

Indonesian Journal of Tropical and Infectious Disease

Vol. 4. No. 4 October–December 2013

Case Report

AWARENESS OF USING RINGER LACTAT SOLUTION IN DENGUE VIRUS INFECTION CASES COULD INDUCE SEVERITY

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ABSTRACT

Background: In 2012, serotype of Dengue Virus had changed from Den-2 and Den-3 to Den-1. In 5–10 years ago, serotype of Den-1 case showed a mild clinical manifestation; but now as a primary case it can also show severe clinical manifestation. One of indicator is an increasing liver enzyme, AST and ALT, with level more than 100–200 U/L. *Aim:* To getting a better solutions for this problem. *Method:* Observasional Study had been done in medical faculty of Airlangga University (Dr. Soetomo and Soerya hospital) Surabaya on Mei–August 2012. There were 10 cases of dengue virus infection were studied, 5 cases got Ringer Acetate solution (Group A) and 5 cases got Ringer Lactate solution (Group B). The diagnosis was based on criteria WHO 2009. *Result:* Five cases of Dengue Virus Infection had showed a liver damage soon after using Ringer Lactate solution; AST and ALT were increasing more than 100–200 U/L; but the other 5 cases showed better condition. It might be due to use Ringer Acetate that did not have effect for inducing liver damage. By managing carefully, all of the cases had shown full recovery and healthy condition when being discharged. *Conclusion:* Using Ringer Acetate as fluid therapy in Dengue Virus Infection is better to prevent liver damage than using Ringer Lactate.

Key words: Ringer Lactate, Ringer Acetate, Dengue Virus Infection, Pediatric Cases, Severity

ABSTRAK

Latar belakang: Pada tahun 2012 serotype virus dengue telah mengalami perubahan dari Den-2, Den-3 ke Den-1. Dalam kurun waktu 5–10 tahun yang lalu, serotype Den-1 menunjukkan manifestasi klinis yang ringan, tetapi sekarang serotype Den-1 ini walaupun sebagai kasus primer ternyata dapat menunjukkan manifestasi klinis yang berat. Salah satu indikator yang digunakan adalah kenaikan enzim AST dan ALT lebih dari 100–200 U/L. *Tujuan:* Berusaha menemukan tatalaksana terbaru dengan hasil yang memuaskan. *Metode:* Studi observasional telah dilakukan di RSUD Dr Soetomo Surabaya & RS Soerya Sepanjang sejak bulan Mei–Agustus 2012. Dari 10 kasus infeksi virus dengue yang diteliti, 5 kasus mendapatkan terapi cairan Ringer Acetate (Kelompok A) dan 5 kasus mendapatkan cairan Ringer Lactate (Kelompok B). *Diagnose Infeksi Virus Dengue* berdasarkan Kriteria WHO 2009. *Hasil:* Lima kasus infeksi virus dengue telah menunjukkan gangguan fungsi hati setelah memperoleh infus cairan Ringer Lactate dan terbukti kadar AST dan ALT meningkat lebih dari 100–200 U/L, tetapi 5 kasus yang memperoleh Ringer Acetate menunjukkan keadaan yang lebih baik. Maka dapat dibuat kesimpulan bahwa terapi cairan pada penderita infeksi virus dengue lebih baik memanfaatkan cairan ringer acetate sebab metabolisme cairan ini terjadi di otot ekstremitas dan tidak mengganggu fungsi hati. Dan berbeda secara nyata apabila cairan yang digunakan larutan Ringer Lactate yang metabolisme di dalam hati. Hal ini sesuai dengan hasil penelitian terdahulu yang mengutamakan bahwa larutan Ringer Acetate yang diberikan kepada penderita infeksi virus dengue tidak mengganggu fungsi hati penderita. *Kesimpulan:* Lebih baik memanfaatkan cairan ringer acetate sebagai terapi infeksi virus dengue daripada menggunakan cairan ringer lactate yang dapat mengganggu fungsi hati.

