

REVIEW ARTICLE

The Autoimmune Mechanism in Dengue Hemorrhagic Fever

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ABSTRAK

Respons imun pada demam dengue/demam berdarah dengue merupakan suatu rangkaian imunopatogenesis yang dimulai sejak target infeksi virus terhadap monosit dan makrofag. Selanjutnya akan menimbulkan suatu kaskade dari viremia di sirkulasi yang menstimulasi mekanisme aferen, mekanisme eferen dan mekanisme efektor melalui interaksi dengan berbagai sistem humoral dan komplemen. Substansi inflamasi yang dihasilkan akan mempengaruhi permeabilitas kapiler dan mengaktifasi faktor koagulasi serta berpengaruh terhadap kerja tingkat endotel. Mekanisme yang melibatkan patogenesis DBD/DSS masih belum jelas. Selama ini berkembang teori infeksi heterologus infection, dimana pada infeksi kedua kalinya terjadi sub netralisasi yang memicu replikasi virus. Mekanisme autoimun merupakan suatu proses autoimun yang dapat memperkaya kanzah pemahaman DBD. Mekanisme autoimun tersebut, menjelaskan respons autoimun oleh infeksi virus yang terdiri dari molecular mimicry, bystander activation dan viral persistence. Patomekanisme auto imun ini berkembang terkait peranan autoantibodi dan tingkat endotel proses disfungsi yang dimungkinkan berperan terhadap memberatnya DBD.

Kata kunci: autoimun, dengue, demam berdarah.

ABSTRACT

The immune response of dengue fever/dengue hemorrhagic fever is a series of immunopathogenesis processes starting from viral infection to the target on monocytes and macrophages. It may consequently cause a cascade of viremia in the circulation that stimulates the afferent, efferent, and effector mechanism by the interaction of the humoral and complement system. The cascade results in inflammatory substance that will affect capillary permeability and activate coagulation factors leading to further effects on endothelial level. The mechanism involving pathogenesis of DHF/DSS is still vague. So far, a theory of heterologous infection has been developed, which explains that on second infection, there is subneutralization that induce viral replication. The autoimmune mechanism development leads to the better understanding of DHF. It also explains the autoimmune response of the viral infection, which consists of molecular mimicry, bystander activation and viral persistence. The development of the autoimmune pathomechanism is related to the role of autoantibody and endothelial dysfunction that may have role in worsening DHF.

Keywords: autoimmune, dengue, hemorrhagic fever.

INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is a reemerging disease that has a long history associated with a fluctuation of mortality and morbidity. Surveillance and epidemiological approach indicate that preventive efforts of the upstream sectors have become a priority that should be maximized. DHF epidemic in an area has become a great concern of Community Health experts and clinicians. They evaluate the epidemic with community approach to prevent further transmission.¹

The course of “mysterious” DHF refers to various clinical spectrums that develop during hospitalization. So far, it has become a great concern for the experts, i.e. there are different clinical conditions with different output of improvement. For example, a patient with a stable hemodynamic condition, subsequently has hematemesis and dengue encephalopathy; while another patient with pulmonary edema and massive pleura effusion, but with a maximal conservative treatment, the patient can have a good recovery.²

In the management of Dengue Hemorrhagic Fever, there is a principle of “everything can happen”. It is inseparable from the principle of host-agent-environment, in which the specific process of virulence and mechanism in the host

is induced by environment that has experienced different immunological changes or has individual variation. Therefore, the management of DHF is an art, which is based on pathogenesis and pathophysiology approach followed by continuous learning of the developed various cases.³

This manuscript is aimed to have a deep discussion on the developing pathogenesis and pathophysiology of DHF and to evaluate the immunopathogenesis process associated with autoimmune mechanism.

