first understood by Hahnemann (1755–1843) after proving the anti-malarial *Cinchona* bark for its capacity to cause symptoms of intermittent fever.[31] The symptoms caused by a substance and those of the disease must not be identical but similar.

Insects of the order Hymenoptera (including bees, wasps and ants) inflict stings causing toxic or allergic reactions. The enzyme phospholipase A_2 in honeybee venom, a major allergen, triggers IgE-mediated anaphylaxis and, co-acting with melittin, is a hemolytic factor. Melittin makes up approximately 50% of the venom dry weight[29]; histamine makes up 0.7 to 1.6%.[32] Some of the allergens contained in honeybee venom, particularly melittin, can affect the processes of thrombolysis, coagulation and smooth muscle tone. Melittin activates the pathway of bradykinin, which is a non-immune mediator but promotes some anaphylactic symptoms.[33] Bradykinin does not appear involved in dengue pathogenesis.[26,34]

Toxic Reactions

Commonly, hymenopteran stinging events involve one to four stings, as seen in data from 400 cases with fatal reactions from anaphylaxis or toxicity. The types of fatal pathology from toxicity, all occurring in honeybee envenomation, are labeled according to the site of occurrence as vascular (e.g., coronary occlusion, generalized hemorrhage, emboli), neurological (e.g., cerebral edema and hemorrhage, necrosis and degeneration of brain and spinal cord), and respiratory, the most common pathology (e.g., obstructing massive edema and secretions). Septicemia after stings may also be fatal. Respiratory and vascular symptoms arise in anaphylaxis but are milder in comparison.[35]

Neurological involvement leading to fatal cerebral edema has occurred in dengue, when dengue hemorrhagic fever and the shock syndrome did not develop.[18]

Anaphylactic Reactions

Three categories of anaphylactic symptoms from insect sting have been identified:

1. Mild: only dermal reactions (urticaria, angioedema).
2. Moderate: dermal reactions and other non-fatal symptoms including mild asthma, dyspnea.
3. Severe: symptoms include loss of consciousness, hypotension, shock, upper airway edema, and/or severe respiratory distress.[36]

Anaphylactic symptoms from Hymenoptera sting also include apprehension, headache, tunnel vision, erythema, flushing, periorbital erythema and edema, pruritus, vomiting, urinary or fecal incontinence, abdominal and uterine cramps, paresthesia in limbs, cyanosis, and rapid pulse in developing shock. The increased vascular permeability is due to histamine and other mediators.[37]

Hymenoptera venom, in particular honeybee venom, is considered the most prevalent anaphylaxis-related inducer of hemorrhage, mostly affecting the uterus ("breakthrough bleeding" or "spotting").[33]

Dengue symptoms, such as tachycardia and respiratory distress,[22] erythema or flushing, edema, blood pressure changes and plasma leak,[22,30] were pointed out as resembling allergic/anaphylactic reactions.

Apis mellifica: Homeopathic Materia Medica

The homeopathic Materia Medica of *Apis mellifica* lists: allergic reactions in general, e.g., anaphylaxis, angioneurotic edema, urticaria[38]; "cold surface of body with feeble pulse (after stings)",[39] an apparent shock reaction; and "stings by bees and wasps and perhaps other insects".[39] A girl, who was stung in the mouth on swallowing a wasp, was rapidly relieved of the suffocative swelling by one dose of *Apis mellifica* (potency unknown).[40]

In acute and chronic states, *Apis mellifica* indicates inflammation and serous effusion, such as into pleural, peritoneal, pericardial and arachnoid cavities. It treats affections of the circulatory apparatus and fluid and has a hemorrhagic (incomplete coagulation) and edematous tendency.[39]

Apis mellifica, homeopathically prepared from the whole bee or the venom (sac),[41] is recommended for an allergic diathesis and any anaphylactic reactions, not just when caused by Hymenoptera sting. It desensitizes persons allergic to honeybee venom and treats toxic reactions from Hymenoptera envenomation. It counteracts raised chronic total IgE levels, as have been found after dengue infection,[25] and thus could help prevent a subsequent severe dengue infection.

One dose of the 200c potency may suffice, to be repeated if needed. This regimen could be applied to an acute dengue infection and would, in theory, address plasma leak, shock reactions and serous effusion (prophylaxis and therapy). The remedy may also be considered in the prophylaxis of epidemic dengue.