Kata kunci: Ringer Laktat, Ringer Asetat, Infeksi Virus Dengue, Kasus Anak, Kegawatan

INTRODUCTION

Since 1968, dengue virus infection has always been found in Indonesia. It is due to increasing the population of *Aedes Aegypti* and *Aedes Albopictus* that now transfer from one case to another case. It is supported by changing of summer to raining season. Global climate can also affect all the event in the world.

In 2009 some hospital in Surabaya and Sidoarjo had found the changing serotype on dengue virus from Den-2 and Den-3 to Den-1. In 5–10 years ago, serotype of Den-1 showed a mild clinical manifestation, but now, it can also show severe clinical manifestation of dengue virus as a primary infection. It can be predicted by test marker of positive NS-1 Dengue test. This virus can cause liver damage.

Based on this finding, we should be careful to treat dengue virus infection cases. Firstly, we should look for the indicators of dengue virus infection suffering for liver damage, that are AST and ALT titers in every case of Dengue Virus Infection. If we find the indicators of liver damage (increasing AST and ALT titers), please don't use Ringer lactate for treating dengue with shock case.

To convince this, researcher want to present this paper to get a better solutions from many aspect.

MATERIALS AND METHODS

Observational study had been studied in Medical Faculty Airlangga University, Surabaya, Indonesia. On Mei–August 2012, there were 10 cases of DVI, 5 cases were given Ringer Acetate (group A), and the other cases were given Ringer Lactate (group B). The diagnosis was made based on criteria WHO 2009.

Group A

Patient 1

A four years old boy was brought by his parents to Soerya Hospital, in emergency Department with the main complaint of fever since 2 days before admission. She also suffered from nausea and cephalgia.

Table 1. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|-------|------|
| 1 | 12,6 | 37,5 | 4860 | 280000 | 113,6 | 49,9 |
| 2 | 10,9 | 31,7 | 3020 | 222000 | | |
| 3 | 11,8 | 35,1 | 2090 | 188000 | | |
| 4 | 11,9 | 34,9 | 4110 | 134000 | | |
| 5 | 11,9 | 36,1 | 4110 | 126000 | | |
| 6 | 12,3 | 37,1 | 6870 | 187000 | 73,5 | 32,6 |

Patient 2

A nine years old girl was brought by his parents to Soerya Hospital, in emergency Department with the main complaint of fever since 3 days before admission. She also suffered from nausea, and cephalgia. She lost her appetite and refuse to eat. She was in a weak condition.

Table 2. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 11,7 | 35,5 | 2490 | 134000 | 36,1 | 15,8 |
| 2 | 11,4 | 34,6 | 4170 | 139000 | | |
| 3 | 11,3 | 33,9 | 3650 | 199000 | 31,1 | 16,4 |
| 4 | 11,1 | 33,5 | 3230 | 263000 | | |
| 5 | 11,4 | 34,6 | 4310 | 408000 | | |

Patient 3

An eleven years old boy was brought by his parents to Soerya Hospital, in emergency Department with the main complaint of fever since 6 days before admission. The fever had been subsided in the third day of fever, but the temperature raised in the fourth day.

Table 3. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|-------|------|
| 1 | 13,3 | 37,8 | 4420 | 34000 | 106,9 | 41,7 |
| 2 | 13,9 | 37,8 | 4420 | 30000 | | |
| 3 | 12,8 | 38,5 | 8230 | 32000 | 142,3 | 59,3 |
| 4 | 13,2 | 39,4 | 9200 | 80000 | | |
| 5 | 11,8 | 34,8 | 9460 | 166000 | | |
| 6 | 12 | 35,3 | 9610 | 150000 | 62,9 | 51,2 |

Patient 4

A ten years old girl was brought by his parents to Soerya Hospital, with the main complaint of fever since 5 days before admission. She had been brought to the doctor before, but the fever stayed. She also suffered from vomit after eating, myalgia and cephalgia.

