


Clinical Manifestations and Complications of Dengue Infection in Children: Insights and Comparisons with Adult Cases

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ABSTRACT

Dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have become significant global health concerns, particularly affecting children more severely than adults. In children, dengue infection is distinct from that in adults due to its higher mortality rate and increased risk of developing dengue hemorrhagic fever or dengue shock syndrome. Clinical manifestations vary by age; children more commonly present with vomiting, rash, and abdominal pain, while adults often experience muscle and joint pain. Symptoms of DHF, a severe type of dengue infection, include abnormal hemostasis, plasma leakage, and protein-losing shock syndrome (dengue shock syndrome/DSS). Dengue infection in children can cause various complications from each organ system. During the critical phase, children are prone to plasma leakage, shock, and bleeding, potentially leading to severe complications such as liver dysfunction, electrolyte imbalance, and organ failure. Proper management and prevention of dengue are required to prevent dengue complications.

Keywords: Children, complications, dengue fever, dengue hemorrhagic fever, dengue shock syndrome.

ABSTRAK

Demam dengue, demam berdarah dengue, dan sindrom syok dengue telah menjadi masalah kesehatan global yang signifikan, terutama karena anak-anak mengalami dampak yang lebih berat dibandingkan orang dewasa. Pada anak-anak, infeksi dengue berbeda dengan pada orang dewasa karena tingkat mortalitas yang lebih tinggi serta risiko yang meningkat untuk berkembang menjadi demam berdarah dengue atau sindrom syok dengue. Manifestasi klinis bervariasi menurut usia; anak-anak lebih sering mengalami muntah, ruam, dan nyeri perut, sedangkan orang dewasa umumnya mengalami nyeri otot dan sendi. Gejala DHF, jenis infeksi demam berdarah yang parah, meliputi gangguan hemostasis, kebocoran plasma, dan sindrom syok kehilangan protein (sindrom syok demam berdarah/DSS). Infeksi dengue pada anak dapat menyebabkan berbagai komplikasi pada setiap sistem organ. Pada fase kritis, anak-anak rentan mengalami kebocoran plasma, syok, dan perdarahan, yang berpotensi menyebabkan komplikasi berat seperti disfungsi hati, ketidakseimbangan elektrolit, dan kegagalan organ. Penanganan dan pencegahan dengue yang tepat sangat diperlukan untuk mencegah terjadinya komplikasi akibat dengue. **Sonia Sudana Kusuma. Manifestasi Klinis dan Komplikasi Dengue pada Anak: Tinjauan dan Perbandingannya dengan Kasus Dewasa.**

Kata kunci: Anak-anak, komplikasi, demam dengue, demam berdarah dengue, sindrom syok dengue.

INTRODUCTION

One of the main viral infections distributed by arthropods globally is dengue, transferred by mosquitoes.[1] It comprises four distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. The two main vectors of this virus are *Aedes albopictus* and *Aedes aegypti*.[2] Dengue infection impacts 128 countries across tropical and subtropical regions, including Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific.[3-5] An estimated 500,000 people with DHF are hospitalized each year; 90% of these are children under the age of five, and 2.5% of them don't survive the illness.[3] Dengue cases have been documented in all 38 provinces of Indonesia, with all four DENV serotypes circulating within the country. Indonesian Health Survey 2023 reports a total of 877.531 new dengue cases in Indonesia, with the highest incidence in West Java Province (17.9%). Children account for 31.8% of these cases.[6]

Dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have become significant global health concerns.[3] Dengue fever, the mildest form, is marked by a biphasic fever, muscle and joint pain, rash, reduced white blood cell count, and swollen lymph nodes. Symptoms of DHF, a severe type of dengue infection, include abnormal hemostasis, plasma leakage, and protein-losing shock syndrome (dengue shock syndrome).[4]

After infection, dengue symptoms usually manifest 5 to 7 days later; in rare occasions,

