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Review Article

Management of Dengue and Post Dengue Complication Syndrome: A Review

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Abstract

One of many hypotheses for the pathogenesis of dengue infection is the antibody-mediated immune response, with a subsequent increase in the production of inflammatory cytokines. For these possible immune mediated post infection complications, there is no recognized or recommended treatment plan. Thus, considerations of a steroids protocol would have a great value considering the immune pathology of dengue equal to other noninfective autoimmune disorders that have been treated successfully with corticosteroids. This review describe acute dengue infections and its immunological changes in each phase and the effective steroid protocol to manage the pre preliminary phase, febrile/ preliminary phase, early critical phase, late critical phase and recovery phase of dengue. This new protocol that is open to change and alteration is proposed.

Keywords: Dengue; Critical Phase; Immune Dysfunction; Steroid Protocol

Abbreviations

WHO: World Health Organization; DSS: Dengue Shock Syndrome; DHF: Dengue Hemorrhagic Fever; CSs: Corticosteroids; IV: Intravenous; MP: Methylprednisolone; HC: Hydrocortisone.

Introduction

The acute manifestations of dengue is followed by three phases; early phase, critical phase and convalescent/recovery phase. Dengue fever and its complication are brought byany of the four distinct serotypes of arboviruses [1] that are mainly found in tropical and subtropical countries. It affects more than 125 countries that are known to be endemic for dengue. One stereotype does not protect against the others and sequential infections can produce a broad spectrum of symptoms, ranging from asymptomatic infection to a severe life-threatening illness such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [2]. World Health Organization (WHO) estimates that around 2.5 billion population worldwide is at risk of dengue infection and 50 to 100 million dengue infections occur annually [3]. Moreover, it includes 500,000 cases of DHF and 22,000 deaths annually. Most of them are children. The incidence has increased 30-fold during the past 50 years [4]. In Sri Lanka 80,732 dengue fever cases, including 215 deaths were reported within the first six months of the 2017 epidemic. Currently there is no therapy available beyond supportive care and untreated complicated dengue fever can have a 50% mortality rate [5].

Therefore, unless a new treatment is introduced to suppress this life threatening immune dysfunction pathology of dengue, 5 million cases of DHF and 0.22 million deaths will definitely occur within the next decade (2018-2028). During the recovery phase also, various clinical presentations were reported, including neurological, cardiac and bleeding manifestations. Many symptoms such as fever, headache, retro-ocular pain, insomnia, alopecia, myalgia, arthralgia, asthenia, anorexia, dizziness or poor appetite, nausea were also found even after two years [6,7].

One of many hypotheses for the pathogenesis of dengue infection is the antibody-mediated immune response, with a subsequent increase in the production of inflammatory cytokines giving rise to various manifestation of dengue [8]. The complications in recovery phase of dengue was also suggested to be caused by appearing

or persistent of immune markers [6]. For these possible immune mediated post infection complications, there are no recognized or recommended treatment plan mainly with the view of suppressing dengue virus induced immune dysfunction. This may be because of the fear of administration of corticosteroid in dengue patients as it is an infective illness.

However it was observed that there is no evidence of viremia in three clinical trials [9-11] and no significant side effects after the administration of low and high oral doses of corticosteroids (CSs)and even high doses of intravenous (IV) corticosteroids in two trials [9,11]. Moreover no evidence of harmful effects of corticosteroids use in critical phase was also found [12]. On the other hand beneficial effects were reported, even in the critical phase [13]. Thus, considerations of a steroids protocol would have a great value considering the immune pathology of dengue equal to other noninfective autoimmune disorders that have been treated successfully with corticosteroids [14-16].

This review describe acute dengue infections and its immunological changes in each phase and the effective steroids protocols found in clinical trials. The critical phase of dengue has been described here as early and late critical phase for descriptive purpose. Finally, this this review suggests a steroids protocol tomanage the pre preliminary phase, febrile/ preliminary phase, early critical phase, late critical phase and recovery phase of dengue.