FROM CLINICAL TO PATHOGENESIS SPECTRUM

The pathogenesis spectrum of DHF starts from the clinical course of DHF in a measurable process. When we evaluate the clinical course of DHF based on 2009 WHO guideline, we can see three phases, i.e. the febrile, critical and recovery phases. Those three phases describe a natural process of viral infection, i.e. in febrile phase, there is viremia; while the critical phase is a characteristic of dengue virus causing plasma leakage and in recovery phase, immune response and endothelial improvement have a role, which is consistent with improved clinical condition.⁴⁻⁷ (Figure 1)

There are some theory that have been developed about the pathogenesis of DHF so

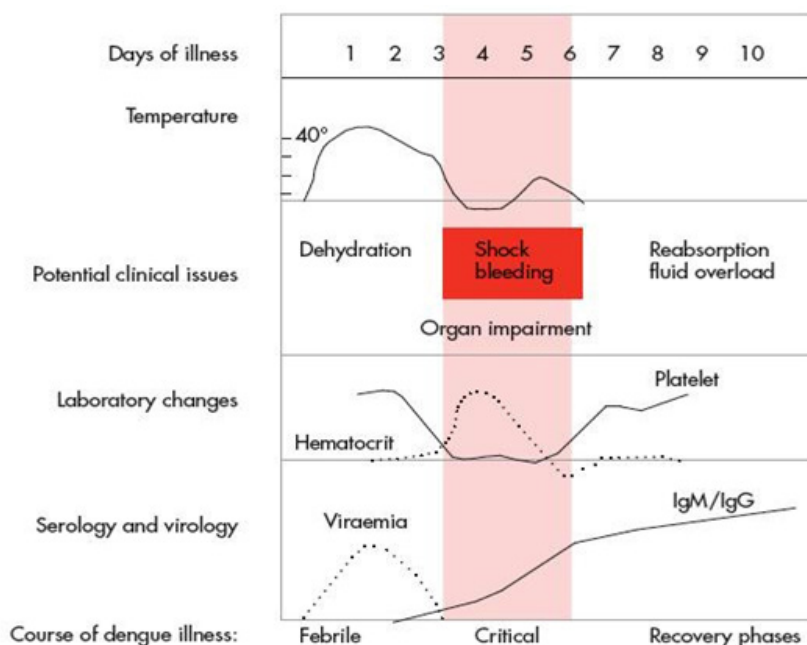


Figure 1. Clinical course of dengue hemorrhagic fever⁷

far, i.e. (1) Primary infection theory (theory of virulence), (2) Secondary infection theory (immunopathology theory), (3) Antigen antibody complex theory, (4) Theory of infection enhancing antibody, (5) Mediator theory, (6) Theory on the role of endotoxin, (7) Theory on the role of lymphocytes, (8) Theory of thrombosis, (9) Theory of apoptosis.^{5,6}

The secondary infection theory has a risk for developing severe infection. The theory of antigen antibody complex is characterized by reduced level of C3, proactivator C3, C4 and C5, which are the markers of severe DHF. The resulted C3a and C5a anaphylatoxins are strong mediators for increased capillary permeability that may lead to plasma leakage. The theory of infection enhancing antibody is based on the phagocytic role of mononuclear cells and the development of non-neutralized antibody. The virus has attack target, i.e. on phagocytes such as macrophages, monocytes and kuppfer cells. The infected macrophage will be activated and releases various inflammatory substances, cytokines and thromboplastin that affect capillary permeability. Moreover, the role of endotoxin is based on the role of shock in DHF that causes intestinal ischemia in addition to ischemia of the tissues. At that time, bacterial translocation can occur from the intestinal lumen into the circulation. Endotoxin, which is the component of outer capsule of negative-gram bacteria,

enters the circulation through activation of cytokines cascade. It leads to shock followed with severe ischemia. The role of lymphocytes is based on the activated lymphocytes on the macrophages, which are exposed to the virus. It releases lymphokines, activates B cells therefore the amount is greater in DHF/DSS. The last theory is the theory of apoptosis, which is based on the physiological process of cell death. The process consists of two phases, i.e. the damage of cell nuclear and changes in cell form and permeability of cell membrane. In severe DHF with severe liver damage, Councilmen bodies can be found.⁶