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severe cases may arise. Research indicates that adults with dengue often experience muscle pain, retroorbital pain, nausea, and joint pain, while children are more prone to vomiting and rashes.[5] In contrast to adults, dengue infections in children are marked by higher mortality rates and a greater likelihood of developing severe forms such as DHF or DSS.[2] Moreover, immunological variables often result in dengue infections being more severe in children.[7] Guzman, *et al*, found that children aged 3 to 4 years had a high death rate of 25.4 per 10,000 infections, which decreased significantly with age, being 15.9 times lower in the 10 to 14-year age group.[8] Research conducted by Sachdev, *et al*, in New Delhi found 25.6% deaths among dengue patients in PICU. Data from the Indonesian Ministry of Health 2022 indicates that 1,236 fatalities were attributed to dengue infection, with children aged 0 to 14 accounting for 63% of these deaths.[9] Dengue fever tends to be more severe in children than in adults because they have a higher risk of developing shock, which can lead to organ failure and potentially result in death.[10]

CLINICAL MANIFESTATION

Dengue fever can take 1 to 7 days to incubate. The disease progresses through three main stages: febrile, critical, and recovery. During the febrile phase, individuals usually experience a sudden high fever that can reach up to 40°C, lasting between 2 and 7 days. Particularly in DHF and DSS patients, about 6% of cases may exhibit a saddleback or biphasic fever pattern. Typically, the fever lasts for at least 24 hours before a secondary rise in temperature, which may continue for another day.[1] The age of the patient has an impact on the variety of clinical symptoms. In infants and young children, the disease may present as an undifferentiated illness with a fever lasting 1 to 5 days, accompanied by pharyngeal inflammation, rhinitis, and mild cough. Rarely, excruciating back pain may appear before the fever.[4] Research conducted by Florez, *et al*, indicates that both adults and children with dengue infection suffer from fever, fatigue, myalgia, headache, and arthralgia. Adults are more likely than children to develop chills and tachypnea. On the other hand, symptoms like abdominal pain and vomiting are more frequently found in children and are rarely seen in adults.[5]

In the critical phase, the fever decreases to around 37.5°C to 38°C, typically between days 3 and 7. This phase, which typically lasts 1 to 2 days, is characterized by increased capillary permeability. During this time, there is often a significant drop in platelet count and a rise in hematocrit levels. This phase may result in shock, organ failure, DIC, or bleeding if improperly handled.[1] A study by Hanafusa in Thailand found that children are more likely to experience epistaxis and gastrointestinal bleeding, while gum bleeding is more frequent in adults.[11] According to laboratory evaluations reported by De Souza, *et al*, in Brazil, abnormalities such as hemoconcentration, thrombocytopenia, leukopenia, and elevated ESR, ALT, and AST levels are more common in adults compared to children. It is thought that the initial dengue infection might provide some protection against plasma leakage in children, with repeated infections by different dengue virus serotypes leading to more severe symptoms.[12] Conversely, research by Namvongsa, *et al,* in Thailand indicates that children exhibit more significant plasma leakage, evidenced by lower serum albumin and sodium levels and a higher incidence of pleural effusion, ascites, and shock. This is attributed to greater microvascular permeability in children.[13]

In the recovery phase, the body gradually reabsorbs the extravascular fluid over 2 to 3 days.[1] Diuresis begins as soon as the patient's hemodynamic condition stabilizes. The hematocrit may either stabilize or decrease due to the dilution effect of the reabsorbed fluid. In addition, platelet counts usually start to rise while the white blood cell count starts to increase.[14]

Neurological manifestations in children with dengue infection may include drowsiness, convulsions, decreased consciousness, and lethargy. Symptoms of bleeding can vary in severity, encompassing signs such as gastrointestinal bleeding and petechiae. Additional symptoms may include pleural effusion, hepatomegaly, vomiting, and abdominal pain.[15] Peripheral or circumoral cyanosis may appear, along with a macular or maculopapular rash. Approximately 20%-30% of DHF cases may advance to shock (DSS). Even in completely aware individuals, DSS can be modest, and it's often linked to elevated diastolic blood pressure and peripheral vascular resistance.[4]

