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Case Report

# Repeated dengue shock syndrome and 'dengue myocarditis' responding dramatically to a single dose of methyl prednisolone

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SUMMARY

The place of steroids in the management of severe forms of dengue is unclear. A retrospective observational study showed the benefits of a single dose of intravenous methyl prednisolone in a highly selected group of patients who developed severe dengue during the febrile phase of infection. We report the case of a 14-year-old boy with dengue who developed three episodes of severe hemodynamic compromise while having high fever, 'myocarditis', third space fluid accumulation, progressive reduction in urine output, and altered mentation, who made a dramatic recovery following a single dose of intravenous methyl prednisolone. Results justify a well powered randomized controlled trial to evaluate the efficacy of this treatment in severe dengue.



## 1. Introduction

The place of steroids in the management of severe forms of dengue is unclear.[1,2] Studies to assess the effects of steroids have all been done in children and with the steroids given at a late stage of dengue shock syndrome (DSS).[2] While some studies have shown no beneficial effects,[2] two studies have shown the benefits of high-dose methyl prednisolone.[2] A retrospective observational study has also shown the benefits of a single dose of intravenous (IV) methyl prednisolone in a highly selected group of patients who developed severe dengue during the febrile phase of infection.[3]

Immune mechanisms may play an important role in the development of severe forms of dengue. Studies have shown participation of tumor necrosis factor alpha (TNF-α), interleukin (IL)-2, IL-6, IL-8, IL-10, IL-12, and interferon gamma (IFN-γ), Th1/Th2 immune reactions, and vascular cell adhesion molecule 1 (sVCAM-1) in the pathophysiology of dengue fever (DF) and DSS.[4] The role of steroids in the management of severe shock or severe respiratory distress is based on its ability to inhibit TNF-α and IFN-γ production, and the inhibition of IL-1β, IL-6, and IL-8.[4] Steroids have been shown to modulate dengue infection by decreasing the cell infection rates.

We report the case of a 14-year-old patient with DF who was given a single dose of methyl prednisolone as rescue medication at the time he developed the third episode of dengue shock while having high fever, third space fluid accumulation, evidence of 'myocarditis', hepatic involvement, and deteriorating levels of consciousness. He made a dramatic recovery following methyl prednisolone. We wish to highlight the possible beneficial effects of a single dose of IV methyl prednisolone used as a rescue medication in severe dengue.

## 2. Case report

A 14-year-old schoolboy was admitted on day 2 of a febrile illness with headache, body aches, and vomiting. He was admitted mainly for IV fluid therapy as he could not retain oral fluids. On admission his blood pressure was 120/80 mmHg and pulse rate was 80/min. His liver was palpable 3 cm below the right costal margin and was mildly tender. There was no splenomegaly or free fluid in the abdomen or in the chest. Based on the initial clinical assessment supported by investigations (Table 1), he was suspected of having dengue and was kept under close observation. He continued to have an intermittent high fever (range 39–41 °C). On day 4 of the illness his blood pressure dropped to 90/60 mmHg with a pulse rate of 90/min. At this stage an electrocardiogram (ECG) showed T wave inversions in the anterior leads (Figure 1) and an echocardiogram showed mild global hypokinesia with an ejection fraction of 50%. However, his cardiac enzymes (troponin I) were normal. Following development of the ECG changes, he was managed with oral solutes and IV fluids (either normal saline or Hartman solution) with extreme care, based on clinical

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**Table 1**
Clinical parameters and hematological and biochemical test results from admission to hemodynamic stability