Dengue pathology

Dengue fever (DF) often presents with fever, rash, headache and myalgia, which are caused by a flavivirus with four distinct stereotype; DENV-1, DENV-2, DENV-3, and DENV-4 [1] An infection with one stereotype does not protect against the others and sequential infections put patients at a greater risk for DHF and DSS [2] that are mainly caused by immunological dysfunction. Dengue virus is injected into the bloodstream during the feeding of mosquitoes on humans and attacks the immune system cells. Firstly, it results in the infection of immature epidermal dendritic cells (DCs) in the epidermis and dermis [17]. Infected DCs then migrate from the site of infection to lymph nodes where monocytes and macrophages are recruited. Thereafter the infection is amplified and the virus is disseminated through the lymphatic system [18]. As a result of this primary viremia, several cells of the mononuclear lineage, including blood-derived monocytes, myeloid DCs and splenic and liver macrophages are infected [19]. In dengue fever pre-existing antibodies (Ig G and Ig M) are associated with antibody-dependent enhancement and complement activation

Dengue during Febrile phase/the preliminary phase

This period is so named from the onset of the dengue symptoms to the earliest plasma leakage stage. The clinical presentations of dengue viral infection range from asymptomatic to severe illness that may lead to death, if not properly managed. The preliminary phase of DF is associated with antibody dependent enhancement (ADE), production of cytokine and chemokines such as IL6, IL 8, MCP 1, TNF alpha and INF, virus replication, killing of infected cells and antibody production. Some of them may affect the integrity of endothelial cell lines [20-22].

Dengue during the early critical phase

In this review, the early critical phase is considered from the beginning of plasma leaking to time before the severe stage of DSS. In DHF the progression of intravascular fluid leakage occurs after 3 - 5 days of fever. Plasma leakage is the pathological hallmark of dengue hemorrhagic fever, which is responsible for the development of severe dengue and DSS [23]. The onset of plasma leakage is characterized by clinical fluid accumulation,(i.e. plural effusion or ascites), liver enlargement of more than 2cm, persistent vomiting, abdominal pain or tenderness and sudden increase in haematocrit (more than 20%).Cardiovascular compromise and intravascular volume depletion is observed during this phase [24,25]. Later patients may develop shock from depletion of intravascular volume and bleeding and this is a medical emergency. It needs prompt and adequate fluid replacement for the rapid and massive plasma losses through increased capillary permeability [26].

Dengue during the late critical phase.

Immunological molecules, such as IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, TGF-1β, TNF-α, IFN-γ, VEGF, MCP-1, GMC-SF, MMIF, ICAM-1, VCAM-1, ICAM-1, TF, PAI-1, PAF, C3a and C5a appear in high concentrations in the later stage of the illness that directly and indirectly contribute to the clinical manifestations and severity of dengue [8,21,24,27]. Tachycardia, thread pulse, narrowing of pulse pressure, delayed capillary refill, oliguria, cold extremities and later profound shock with undetectable pulse, spontaneous bleeding, and multi organ failure can be seen in this stage [27-29]. Furthermore, tissue hypoxia, PH imbalance, electrolyte imbalance and subclinical infection or septicemia may be detected in some instances [26]. The prognosis in the critical phase mainly depends on the early recognition and treatment of shock.

Description	Early phase	Early Critical	Late Critical	Recovery
Immune markers	ADE. Cytokineproduction. Virus replication.Viremia,thrombocytopenia ,antibody production. IL-6, IL-8, MCP 1, TNF-α, INF production [21]. In primary dengue infection = IgG negative or their ratio of IgM to IgG was >1.2,while patients with secondary dengue infection were IgG positive or their ratio of IgM to IgG was <1.2 [30].	Plasma leakage is the pathological hallmark of dengue hemorrhagic fever, which is responsible for the development of severe dengue and DSS [23].	Immunological molecules, such as IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, TGF-1β, TNF-α, IFN-γ, VEGF, MCP-1, GMC-SF, MMIF, ICAM-1, VCAM-1, ICAM-1, TF, PAI-1, PAF, C3a and C5a appear in high concentrations [8,21,24,27].	Higher titers of anti-dengue IgG antibodies. Release of pro-inflammatory cytokines
Treatment used in clinical trials and in clinical practice	In clinical trial- IV methyl prednisolone: 15 mg/kg single dose, within 120 hours of onset of fever [10].	In a clinical trial- IV methyl prednisolone: 10–30 mg/kg day. Single or repeated dose [31].	In a clinical trial -IV methyl prednisolone 1g .signal dose [13].	In clinical practice- Intravenous immunoglobulin (IVIg), plasma exchange and Steroids for neurological complications

Table 1

Dengue during recovery phase

Management of recovery phase of dengue has not received much attention globally compared to the dengue illness and its complication. Therefore, a proposal for management of post dengue complication is also important. Thus, in this review, the recovery phase of dengue is divided into the early phase recovery phase, intermediate recovery phase and late recovery phase.