COMPLICATIONS

Frequent complications in infants and young children include high fever, febrile seizures, and loss of fluid and electrolytes. During the fluid reabsorption phase, hypervolemia can become life-threatening, indicated by a drop in hematocrit and a widened pulse pressure. Heart failure, acute pulmonary edema, and respiratory issues are possible outcomes of this condition.[4,3] Additionally, though less frequent, prolonged fatigue, mental depression, bradycardia, and ventricular extrasystoles can develop in children after the febrile phase.[4] Dengue fever with hemorrhage may occur alongside pre-existing conditions such as peptic ulcers, severe thrombocytopenia, and trauma.[3]

Unlike children, adults are more likely to experience complications involving the kidneys and liver. This is because the more developed immune system in adults can trigger more intense inflammatory responses and increase the likelihood of organ involvement.[16] Although less common, kidney and liver issues can also occur in children. Mikhael, *et al*, observed that the most common complications of dengue infection in infants are pleural effusion, hypoalbuminemia, hyponatremia, hypocalcemia, and liver involvement. Increased blood vessel permeability causes plasma leakage, which causes albumin to be released from the circulation and causes hypoalbuminemia. Liver damage also contributes to this condition.[2]

Acute renal failure has been reported in 3% of dengue shock patients, and it is linked to high fatality rates. Other complications may include aplastic anemia, rash, severe thrombocytopenia, respiratory problems, cholecystitis, pancreatitis, and acute abdominal issues. According to a study in South Odisha, India, by Mishra, *et al*, 47.42% of children who had dengue infection had elevated aspartate transaminase (AST) which was significantly more compared to elevation of alanine transaminase (ALT). Myocyte involvement might be the cause.[7]

TREATMENT

Supportive care is the mainstay of treatment for mild dengue fever. It is recommended to have bed rest during the febrile phase and to use antipyretics to maintain a body temperature below 40°C, with paracetamol being the preferred choice.[4] NSAIDs and aspirin are not recommended because


they can aggravate gastritis or bleeding.[17] Adequate fluid intake is necessary, but caution should be exercised to avoid overhydration in infants and young children.[3]

Management of DHF and DSS includes quickly evaluating vital signs, hemoconcentration, dehydration, and electrolyte abnormalities.[4] Careful fluid resuscitation is essential for managing the critical phase of dengue. When it comes to fluids, crystalloids are usually the primary option, with the exception of extremely young infants under 6 months old, who may utilize 0.45% sodium chloride.[18] Intravenous fluid therapy should not extend beyond 24 to 48 hours for patients in shock. For those not experiencing shock, the therapy might be needed for up to 60 to 72 hours. The recommendation to limit IV fluid therapy to 24 to 48 hours in dengue patients with shock is to avoid complications associated with over-resuscitation. For patients who are not in shock but still require fluid therapy, the situation is less critical. The needs for IV fluids can be based on factors like maintaining hydration and electrolyte balance and supporting the body's response to the illness. The recommendation to extend therapy up to 60 to 72 hours reflects the time needed to adequately manage fluid balance and ensure recovery.[3] Prophylactic platelet transfusions are not advised.[18] Study by Sharma, *et al*, showed that the strategy of prophylactic platelet transfusions did not provide any advantage to supportive care in terms of risk of bleeding, hospital stay, or prevention of non-hemorrhagic complications of dengue infection. Instead, platelet transfusion was associated with more adverse events compared to those who were managed conservatively.[19]

It is essential to monitor the patient continuously for at least 48 hours since shock may occur or return abruptly early in the course of the disease.[4] A study involving 25 children with DHF grade 2 and 3, who had active bleeding, demonstrated short-term control of bleeding with recombinant factor VIIA, but did not show any overall benefit. There is no data to back up the claims made regarding the use of corticosteroids in DSS and their ability to stop the disease from getting worse.[18] If blood pressure normalizes after fluid resuscitation but organ impairment continues, the patient should receive targeted supportive care, which may include peritoneal dialysis, continuous renal replacement therapy, and mechanical ventilation.[3] The use of vasopressors has not significantly decreased mortality compared to basic supportive care.[4] When bleeding occurs, it should be attempted to control it whenever possible. For example, severe epistaxis may be controlled by nasal packing. Emergency blood transfusion is life-saving if hematocrit falls.[3]