CLINICAL SPECTRUM OF WARNING SIGN ON IMMUNOPATHOGENESIS

The 2009 WHO guideline describes that there is a clinical spectrum of warning sign such as abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, liver enlargement and increased hematocrit along with reduced platelet count. The warning sign is a clinical process, which is a manifestation of a complicated immunopathogenesis process.⁷

The warning signs in DHF indicate progressive course of immunopathogenesis of viral infection on vascular changes, target organ and changes at endothelial level. If it is not managed well, it may result in plasma leakage, bleeding, organ dysfunction, which are the

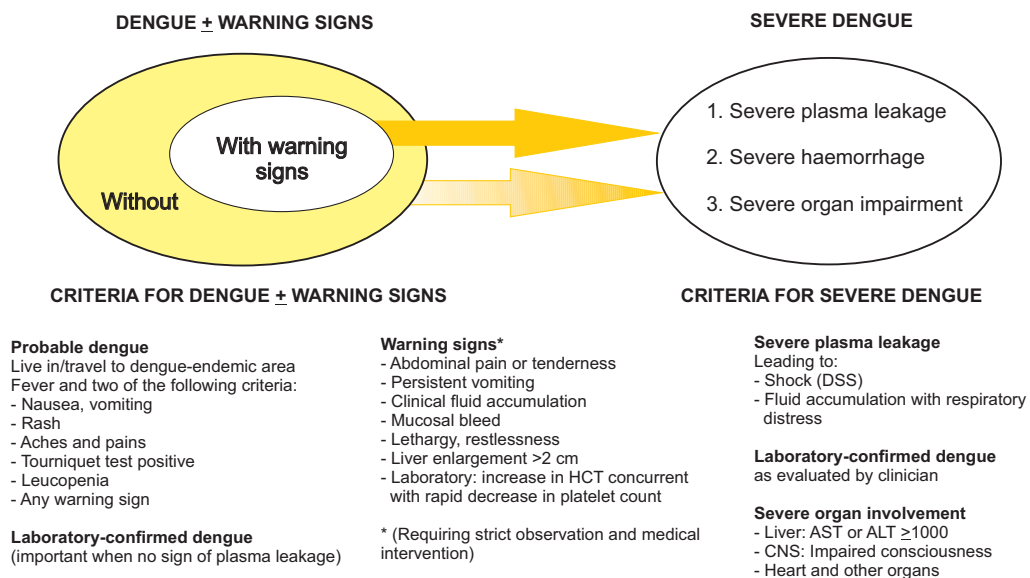


Figure 2. Classification and the severity of dengue cases⁷

criteria of severe dengue. Warning signs actually should be treated as the emerging clinical process on the surface along with a good understanding on the ongoing immunopathogenesis process.⁷

As we have known, the female mosquito of *Aedes aegypti* bites human and injects virus into the circulation. The dengue virus is later attached to monocytes through receptor factor and it enters the monocytes.^{3,8} In this condition, there is an afferent mechanism, in which the virus has been developed through union and attachment of several segments of the genes and therefore, the receptor factor is developed. Subsequently, the efferent mechanism occurs, i.e. the monocytes containing virus are distributed to liver, spleen, intestines and bone marrow; thus, viremia occurs. In the next step, there is an effector mechanism, in which the infected monocytes will have an interaction with various humoral systems such as complement system by releasing inflammatory substances, cytokines and thromboplastin that will affect capillary permeability and activates coagulation factors.⁸

Another approach suggests that the dengue virus will attack macrophages and it will replicate in the langerhans cells and macrophages of the spleen. Furthermore, it stimulates the T cells arrangement, cross reactivity of T cells with low avidity and cross reactivity of specific T cells, which will increase the production of specific and cross reactive antibodies.⁹ In the next phase, there is a simultaneous cross reaction between antibody and platelets as well as cross reactivity between plasmin and specific product. The process will then further increase the role of antibody in increasing virus titer and on the other hand, there is a cross reaction of antibody and endotheliocytes. Next, there is replication effect inside the selective endotheliocytes; therefore, apoptosis occurs resulting in endothelial dysfunction. Meanwhile, stimulation of soluble mediators also occurs, i.e. the TNF α , IFN γ , IL-1, IL-2, IL-6, IL8, IL-10, IL13, IL18, TGF β , C3a, C4b, C5a, MCP-1, CCL-2, VEGF, NO, which causes imbalanced profile of cytokines and other mediators that subsequently causes coagulation disorder and endothelial dysfunction.⁹