| | **2** | **4** | | **5** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (24 h clock) | 12.00 | 06.00 | 18.00 | 06.00 | 07.00 | 12.00 | 14.00 | 16.00 | 19.00 | 20.00 | 00.00 |
| Temperature, °C | 38.8 | 39.2 | 38.9 | 39.2 | | 39.5 | 37.8 | 37 | 40.2 | 37 | 37 |
| Pulse/min | 80 | 92 | 110 | ?? | 120 | 140 | 140 | 140 | 164 | 118 | 90 |
| BP Supine (mmHg) | 120/80 | 110/80 | 96/65 | 70/?60 | 70/60 | 92/73 | 70/? | 117/74 | ?60 | 108/65 | 117/72 |
| BP Standing (mmHg) | 110/80 | 110/80 | 90/60 | ?? | 120 | | | | | | |
| Capil. Filling T (S) | 2 | 2 | 2 | >3 | >3 | >3 | >3 | <3 | >3 | 2 | 2 |
| Resp Rate (/min) | 18 | 18 | 18 | 28 | 28 | 40 | 36 | 30 | 44 | 24 | 24 |
| UOP | | 1.5l/24 h | | 0.4l/6 h | 0.1 ml/kg/h | 0.6 ml/kg/h | 0.6 ml/kg/h | 0.8 ml/kg/h | 0.2 ml/kg/h | 0.8 ml/kg/h | 1.4 ml/kg/h |
| Input iv (l) | | Crystalloid 1.5l + 0.25l bolus | | Crystalloid 0.5l bolus 0.5l Dextran | | Crystalloid 2 ml/kg/h | Dextran 0.25 l | Crystalloid 2 ml/kg/h | Dextran 0.25l + **MP** | Crystalloid 1 ml/kg | Crystalloid 0.5 ml/kg |
| Input Oral (l) | 1.1 | 1.7 | | | | | | | | | Rest |
| Pleural Effusion | Nil | Nil | Mild | | Mild | Mild | Moderate | Moderate | Moderate | Moderate | Moderate |
| Ascites | Nil | Nil | Nil | | Mild | Mild | Mild | Moderate | Moderate | Moderate | Moderate |
| Hb (g/dl) | 13.9 | 14.3 | 15.1 | 16.0 | 17 | 15.2 | | | | | 13.5 |
| PCV (Fl) | 41.5 | 43.2 | 45.9 | 49.9 | 48.2 | 40 | 51 | 49 | 51 | 48 | 48 |
| Platelet ($\times 10^9$/l) | 131 | 55 | 17 | 10 | | 4 | 3 | 4 | 2 | 4 | |
| WBC L ($\times 10^6$/l) | 2.8 | 1.5 | 1.6 | 2.2 | | | 1.2 | | 1.3 | | |
| CRP (iu/l) | | 6 | | | 24 | | | | | 48 | |
| Serum Protein (g/dl) | | | | | 4.81 | | | | | | |
| Serum Albumi (g/dl) | | | | | 3.1 | | | | | | |
| $Ca^{++}$ (ionizd) mmol/L | | | | | 1.10 | | | | 1.13 | | |
| Serum creatinine (mg/dl) | | | | | 1.06 | | | | | | |
| AST (IU/l) | 96 | | | | 407 | | | | | | |
| ALT(iu/l) | 73 | | | | 171 | | | | | | |
| Serum cholesterol | | | | | 73 | | | | | | |
| ECG | | T inv | T inv | | T inv | | T inv | T inv | T inv | Norm | Norm |
| Blood pH | | | | | 7.4 | | 7.3 | | 7.3 | | |
| Arterial $O_2$% | | | | | 96 on 100% | | 92% | 94% | 94% | 96% | 96% |

BP, blood pressure; UOP, urine output; IV, intravenous; MP, methyl prednisolone; Hb, hemoglobin; PCV, packed cell volume; WBC, white blood cells; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ECG, electrocardiogram; T inv, T wave inversions.