PREVENTION

Efforts to prevent dengue infection include various measures such as personal protection, environmental management, and vector control. The most effective way to prevent dengue is to avoid mosquito bites. Stay indoors during peak mosquito activity, which occurs 2 hours before sunrise and 2 hours before sunset. Using insect repellent on exposed skin is also advantageous. It is advisable to use mosquito nets while sleeping.[20] The chance of getting bitten by a mosquito can be decreased by wearing loosely fitting and thick clothes. Additionally, household insecticidal products are widely used for personal mosquito protection.[3]

Numerous vaccines targeting dengue types 1-4 are currently in development. Two dengue vaccines have been licensed, CYD-TDV and TAK-003. CYD-TDV is a live recombinant tetravalent dengue vaccine, given in a 3-dose series with 6-month interval doses, for individuals aged 9 to 45 years. Prior to immunization, a person must be screened for previous dengue infection. TAK-003 is the second dengue vaccine to be licensed. TAK-003 is a live attenuated vaccine that includes weakened strains of dengue virus serotypes 1, 2, 3, and 4. According to WHO standards, the immunization protocol consists of two doses spaced three months apart that target certain age groups and conditions. WHO advises using TAK-003 for children aged 6 to 16 years in areas with high dengue transmission.[21]

Environmental management focuses on altering environmental factors to reduce vector breeding and lower human-vector-virus interactions. *Aedes aegypti* and *Aedes albopictus* can be managed by eliminating standing water sources, controlling solid waste, altering artificial breeding grounds, and improving house design. Water storage containers should always be covered with tightly fitting lids.[3]

Vector control can be achieved through both biological and chemical methods. Biological control is the introduction of organisms that parasitise, prey on, outcompete, or otherwise reduce the numbers of the target species. Larvivorus fish (*Gambusia affinis* and *Poecilia reticulata)* have been extensively used for the control of larvae of *Aedes aegypti* in large waterbodies in many countries in Southeast Asia.[3] *Wolbachia pipentis* is an obligatory intracellular bacterium that works well as a mosquito repellent. *Wolbachia pipentis* is common, maternally inherited and infects many species of insects but does not naturally occur in *Aedes aegypti* mosquitoes. When certain strains of Wolbachia are transinjected into *Aedes aegypti*, the mosquito becomes resistant to DENV and other arboviruses. In Yogyakarta, introducing Wolbachia into *Aedes aegypti* mosquitoes led to a 77% reduction in symptomatic dengue cases among individuals aged 3 to 45 years.[22]

Chemicals have been used to manage *Aedes aegypti* since the early 20th century. Modern methods include larvicide application and space spraying.[3] Larviciding is usually limited to domestic-use containers. Three larvicides can be used for treating water containers: temephos 1% sand granules, pyriproxyfen, and *Bacillus thuringiensis H-14*. The application of larvacide is safe and has a low toxicity level for humans. Four main classes of chemical insecticides are used to control *Aedes aegypti*: organochlorines, organophosphates, carbamates, and pyrethroids.[23] Space spraying, which involves dispersing fine droplets of insecticides into the air to kill adult mosquitoes, has been ineffective, as indicated by an increase in DHF cases. Consequently, the use of space spraying or fogging should be limited to times of epidemic.[3]

CONCLUSION

Dengue is a mosquito-borne virus and is one of the leading causes of viral diseases transmitted by insects worldwide. It can lead to dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Children and adults exhibit differences in clinical manifestations and complications of dengue. Healthcare providers need to be aware of these variations when evaluating potential cases of dengue infection. Proper management and prevention of dengue are required to prevent unwanted dengue complications.

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