Table 4. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 14,3 | 40,5 | 3610 | 36000 | 91,5 | 26,2 |
| 2 | 14,3 | 40,8 | 3640 | 36000 | | |
| 3 | 13 | 38,4 | 10780 | 35000 | 68,6 | 27,7 |
| 4 | 12,6 | 36,5 | 8110 | 46000 | | |
| 5 | 12,4 | 34,8 | 7770 | 94000 | | |
| 6 | 12,8 | 36,0 | 6630 | 196600 | 42,8 | 55,4 |

Patient 5

A nine years old girl was brought by his parents to Soerya Hospital, in emergency Department with the main

complaint of fever since 2 days before admission. She also suffered from nausea, and cephalgia.

Table 5. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 15,3 | 44 | 3140 | 91000 | 60,9 | 27,3 |
| 2 | 14,7 | 42 | 5050 | 60000 | | |
| 3 | 13 | 36,7 | 4210 | 42000 | 57,3 | 25,2 |
| 4 | 12,5 | 35,6 | 4970 | 53000 | | |
| 5 | 12,1 | 34,6 | 4840 | 120000 | | |
| 6 | 12,2 | 35,4 | 5990 | 213000 | 56,9 | 47,2 |

Group B

Patient 1

A twelve years old boy was brought by his parents to Dr. Soetomo Hospital, in emergency Department with the main complaint of fever since 2 days before admission. He also suffered from heavy cephalgia.

Table 6. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|-------|-------|
| 1 | 12,6 | 39,5 | 3660 | 214000 | 36,8 | 18,9 |
| 2 | 11,5 | 35,9 | 3300 | 155000 | | |
| 3 | 13,1 | 40,8 | 3740 | 54000 | 809,1 | 382,6 |
| 4 | 15,2 | 46,4 | 5220 | 33000 | | |
| 5 | 12,9 | 39,6 | 8100 | 56000 | | |
| 6 | 11,5 | 35,1 | 7540 | 85000 | 179,4 | 178,1 |
| 7 | 12,1 | 36,2 | 11100 | 163000 | 137,1 | 147,7 |

Patient 2

A nine years old boy was brought by his parents to Dr. Soetomo Hospital, Surabaya in emergency Department with the main complaint of clammy extremities since 7 hours before admission. He suffered from acute and continues high grade fever for 5 days and subside suddenly. He also complained of headache, retroorbital pain, melena and myalgia. There was a history of contact to person with dengue hemorrhagic fever in his neighborhood.

Table 7. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 17,9 | 52,1 | 5400 | 29000 | 1360 | 566 |
| 2 | 16,8 | 43 | 2000 | 32000 | | |
| 3 | 10,6 | 27 | 7100 | 20000 | 7050 | 3541 |
| 4 | | | | | | |
| 5 | 12,5 | 35 | 7400 | 85000 | 1367 | 1037 |

Patient 3

A three years old boy was referred from Mojokerto hospital with hepatic comme on Dr. Soetomo hospital in emergency department., with the main complain of fever since 5 days before. One day before admission he had clammy extremities. He also complained of nausea and vomiting and refuse to eat since 1 day before admission. No sign of bleeding was found in this child.

Table 8. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 10,3 | 31,9 | 14600 | 15000 | 3154 | 1274 |
| 2 | 10,7 | 30 | 20500 | 85000 | | |
| 3 | 9,7 | 30,9 | 11000 | 75000 | | |
| 4 | | | | | | |
| 5 | 8,8 | 28,4 | 3500 | 100000 | 1254 | 1069 |

Patient 4

A seven years old boy was brought to his parents in Dr Soetomo Hospital emergency department with main complain of fever. He suffered from fever since 4 days before admission. The fever was suddenly continues and high grade. He also complained of headache, and difficult to sleep. There was no history of bleeding. He felt nausea and vomit which made he lost his appetite. There was no history of contact to person with dengue hemorrhagic fever in his neighborhood.