- **Early recovery phase:** After the critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48 to 72 hours and the appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues [24,32]. However, some patients may exhibit some symptoms and signs such as a confluent erythematous or petechial rash in small areas of normal skin, pruritus and bradycardia [32]. If excessive intravenous fluids have been administered during the critical and/or recovery phases, respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure may occur.

- **Intermediate recovery phase:** This phase starts after few days of early recovery phase and neurological manifestations were reported during this phase. They include depression, convulsions, intracranial thrombosis, myelitis, mononeuropathies, polyneuropathies, encephalopathy, encephalitis, aseptic meningitis, intracranial haemorrhage, hemi facial spasms, peripheral facial paralysis and Guillain–Barre syndrome [33]. Dengue induced immune dysfunction may be the cause for these neurological complication [34-36]. Therefore, it could be suggested that these neurological complications could be reduced or prevented by the use of immune suppressive corticosteroid drugs during the preliminary, early and late critical phase and recovery phase of dengue illness.

- **Late recovery phase:** Some of the dengue symptoms can persist for up to 6 months after DHF [37]. Clinical sequelae were also seen following 2 years after the infection associated with alterations in some immunological parameters [6]. It was found that more than half (56.7%) of the study participants reported having many dengue symptoms following symptomatic dengue disease such as fever, headache, retro-ocular pain, insomnia, alopecia, myalgia, arthralgia, asthenia, anorexia, dizziness or poor appetite, nausea, vomiting, itch and bleeding (vaginal bleeding, epistaxis). In addition it was highlighted that higher titers of anti-dengue IgG antibodies were seen in those with persistent clinical manifestations. Thus it has been suggested that the long-term persistence of clinical symptoms in dengue-infected persons, may be due to a failure in properly clearing the immune complexes that may then stimulate the release of pro-inflammatory cytokines to give rise to such symptoms [6,7]. Therefore, it can be proposed that a therapeutically effective steroid protocol can be used to diminish this immunologically induced morbidity during late phase.

Description	Early recovery phase	Intermediate recovery phase	Late recovery phase
Clinical presentation	Confluent erythematous or petechial rash in small areas of normal skin, pruritus and bradycardia [32]. If excessive intravenous fluids have been administered during the critical and/or recovery phases, respiratory distress from massive pleural effusion and ascites, pulmonary oedema or congestive heart failure may occur	Depression, convulsions, intracranial thrombosis, myelitis, mononeuropathies, polyneuropathies, encephalopathy, encephalitis, aseptic meningitis, intracranial haemorrhage, hemi facial spasms, peripheral facial paralysis and Guillain–Barre syndrome [33].	fever, headache, retro-ocular pain, insomnia, alopecia, myalgia, arthralgia, asthenia, anorexia, dizziness or poor appetite, nausea, vomiting, itch and bleeding (vaginal bleeding, epistaxis)
Existing Treatment	Treat accordingly and avoid fluid over lord	Standards treatment of steroids for neurological diseases. Intravenous immunoglobulin (IVIg) appears plasma exchange for GBS.	Symptomatic
Propose additional or new treatment	32 mg oral methyl prednisolone for three days. If patients test positive for higher titers of anti-dengue IgG antibodies or other immune markers	32 mg per day of oral methyl prednisolone for seven days and tailed off gradually within 2 months.	32 mg per day of oral methyl prednisolone for seven days and tailed off gradually within 2 months. . If symptoms are severe or show high morbidity, IV of MP 125 mg is recommended for use as a loading dose