In the liver, replication will occur in the hepatocytes and kuppfer cells. Necrosis and/or

apoptosis occur, which reduces liver function, releases toxic product into the circulation, increases coagulation function, increases platelet consumption, activates the fibrinolytic system and causes coagulation disorder.⁹ Dengue virus that attacks macrophages in the hepatocytes is characterized by hepatitis (increased SGOT and SGPT), apoptosis, overproduction of IL-6 and oxidative stress that may result in RANTES.¹⁰

Endothelial damage is initiated by viral intervention on monocytes that causes excessive cytokine production and inversed ratio of CD4/CD8. The excessive cytokine production and IL-6 will stimulate the development of atypical lymphocytemia that activates platelets, Anti DV Ab, anti platelet autoantibody (Anti NS1 Ab) and Anti EC Antibody. The virus also attacks neutrophil that may lead to bandemia. Through abnormal activity, it causes CD 69 excretion, reduced CD4/CD8 ratio and excessive cytokine production. The process causes endothelial damage, which is characterized by apoptosis, release of thrombomodulin, IL6, IL8, RANTES, reduced tPA/PA1 ratio, ICAM expression, cell-mediated damage (PMC, PBMC), antibody-mediated damage (Anti DV Ab, Anti Ec Ab) and complement activation.¹⁰

Bleeding as a warning sign is caused by three major hemostasis disorders, i.e. vasculopathy, platelet disorder and reduced serum level of coagulation factors. At the initial phase of fever, the bleeding is caused by vasculopathy and thrombocytopenia; while in the shock and prolonged shock phase, the bleeding is caused by thrombocytopenia, which is followed by coagulopathy, particularly due to disseminated intravascular coagulation (DIC) and increased fibrinolysis. The clinical manifestations of vasculopathy are petechiae, positive result of Rumpel Leed test, plasma leakage as well as electrolyte and protein leakage into the extravascular cavity. The major etiology of vasculopathy is the release of C3a and C5a anaphylatoxin.^{8,11}

At the initial phase of the disease (the 1st up to 4th day), reduced platelet production is the cause of thrombocytopenia. At that time, the bone marrow appears to have mild hypocellular state and there is increased megakariocytes in

various types of maturation. The virus directly attacks myeloid and megakaryocytes. The platelet count at that time may reach 20,000 – 50,000/mm³. On the 5th to 8th day, thrombocytopenia occurs particularly due to platelet destruction in the circulation. The attached immune complex on the surface of platelet facilitates platelet destruction through reticuloendothelial system in the liver and spleen that causes thrombocytopenia in the shock phase. Platelet destruction is also caused by endothelial damage, immune complex reaction, specific platelet antibody or DIC due to prolonged shock. In this phase, there is increased number of megakaryocytes in the bone marrow. The PAF release may be due to platelet and monokine activation. Simultaneously, increased PAF level as well as TNF α , IL-1, IL-6, IL-8, C3a, C5a and histamine causes endothelial malfunction of the capillaries and therefore, plasma leakage and hypovolemic shock occur.^{8,11}

By evaluating the above mentioned discussion, it is clear that the clinical descriptions of warning signs in DHF are actually an iceberg phenomenon, i.e. there is a relatively complicated ongoing immunopathogenesis process and we do not know whether it will be more severe or not.