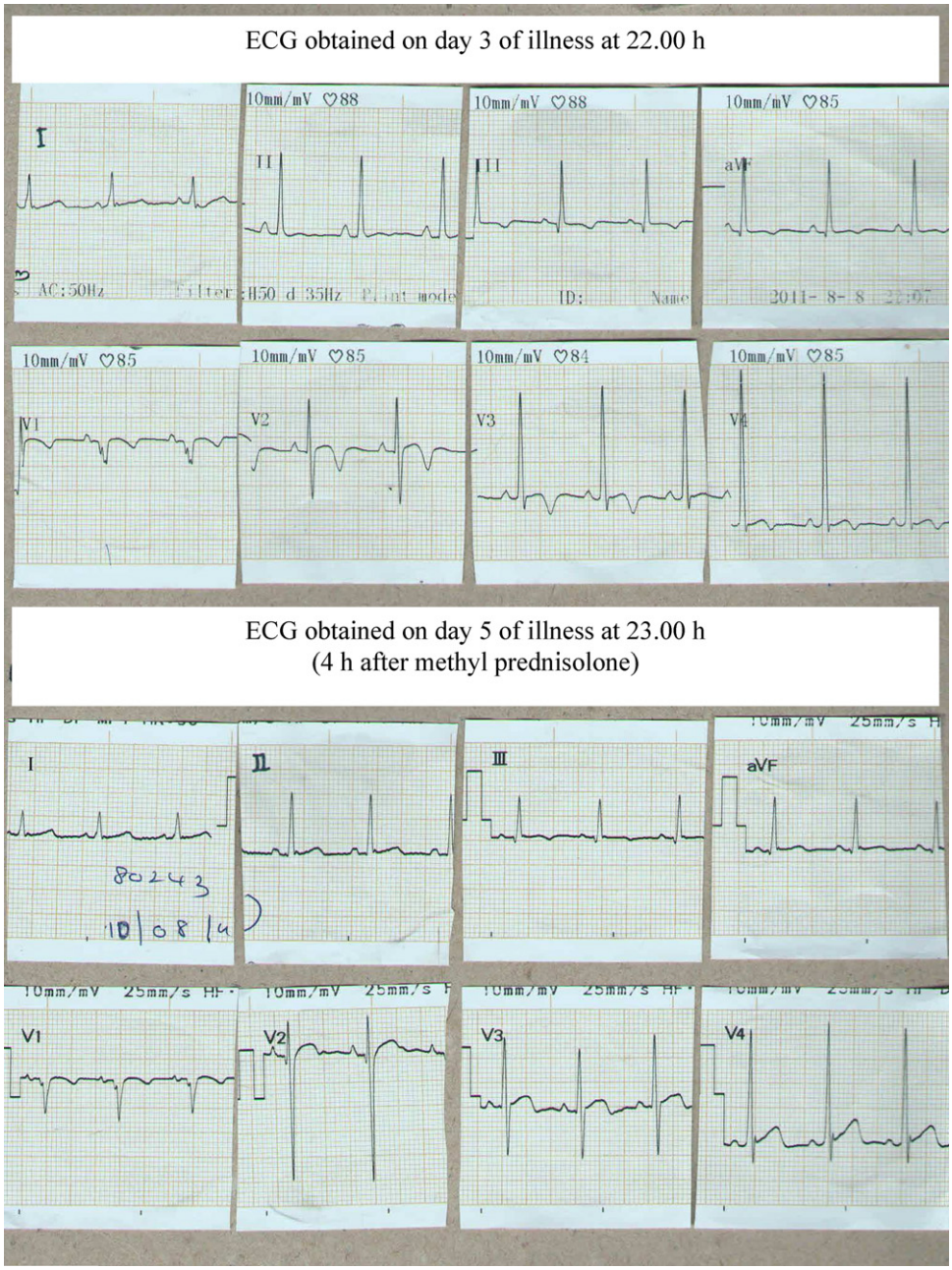


**Figure 1.** Evidence of myocarditis; ECG abnormalities.

parameters, hematological parameters, and fluid balance monitoring. On day 5 of illness, around 06.00 h, he suddenly collapsed with absent peripheral pulses and an unrecordable blood pressure (Table 1), suggesting the development of DSS. As advised in the dengue management guidelines, he was rapidly resuscitated with IV fluid boluses and dextran calculated for a period of 48 h according to his body weight of 52 kg.[5] The resuscitation was successful, and he was transferred to intensive care for close monitoring as he had evidence of myocarditis.