Table 2

New suggested Protocol to manage dengue immune pathology

Cortisol is a natural steroid and mean serum cortisol levels during the acute stage was two-fold higher than in the convalescent stage in cases of DHF [38]. Furthermore the average serum cortisol level in patients with DHF was found to be higher than that of the patients with DF [39]. These tend to give the message that higher levels of natural cortisol is used to self-control dengue illness pathology or to combat with the deregulation of the immunity. In fact, the complete recovery after dengue infection clearly indicates the presence of human-adapted protective steroid mechanism against dengue virus in humans. However, the patients without self-limiting recovery of dengue may need synthetic CSs or other drugs to suppress the immune pathology although the body cortisol is higher than normal. For instance, asthmatic patients, who also have higher levels of natural body cortisol levels during an acute asthmatic attack than in the normal state [40] are treated with moderate or high doses of steroids irrespective of their increased plasma cortisol. On the other hand children with absolute or relative adrenal insufficiency in septic shock may also benefit from low dose of hydrocortisone for 7 days [41]. Thus, it can be concluded that a recommended dose corticosteroids may be essential to settle the excessive immunological pathology in DF to prevent DSS in risk identified patients.

However, there is no consensus regarding the minimal effective dosage, length of treatment and the route of administration for systemic corticosteroid treatment inDF/DSS/DHF. In practice, varied treatment regimens for DSS/DHF have been adopted, based largely on the clinical experience, investigation findings and many clinical trials in dengue, performed over the last 50 years. For instance, it was noted in theliterature that MP was studied in-depth in dengue immune pathology and was used in many clinical trials than any other steroid [12,13,31,42]. In this review we considered the doses, the type, the route of administration and the duration of steroids used for suppression of immune markers, increase platelet count, reduce viral replication, reduce formation of NS-1 antibody and reduce complement activation. This protocolis a supportive guideline of steroids, to control immune pathology in dengue. Therefore, patients who are treated with corticosteroids are kept under observation on current dengue management guidelines. In addition the doses can be adjusted according to investigation findings, as well as the clinical condition. For patients with disabling dengue complications and symptoms that do not respond to the initial high-doses of steroid treatment, plasmapheresis is suggested on an individual basis. In consideration of the above data and other evidence, a new protocol that is open to change and alteration is proposed.

Prevention of DF

No research has been done to assess the effectiveness of administration of CSs immediately after the mosquito bite or during the incubation period named as prepreliminary phase. But administering a stress level dose of cortisol or hydrocortisone in infection (two times the normal level) could be assumed to help during the incubation period to suppress the initial pathogenesis. Therefore, it is proposed that research should be conducted to assess the effectiveness of this before it is put into clinical practice.

Immediate after mosquito injection

Local application of corticosteroids at the site of the bite can be suggested to reduce viral replication in dendrite cells and distribution via dendrite cells. This can be used for people who are at risk in dengue epidemic areas where:(i). Mosquitoes are identified as dengue virus carriers (ii). History of previous dengue infection in people who are at risk of severe dengueinfection; such as obese persons, pregnant mothers infants and children (iii). Immunocompromised patients (diabetics, cancer patients and others with other infections). Any contraindication for steroids must be considered before the application.

During incubation period

Low oral dose of (20 mg) hydrocortisone or 4-12 mg methyl prednisolone twice daily for three days. The pharmacological effect is suggested to be by reducing the production of cytokines and chemokines and viral replication. This can be used for people who are living in dengue epidemic areas. Patients with higher titers of anti-dengue Ig G antibodies or dengue antigen, may benefit from 125-500mg IV Methyl prednisolone as a loading dose, while oral treatment is continued.

The use of corticosteroids at preliminary phase (from the onset of fever)

Administer 8mg of oral methyl prednisolone three times a day (32 mg/day) for seven days. Patients who are (i) at risk of dengue as above or clinically deteriorating (ii) or platelet count is below 100000/cumm3 and other significant early shock signs, should be given 125-500mg IV Methyl prednisolone as a loading dose and 8mg of oral methyl prednisolone three times a day (32 mg/day) and continued for seven days.

The use of corticosteroids at the critical phase

Membrane stabilization, inhibition of compliment and modulation of immune components are suggested benefits of the administration of higher IV doses of steroids.

- **The use of corticosteroids at early critical phases**: IV 125-500mg of methyl prednisolone as a loading dose and 40mg per day of oral methyl prednisolone continued for three days or can be repeated for 3 to 5 days according to severity. Other possible methods include 50 mg of IV hydrocortisone 4 times per day for four to five days. A daily dose of 40mg oral methyl prednisolone can be continued three to five days in less severe cases.