AUTOIMMUNE MECHANISM OF DHF

Autoimmune mechanism of DHF is a pathomechanism process that so far has been tried to provide answers on the mechanism of various clinical variations and various severity problems in the clinical domain. A study by Falconar explains that autoimmune response of DHF infection consists of molecular mimicry, bystander activation and viral persistence. Using animal experimental study, it shows that DEN-V NS1 antibody causes cross reactivity with coagulation protein in human as well as with integrin/adhesion protein, endothelial cells and platelets. Subsequently, the cross reactivity of DENV-NS1 monoclonal antibody causes bleeding.¹³ The study also reveals that antibody in the serum of dengue patients has cross reactivity with endothelial cells. The antiplatelet serum level and autoantibody of endothelial cells of patients with DHF/DSS are higher than patients with Dengue fever. Therefore, the experimental study demonstrates

that anti DEN V NS1 antibody has partial cross reactivity and apoptosis with endothelial cells. It is also associated with platelet autoantibody and the anti DEN V NS1 activates inflammation in the endothelial cells. In this case, the molecular mimicry occurs between the component of dengue virus and the elements of platelets and endothelial system.¹³ Another study suggests a hypothesis on autoimmune mechanism that causes symptoms of DHF and the NS1 protein releases molecular structural mimicry that resembles human platelets, endothelial cells and coagulation protein. The level of antibody is increased in experimental rats and the DEN V NS1 has cross reactivity with epitopes mimetic of human platelets and endothelial cells; therefore, the platelet life is shorter and it increases vascular permeability in the in vitro system.¹¹

MOLECULAR MIMICRY AND BYSTANDER ACTIVATION

In the development of DHF immunopathogenesis, there is an excessive immune activation and cytokine production affecting the monocytes, endothelial cells and hepatocytes as well as abnormal production of autoantibody against endothelial cells and platelets. It causes disruption of immune response in clearing virus including changes in CD4/CD8 ratio.

Moreover, the molecular mimicry occurs between endothelial cells/platelets and antigens of dengue virus. Platelets and endothelial cells are bound by cross reactive antibody of anti dengue virus such as the anti NS1 or the anti prM antibody. IFN γ activates macrophages to perform phagocytosis of opsonin target. The autoantibody then will initiate cell dysfunction. IFN γ activates macrophages that phagocytose the autoantibody covering the platelets and endothelial cells, which results in thrombocytopenia and endothelial cell damage. The short-term hemophagocytic activity is caused by post-acute infection of dengue virus.¹²

So far, there are some mechanisms explaining autoimmune response against viral infection. Among the newest mechanisms that explain autoimmune response by viral infection are molecular mimicry, bystander activation and

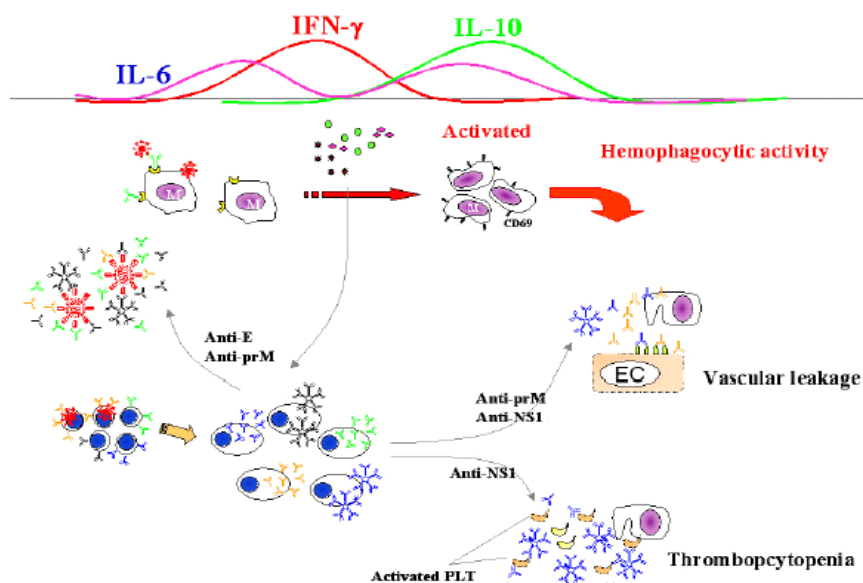


Figure 3. Immunopathogenesis of DHF¹²

viral persistence. Antibody against plasminogen peptide can be detected in 70% serum of patients who have acute phase in Thailand. Similar findings are also found in Tahiti, in which similar antibody is detected and correlated to secondary infection and bleeding. A study in Thailand shows that the serum of patients who have convalescent phase for 1-4 months in 16 patients with Dengue Fever has actually responded to 759-799 human plasminogen peptide and has moderately reduced the activity of serum plasmin.^{13,14}