While in intensive care he continued to have a high fever (39–41 °C) and tachycardia >110/min, and he developed two further episodes of severe hemodynamic compromise similar to the first episode, at around 14.00 h and 19.00 h on the same day. At the time of both episodes, he was given boluses of dextran infusion. Although he could be resuscitated with a dextran bolus at 14.00 h, it was unsuccessful at 19.00 h. During the latter episode he had a pulse rate of 160/min in addition to a poorly recorded mid-arm systolic blood pressure of 70 mmHg and evidence of myocarditis on ECG. His extremes were cold and lower limb pulses were not palpable. He was confused, restless, and was in respiratory distress. His temperature was 40.2 °C and he had a right-sided moderate pleural effusion and moderate ascites. The respiratory rate was 36/min and capillary $O_2$ saturation was 96% while on 100% $O_2$ via a face mask. His urine output dropped to less than 0.2 ml/kg/h.

These complications made it extremely difficult to make decisions on the amount and type of fluid to be used for fluid resuscitation. As the patient's condition was deteriorating rapidly a single dose of methyl prednisolone 500 mg in 200 ml saline was given IV over 20 min as a rescue medication. A single dose of meropenem 1 g IV was also given in order to counter any possible sepsis. He had defervescence within 30 min of being given methyl prednisolone (Figure 2), became more alert, and started to communicate. Within 1 h, his pulse rate had reduced to 96/min, his blood pressure remained stable above 100/80 mmHg, and his

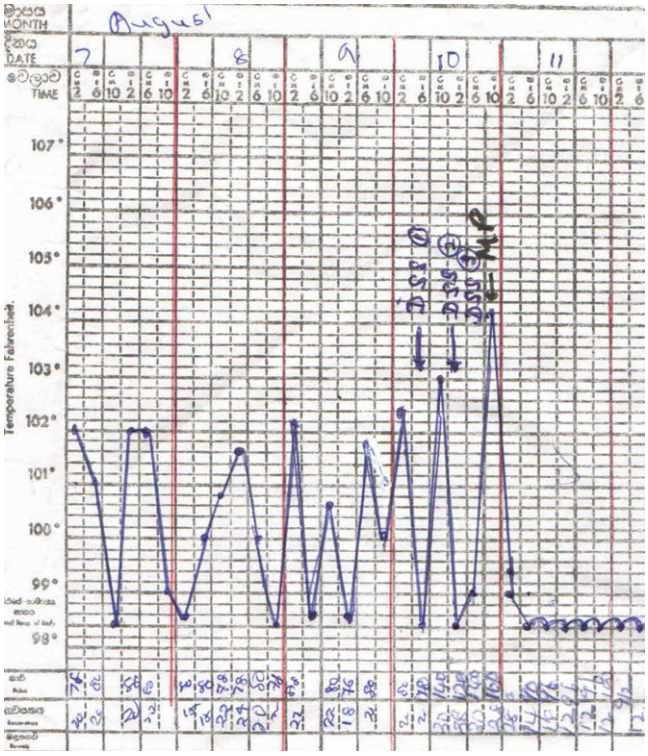


**Figure 2.** Temperature chart of the patient, demonstrating rapid defervescence following methyl prednisolone.

urine output increased to 0.8–1.4 ml/kg/h. His ECG became normal after 3 h and a follow-up echocardiogram done after 12 h showed an ejection fraction of 55%. His clinical parameters and haematological and biochemical parameters on day 4 and 5 of illness are shown in Table 1.

He did not develop evidence of sepsis or an increase in blood glucose levels and continued to improve. As a precautionary measure, meropenem was continued for 3 days. He was positive for dengue IgM and IgG antibodies on day 6 of illness, and a serum sample collected on admission (which was stored as part of a dengue surveillance study) was analyzed in December 2011, and was positive for both dengue PCR and NS1 antigen, confirming the diagnosis.