Table 9. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|------|-----------|------------|------|------|
| 1 | 15,8 | 48 | 7400 | 26000 | 2824 | 1011 |
| 2 | 16,8 | 43 | 2000 | 32000 | | |
| 3 | 10,3 | 36,6 | 7600 | 22000 | | |
| 4 | 10,4 | 29,6 | 9700 | 73000 | 1107 | 537 |
| 5 | 8,8 | 26,7 | 9800 | 1122000 | | |

Patient 5

An overweight-eleven years old boy had been referred from Bangkalan to emergency room in Soetomo Hospital, with main complaint fever, cephalgia, headache, vomiting, dyspnea, and restless since 4 days before and had been managed in Bangkalan hospital as dengue Virus Infection, and got Ringer Lactate solution for early recucitation, but the condition became worse, and referred to Soetomo Hospital.

Table 10. Result of laboratory examination

| Day of admission | Hb | Hct | Leukocyte | Trombocyte | AST | ALT |
|------------------|------|-----|-----------|------------|-----|-----|
| 1 | 13 | 47 | 9400 | 200000 | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | 18 | 55 | 7000 | 40000 | | |
| 5 | 16 | 47 | 9100 | 80000 | 275 | 405 |
| 6 | 15,7 | 45 | 9800 | 29000 | | |

RESULT

In our cases, all of the patient were observed intensively in Pediatric Intensive Care Unit and treated conservatively. Five cases (Group A) had got Ringer Acetate since the first day came to the hospital. They showed naturally clinical manifestation and recovered well. One case showed ALT,

AST increase more than 100 I/U but in short time showed recovery.

Five cases (Group B) had got Ringer Lactate in an early day of admission in hospital. Three cases showed increasing AST and ALT more than 1000 and showed encephalopathy and become severe. Patient no 4 got transfusion of FFP which indicator were abnormal coagulation profile. Patient no 2 had got PRC transfusion to replace the blood loss from intestinal bleeding. All of the involved organ were recovered along with recovery process of the disease.

DISCUSSION

To manage Dengue Virus Infection cases in our hospital, as a clinician or a doctor in charge should identify the cause of infection by doing the physical and laboratory examination. It should be correlated with criteria or sign & symptoms of the cases:

1. Severe cases have to be handled in emergency room or intensive care unit.
2. Early and mild case could be handled in general practitioner practice or pediatrician clinic.

A primary or secondary antibody response can be observed in patients with dengue virus infection. In primary dengue virus infection, IgM antibodies develop rapidly and are detectable on days 3–5 of illness, reach its peak at about 2 weeks post infection and then decline to undetectable levels over 2–3 months. Anti dengue virus IgG appears shortly afterwards. Secondary infection with dengue virus results in the earlier appearance of high titers of IgG before or simultaneously with the IgM responses.^{2,4}

Everyday, one or two cases could be inpatient in our hospital, for making a proper diagnosis and well recovery.

During three decades, the World Health Organization (WHO 1997) has recommended the classification of dengue virus infection in: dengue fever (DF) and dengue hemorrhagic fever (DHF) with or without dengue shock syndrome (DSS). In order to be regarded as a DF (or classical dengue) case, the patient must present fever and two symptoms out of the following: headache, retroocular pain, osteomyoarticular pains, rash, leucopenia, and some kind of bleeding. The DHF requires the presence of the four following criterias: a) acute sudden onset of high fever for 2 to 7 days; b) some kind of spontaneous bleeding, usually petechiae, or at least having a positive tourniquette test; c) thrombocytopenia lower than $100,000/\text{mm}^3$; and d) plasma leakage, evidenced by a 20% elevation of the hematocrite, or by a 20% decrease of the hematocrite after the critical stage, or by the verification of pleural leakage, ascites or pericardial leakage by means of image studies. The course of the dengue disease goes through 3 clinical stages: the febrile stage, the critical stage, and the recovery stage.⁶ (see figure 1)