AUTOIMMUNE REACTION AT ENDOTHELIAL LEVEL

A study mentioned by Chiou FL (2003) has found a cross reactivity between the serum of dengue patients and endothelial cells. There are higher percentages of endothelial cell reaction in DHF/DSS than DF. The higher percentage of endothelial cell reaction against Ig M is also higher compared to against Ig G. The study demonstrates that the activity of endothelial cell binding and serum of dengue patients, which induces apoptosis of endothelial cells through caspase – dependent pathway, is inhibited by NS1 pre treatment. The presence of antibody against NS1 production following the infection of dengue virus explains cross reactivity between the serum of patients and endothelial cells. The study concludes that the cross reactive antibody

against endothelial cells indicates that there is a dysfunction that may have a role in pathogenesis of dengue infection.¹⁵

The study by Chiou FL demonstrates that there is an antibody against non-structural NS1 protein of dengue virus, which is originated from rat and it has cross reactivity with human endothelial cells and vascular endothelium. After there is an endothelial binding by the anti NS1 antibody, it causes apoptosis of endothelial cells on the caspase dependent pathway. In this process, the capacity and the expression outcome of NO synthesis (iNOS) are observed. The addition of NO synthetase inhibitor N nitro L arginine methyl ester. Further studies describe that the expression of Bcl2 and Bclx are reduced, both on the mRNA and protein level, which is characterized by increasing p53 and Bax following the treatment using anti NS1. The study evaluated the release against cytochrome and the effect due to inhibition by N nitro L arginine methyl ester. Based on the study, it can be concluded that anti NS1 Ab is an autoantibody that has cross reactivity with the uninfected endothelial cells by inducing intracellular signal

that lead to NO production and apoptosis. Cell damage and endothelial cell apoptosis may be related to disruption of endothelial barrier that causes transient vascular leakage in dengue vasculopathy and it has some contribution in the pathogenesis of dengue diseases.¹⁶

A study by Chungue (1994) suggests an analysis that although most of dengue fever can have complete recovery, but plasma leakage may be important factor for severe dengue into DSS. In the study, it is stated that the development of antibody and cross reactivity against plasminogen has been reported to have a high percentage in Thailand patients with DF and DHF/DSS. The correlation between the detection on plasminogen cross reactive antibody and bleeding has been evaluated in 88 children in Tahiti who had type 3 dengue virus. The results show that there were 59 children with and 29 children without bleeding. The plasminogen cross reactive antibodies were found in acute and convalescent serum and the antibodies were parallel to the cross reactivity on protein E of dengue virus. The antibodies are more commonly found in children with secondary infection than those with primary infection. The plasminogen cross reactive antibodies is not related to the development of DHF/DSS or thrombocytopenia. The results are consistent with the possibility that plasma cross reactive antibodies have important role as the etiology of bleeding in dengue viral infection.¹⁷

A study by Henchal (1998) demonstrates that in non-neutralization, the serotype of specific anti NS1 monoclonal antibody has partially protected the rats that had been infected by the deadly intracerebral dengue virus type 2. There is no correlation between the persistent complement activity and the protective capacity among the individuals on the monoclonal antibodies or whether the partial protective antibodies results in longer survival or reduced mortality. Complete protection, which is achieved following the immunization using polyclonal neutralization antibody, is reached by some individual antibodies and the complement increases to high titer using homologous virus. Some groups of the rats have increased morbidity rate after having immunization with combined

protection of monoclonal antibodies that bind the overlapping epitope. The results may have impacts on the design of recombinant dengue vaccine, which may give some inputs of specific antigenic domain.¹⁸