## 3. Discussion

This patient with dengue developed three episodes of severe hemodynamic compromise within 12 h on day 5 of clinical illness. All three episodes occurred while being closely monitored. He had a high fever throughout his illness, including during the three episodes of DSS. The highest recorded fever and the worst hemodynamic compromise occurred during the last episode, which resulted in restlessness and altered mentation. He did not have febrile fits and, in retrospect, his metabolic screening showed no abnormality to account for an altered level of consciousness. The first two episodes of shock were managed successfully with IV fluid boluses (both crystalloids and colloids), as recommended in the guidelines. However, our patient had evidence of myocarditis from the outset and we had to be cautious not to overload the patient with fluid to prevent myocardial strain and also possible pulmonary edema during the recovery phase.[6] At the time of the third episode of DSS he had clear clinical evidence of third space fluid accumulation, later confirmed by chest X-ray obtained on day 5 of illness (Figure 3) and by ultrasonography. The presence of high fever, severe hemodynamic compromise, reduced mentation,

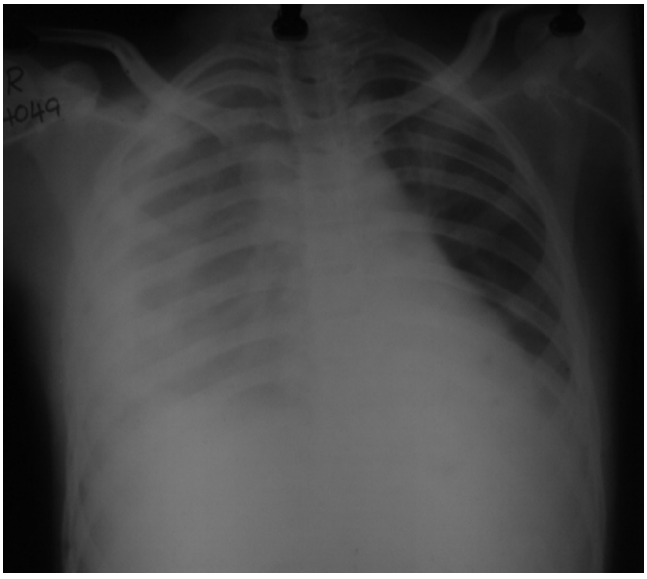

**Figure 3.** Chest X-ray of the patient obtained on day 5 of illness.

myocardial involvement, reduced urine output, and third space fluid accumulation, all suggested a rapidly deteriorating clinical scenario. Based on our previous experience,[3] we were compelled to administer a single dose of methyl prednisolone as a rescue measure. This led to a dramatic recovery with rapid defervescence, hemodynamic stability, reversal of ECG changes, and improvement in urine output, similar to our previous experience.

The clinical predicament of this patient was most likely due to DSS with myocarditis, hepatic involvement, and encephalitis or encephalopathy. We excluded the possibility of septic shock based on cold peripheries with the absence of peripheral pulses at the time of shock. There was also no evidence of bacterial infection in the blood picture (absence of neutrophil toxic granules) and the white blood cell count remained low until day 6. However, his C-reactive protein was mildly elevated on day 4 and remained elevated after the successful resuscitation. He did not develop fever or evidence of septicemia after being given the methyl prednisolone. The possibility of an anaphylactoid reaction to colloid solutions that responded to methyl prednisolone is unlikely, as he had previously received colloid solutions on two occasions (7.00 h on day 4 and 14.00 h on day 5) without developing reactions. In fact his hemodynamic parameters improved on both occasions. The third bolus of dextran was given at 19.00 h only after he collapsed.

In Sri Lanka the most severe outbreaks of dengue were recorded in 2004 with 15 457 cases and 88 deaths (case fatality rate (CFR) 0.5%), in 2009 with 33 081 cases and 334 deaths (CFR 1%), and in 2010 with 34 105 cases and 246 deaths (CFR 0.7%). From the launch of the new management guidelines for DF in 2011 up to mid-June, there were 9136 cases with 73 deaths (CFR 0.7%). These figures highlight the increase in dengue cases with a static CFR despite the institution of newer resuscitation regimes. The occurrence of severe DSS with or without severe organ involvement (myocarditis, hepatitis, and encephalitis) is the most likely reason for mortality not decreasing, and an improving fluid resuscitation alone may not be sufficient to reduce mortality.

We feel that our observation of the apparent beneficial effects of a single dose of methyl prednisolone in the present case and in the past[3] warrants a randomized controlled trial to address this issue.

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*Conflict of interest*: None declared.

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