WHO 2009 has divided Dengue Virus infection into 3 grade of disease, 1) Dengue virus infection without warning sign (we also can say *probable* dengue infection); 2) Dengue virus infection with warning signs (such as: abdominal pain, persistent vomiting, bleeding, etc) and the worst is 3) Severe dengue, which severe plasma leakage leading to hypovolemic shock and also it could be fluid accumulation leading to respiratory distress. Severe bleeding and severe organ impairment also could be occurred. It could be evaluated by laboratory findings; increasing of AST and ALT more than 1000.⁵ (see figure 2)

Clinical diagnosis of DHF was based on WHO criteria. Hepatomegaly is a common but not constant finding. Liver involvement in Dengue Virus Infection occurred because dengue virus antigen has been found in liver; hepatocytes and kupffer cells support the viral replication. In some countries, however, hepatomegaly varies from one epidemic to another, suggesting that the strain or serotype of virus may influence liver involvement. Elevated liver enzyme levels are usually happen. Serum AST and ALT were used as a measure of cellular injury. The elevation is usually mild, but in some patients, AST and ALT level reach 500 to 1000 U/L. Leucopenia is common; thrombocytopenia and hemoconcentration are constant findings in Dengue Virus Infection.⁵

Haemorrhagic manifestation in Dengue virus Infection patients are not common, and within mild to severe. Skin hemorrhage, including petechiae and purpura, are the most common, along with gum bleeding, epistaxis, menorrhagia, and gastrointestinal bleeding. The pathogenesis probably derives from vasculopathy, platelet deficiency and dysfunction, and blood coagulation defects.⁵

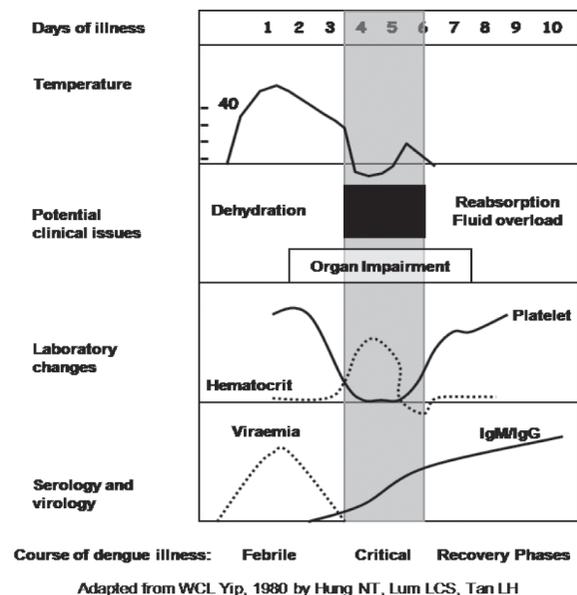


Figure 1. The Course of Dengue virus infection (WHO, 2009)

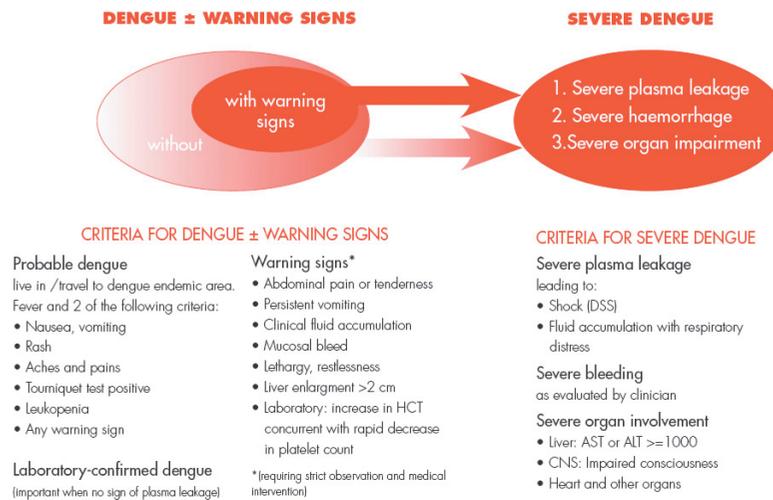


Figure 2. Level of severity of dengue virus Infection cases (WHO, 2009)

Our study is focused in using Ringer Lactate as a fluid therapy. Ringer Lactate was usually used in health centre and hospital for Dengue Shock Syndrome since 1969. But sometimes it could be found some cases that becoming more severe so that the patient had to be admitted in Dr. Soetomo Hospital Surabaya, as a top referral hospital in East Java, Indonesia. Therefore if there was a severe case with liver damage, we try to evaluate the patient and change the fluid resuscitation with Ringer Acetate.