- **The use of corticosteroids at late critical phase**: Hydrocotisone or other steroids with high mineralocorticoid action and oral steroids should not be given during this phase. 500mg to 1g IV of methyl prednisolone for three days followed by 32 -64 mg/kg of oral methyl prednisolone for 4 days can be used.

Use of corticosteroids in recovery phase:

- **Early recovery phase:** A daily dose of 32 mg oral methyl prednisolone for three days is recommended. If patients test positive for higher titers of anti-dengue IgG antibodies or other immune markers, oral methyl prednisolone should be continue as mentioned in the late recovery phase

- **Intermediate recovery phase:** For neurological complications, intravenous immunoglobulin (IVIg) appears as effective as plasma exchange. If patients having other post dengue symptoms and test positive for higher titers of anti-dengue IgG antibodies or other immune markers, the treatment should be followed by oral methyl prednisolone 32 mg per day for seven days and tailed off gradually within the 2 months.

- **Late recovery phase:** Patients with dengue symptoms following symptomatic dengue disease (DF or DHF) and are positive for higher titers of anti-dengue IgG antibodies or other immune markers are candidates for this treatment protocol. It is suggested to treat them with 32 mg per day of oral methyl prednisolone for seven days and tail off gradually within 2 months. If symptoms are severe or show high morbidity, IV MP 125 mg is recommended as a loading dose.

Caricapapaya leaf extract

Recent reports have claimed possible beneficial effects of C. papaya L. leaf juice in treating patients with dengue viral infections.In studies, a significant difference of increasing platelets count and white cell counts in dengue fever patients were observed after administration of the leaf extract [43-45]. A Multi-centric, Double-blind, Placebo-controlled, randomized, prospective study and a systematic review and meta-analysis also concluded that Carica papaya leaf extract significantly increase the platelet count with fewer side effects and good tolerability [46,47]. In another study Carica papaya leaf leaf extracts showed a significant inhibition of hemolysis *in vitro* and this can have a therapeutic effect on disease processes causing destabilization of biological membranes [48]. Senthilvel, P. showed that anti-dengue activity of extracts from Carica papaya can be due to flavonoid quercetin, which has high binding energy against NS2B-NS3 protease, that is crucial for virus

replication. In fact, many such potential immune suppression and anti- inflammatory actions of phytochemicals found in Caricapapaya extract, were quite similar to corticosteroid functions.

Conclusion

Corticosteroids as a treatment in dengue can be suggested to suppress dengue immune pathology because these is no risk of viremia or any other significant adverse effects or complications during both the early and critical phases of the disease with steroids. A sustained therapeutic blood levels should be maintained in the management of dengue immune pathology using a higher receptor affinity corticosteroids for required time duration. Further clinical trials using pharmacologically and immunologically accepted standard steroid protocols are warranted to validate this conclusion.

This explanation has the following advantages: (a) it provides an immunological link between all phases of dengue and steroid treatment (b) it offers scope for corticosteroid based treatment as an approach for treatment for dengue (c) it provides a better understanding of newly proposed corticosteroid treatment for dengue on its immunological base (d) it provides and opens to a well-known arguments which is completely new to dengue, but with strong scientific evidence to approach a novel steroid protocol based treatment. (e) it offers scope for primary and secondary treatment with steroids as a preventive treatment plan for complications of all phases of dengue as well (f) Finally, it offers a novel coherent picture of the immune pathology of dengue related to the pharmacological approach of corticosteroid treatment. The value of such a scientific explanation and steroid treatment protocol management of dengue cannot be underestimated. Leaving aside or attempting to ignore, the value of steroid treatment, seems to be a marked deficient and inaccurate approach in the field of immunology, pathology and pharmacology.

Declarations

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Availability of Data and Material: The data set for this publication is available upon request from the authors

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Author Contributions

SMRB conceived the review and designed the study; SMBR , DMPKUR, KS,DIAW and HMMTBH performed the literature search, extracted and reviewed the data , drafted the manuscript. HMMTBH revised the manuscript. All authors read and approved the final manuscript.

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