According to a study by Valde (2008), the antibodies against the protein of type 2 and type 4 dengue viruses were found in the serum of acute phase of 10 patients with primary and secondary dengue fever and dengue hemorrhagic fever that had been evaluated using western blotting technique. In the first group, the immune response was almost undetected, while in the second group, more protein was detected using strong reaction. Anti E, NS3 and NS5 antibodies were detected in most cases. The implementation is possible for initial diagnostic of antigen detection.¹⁹

Evaluating the above mentioned discussion, we know that immunopathologic mechanism has a role in the pathogenesis of DHF. The dengue antibodies have been reported to mediate three biological functions in vitro, which contribute on prevention and controlling viral infection, i.e. neutralization, complement-mediated cytolysis and antibody-dependent cell mediated cytotoxicity. The antibody level can be increased in dengue viral infection through ADE phenomenon. The response of antibody in secondary infection is characterized differently from the primary infection. The protein of dengue virus can stimulate antibody production. However, there are only limited studies that have evaluated the response characterization to define how antibody is correlated to recovery or severity of dengue infection. The studies are about the definition of immune response on structural and non-structural protein. Serum samples were taken in 5-7 days since the onset of the disease and 20 cases were confirmed serologically. Ig M anti dengue were detected in all samples. Serum of 5 patients with dengue virus (all with primary infection) and 15 patients with DHF (5 with primary and 10 with secondary infection) were evaluated using western blotting. Monoclonal and polyclonal dengue antibodies and the serum of non-immune infected dengue patients were used as the control. Total immunoglobulin of at least one or two Den-4 antigen protein was demonstrated

in 9 of 90 cases of primary infection (90%). No NS1 antibody could be detected in some serum of primary infection cases; while 4 of 10 cases with secondary infection (40%) had NS1 antibody. The response against the envelope (E) and NS5 protein was consistent, both in primary or secondary infection. Anti NS3 antibody was not detected, either in the primary or secondary infection. There was more limited responses observed using Den-2 antigen. In contrast, there

was an extensive response of E antibody only in the cases of secondary infection, but the response was larger (80%) and more intensive when it was observed with Den-4 antigen. Natural dengue virus infection in human and potent antibody response can be easily measured using some serologic tests. The quality of antibody response to dengue virus has not been extensively studied and it is based on the previous reports. Both in primary and secondary infection, the anti E