Since 1968, Ringer lactate had been used for early treatment of cholera disease which the patient suffered from hypovolemic shock due to massive diarrhea. The result was proven good. From this experience, Ringer Lactate was also used to treat Dengue Shock Syndrome, but after 30 years using this protocol for DSS resuscitation, there were more cases become severe and difficult to manage.³

In 1997, in WHO course of DHF had been done in Bangkok. I had followed the course as a fellowship doctor

from East Java, Indonesia. I got information that don't use Ringer lactate in a case with liver damage. Based on this experience, until now I always remind the statement of our WHO teacher there, that we have to be careful in using Ringer Lactate in a case with liver damage, especially AST and ALT > 100–200. To make sure this information, we try again to study the new pathophysiology of Dengue Virus Infection (see figure 3)

Focusing on pathogenesis of hemorrhage in DHF (see figure 3) and update pathogenesis of DHF (see figure 4). Severity can occur due to virus replicate in hepatocyt and kupffer cells and induce necrosis as an apoptosis in liver and it's function damage.¹

This event can be promoted by using Ringer lactate. It is due to Ringer Lactate is metabolized in liver so if this solution is used, liver damage can be occurred more severe.

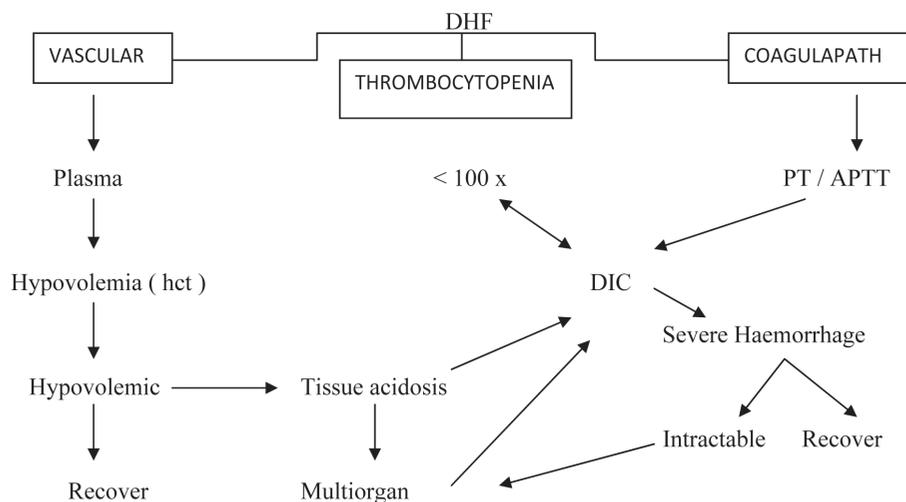


Figure 3. Pathogenesis of haemorrhage in DHF (Malaysia Ministry of Health, 2003)