Discussion

Seen from a global perspective, the dengue burden is particularly high in India and Indonesia. Pakistan, Bangladesh, China (South), Philippines, Nigeria and Brazil are other countries with a high dengue occurrence.[1] As allopathic antiviral therapies and generally established vaccines are lacking, the alternative or complementary therapy of homeopathy has come into focus, as in India and Brazil, where the single remedy *Eupatorium perfoliatum* is recommended for epidemic dengue and its prevention.[3,42] It indicates dengue's influenza-like state, with breakbone pains, soreness of eyes, restlessness, thirst before a chill, minimal perspiration and hepatitis, the latter being commonly present in patients.[3] It has been used in combination remedies,[3,10–12] as in a 30c complex with *Phosphorus* (protects the liver) and *Crotalus horridus,* with preliminary positive[3] and more established positive results (Brazil).[10]

Dengue patients in Bangalore, India, have responded well to a single selected remedy, the classical individualized approach. They received the 200c potency of either *Lycopodium clavatum, Ptelea trifoliata, Pyrogenium, Phosphoricum acidum, Arsenicum album, Ferrum metallicum* or *Thlaspi bursa pastoris.* One patient needed two remedies, namely *Arsenicum album* followed by *Pyrogenium.* Remedies were effective even when platelet counts had plummeted. The homeopathic effect ensured a quick return of normal platelet levels,[8] as similarly observed in Pakistan in homeopathically treated patients versus controls[12] and in Delhi, India, in homeopathically treated patients versus the control group's nearly 2-day delay before reaching 100,000/mm^3, the intermediary platelet level.[9]

The remedy *Crotalus horridus* was used in a combination medicine[3,10,12] to address dengue hemorrhagic fever[3,12] and influence hemoconcentration, vascular permeability and circulation, thereby preventing and targeting dengue shock syndrome.[10] It was administered successfully as single remedy to 112 (81.2%) patients in a cohort of dengue patients with thrombocytopenia, when only scant indications for individualized prescribing existed due to the administration of allopathic medicines.[9]

This article targets the specific life-threatening phase of dengue shock syndrome, proposing the single medicine *Apis mellifica* as a prophylactic and curative therapy, taking into account the potential escalation of dengue hemorrhagic fever to an anaphylactic-like state. The present study, as a limitation, cannot document dengue cases responding to *Apis mellifica,* though it provides useful information on dengue disease progression, anaphylaxis and *Apis mellifica.* Clinicians, on assessing dengue patients, may consider the medicine as a therapeutic option.

Medicines indicated for the escalation to shock also include *Pyrogenium* and *Carbo vegetabilis*. *Pyrogenium* was selected for individual dengue patients who were free of shock.[8,9] It treats soreness and aching of body, restlessness, incongruence between pulse rate and temperature, and sepsis[38] (which can lead to septic shock). *Carbo vegetabilis,* formerly used in yellow fever, indicates collapse with coldness and also hemorrhages. The whole surface of the body may be cold. Cold limbs or knees are noted. The breath, sweat and face are cold, with faint pulse, stagnating blood in capillaries, ecchymoses and cyanosis.[43]

Other homeopathic therapies in infections include blood isodes[44,45] and nosodes prepared from the inciting agent.[46]

Non-homeopathic honeybee venom, as reviewed in 2020, has shown anti-inflammatory effects accredited to melittin and phospholipase A_2. It has been active against viruses including HIV and influenza A H1N1. Moreover, beekeepers in China's Hubei Province, epicenter of the COVID-19 outbreak, were noted as partially immune to the virus, with or without a previous infection with the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). Bee venom was suggested to have a possible prophylactic or therapeutic effect in COVID-19, as when used as a "vaccine". The venom, by inducing production of IgE, causes allergic reactions but also allows for an immune response to various antigens.[47]

Conclusion

As analyzed in this article, dengue virus acts allergen-like in sequential, though also initial, infection by triggering processes that induce release of vasoactive mediators enabling plasma

leak, hypovolemia, hypotension and shock. *Apis mellifica,* indicating these symptoms, is suggested as a preventive and curative homeopathic therapy. Volume replacement therapy remains the crucial clinical allopathic intervention preventing and diverting the shock syndrome. This article provides a basis for future homeopathy studies that could be helpful in evaluating the clinical benefit of *Apis mellifica* in dengue.

Highlights

- Dengue virus has four antigenically distinct serotypes, and initial infection with a serotype causes the pertaining immunity.
- Secondary infection with a heterologous serotype can cause dengue shock syndrome via antibody-dependent-enhancement, which involves IgG and triggers release of vasoactive mediators, as from mast cells, enabling plasma leak and shock.
- Dengue shock syndrome, however, can occur in both primary and secondary infection, which points to the role of IgE in the release of vasoactive mediators from mast cells, and IgE is known as particularly elevated in patients with a primary or secondary infection and who develop the shock syndrome.
- The biochemical events and symptoms of dengue shock syndrome resemble those of IgE-induced anaphylaxis, and the homeopathic remedy *Apis mellifica,* which treats such anaphylaxis, is a suggested prophylactic and curative therapy for dengue shock syndrome.

Conflict of Interest

None declared.

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