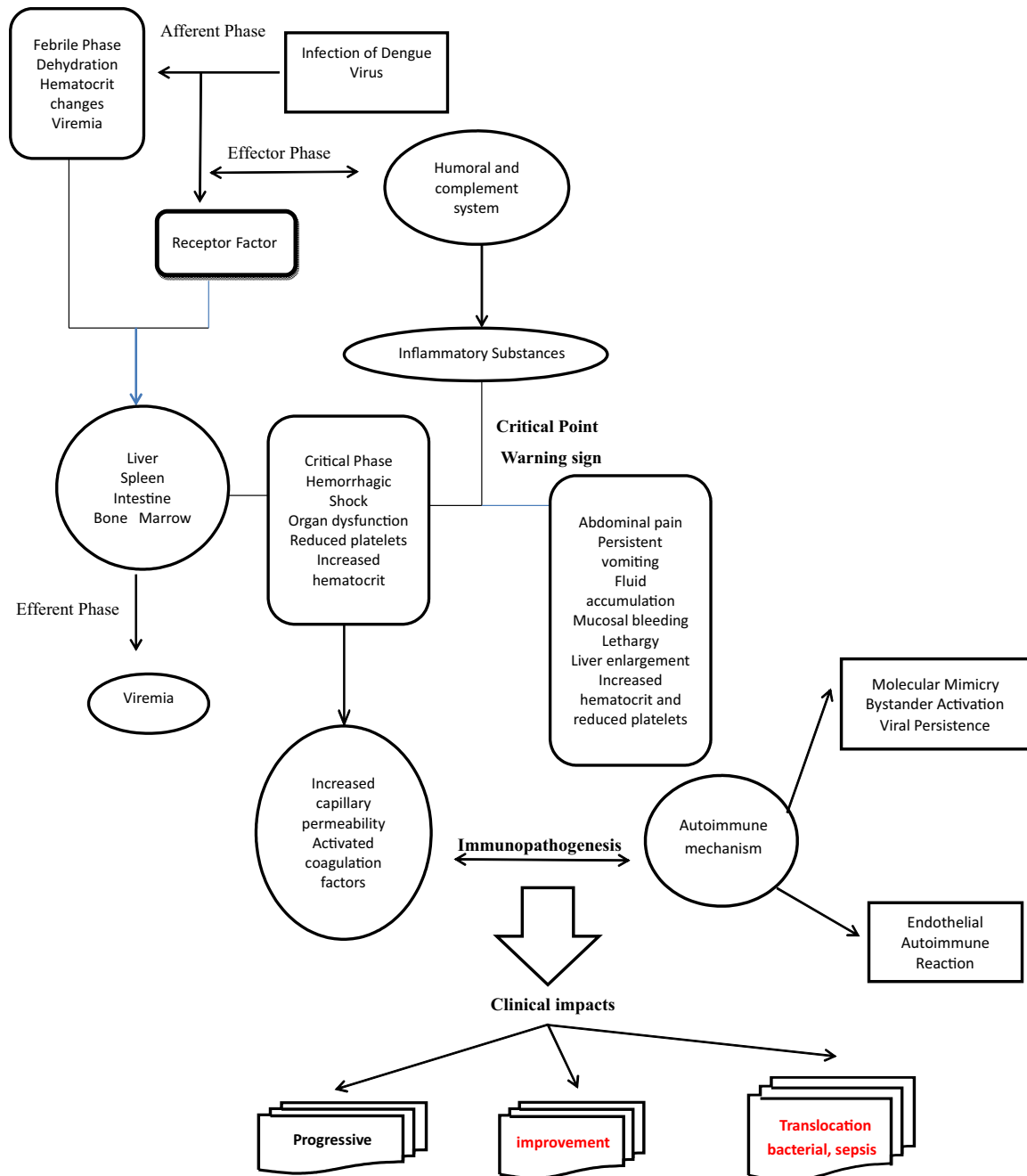


Figure 4. The serial of clinical process and warning signs of DHF along with autoimmune mechanism as an intertwining connection.

antibody are more commonly detected. This fact is probably correlated to the role of protein E, i.e. the surface of major protein and viral antigen is essential in biological terminology of virus, humoral immunity and protection. It is interesting to be noted that in the study that there is a response of NS 5 on non-structural protein with polymerase activity. Some authors have reported a significant antibody response to NS3 protein, both in primary or secondary infection.¹⁹

CONNECTING THE AUTOIMMUNE MECHANISM AND CLINICAL IMPACTS

Autoimmune mechanism in DHF is certainly expected to open the isolated knowledge in understanding the process and pathogenesis of DHF. Deep discussion on this issue will bring some understanding points that can be a reference when we deal with severe dengue hemorrhagic fever. It includes how to understand a clinical process and warning signs of DHF along with autoimmune mechanism as an intertwining connection. The serial of process can be described in the **Figure 4**.

CONCLUSION

Dengue Hemorrhagic Fever is a reemerging disease and the clinical course is through febrile phase (viremia) by activation of inflammatory cytokines – critical phase, which is characterized by increased capillary permeability and organ dysfunction as the warning signs and recovery (improvement) phase. The clinical course of warning sign is a form of clinical manifestation of the ongoing immunopathogenesis process including an autoimmune mechanism process characterized by pathomechanism at endothelial level, i.e. molecular mimicry, bystander activation and viral persistence. The autoimmune mechanism with different grades and spectrums determines whether a DHF infection can have a recovery or worsen condition.

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