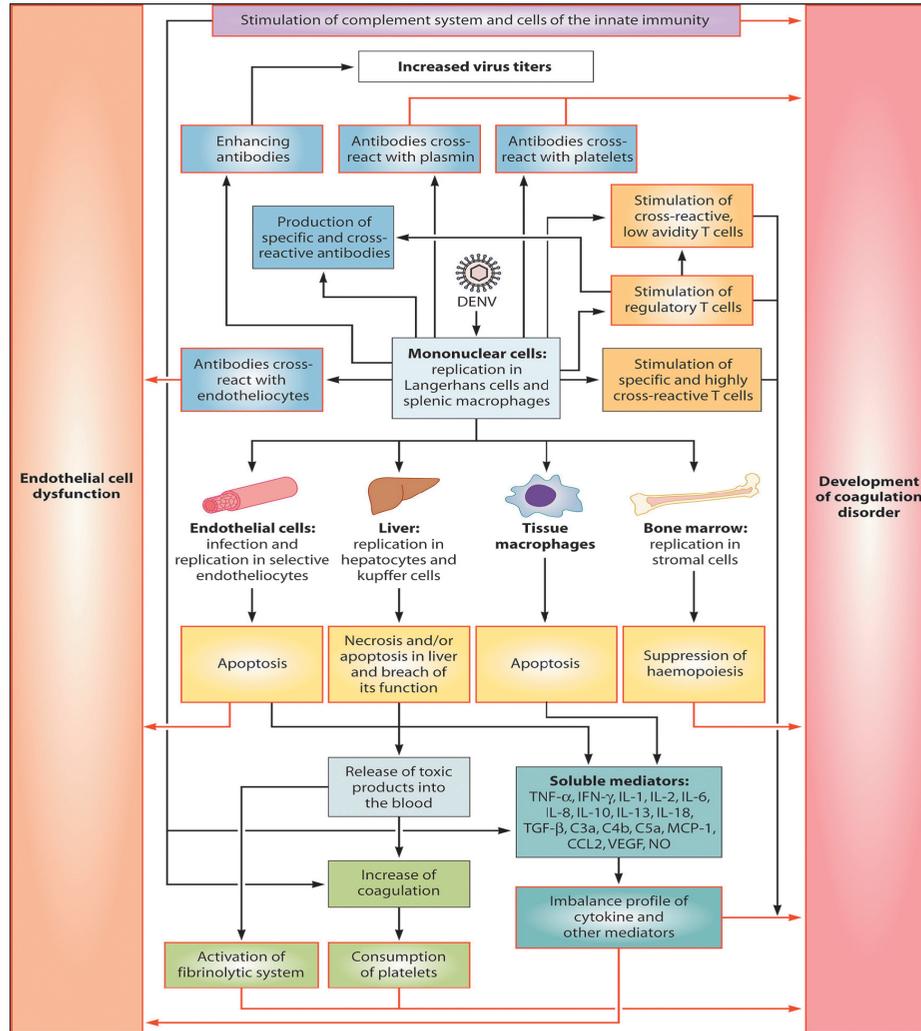


Figure 4. Update pathogenesis of Dengue Virus Infection in 2009 (WHO, 2009)

SUMMARY

Ten Cases of dengue Virus Infection had been observed intensively in pediatric Care Unit and treated conservatively. Five cases as a Group A got Ringer Acetate and 5 cases as Group B got Ringer Lactate before referred or on the first day admission in Dr Soetomo Hospital; recucitation start with 5–7 ml / kg BW / hour for 1–2 hours then reduce 3–5ml / kg BW / hour for 2–4 hours and then reduce to 2–3 ml / kg BW / hour or less. According to the clinical respond, if the hematocrite remains the same or rises only minimally continues with the same rate (2–3 ml / kg BW / hour) for another 2–4 hours, but if vital signs are worsening and hematocrit is rising rapidly, increase rate to 5–10 ml / kg BW / hour for 1–2 hours. Intravenous fluids usually needed only 24–48 hours, and should be reduced gradually which haematocrite level decreases.

Patient with warning signs should be monitored by health care provides until the period of critical phase is over.

We prefer using Ringer Acetate to ringer Lactate, due to Ringer Acetate has some benefit, such as:

1. Ringer Acetate is metabolized in muscle and could be tolerated in patient with liver dysfunction.
2. Acetate metabolism is faster than lactate metabolism.

CONCLUSION

Using Ringer Acetate as fluid therapy in Dengue Virus Infection is better to prevent liver damage than using Ringer Lactate.

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