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## Severe Dengue: Lessons learnt from an observational study

Large, multicenter- or population-based epidemiological studies help in describing incidence, prevalence and risk factors of the disease studied and also help in studying trends over time and the impact of preventive policies which are of importance in public health. On the other hand, many insights of clinical importance can be gained by single center smaller observational studies specially for common infections like Dengue, similar to the one published in this issue of IJA by Dr. Shastri *et al.*<sup>[1]</sup> In this study, only 5% of 137 patients, who were admitted to intensive care unit with confirmed Dengue were above the age of 65 years, thus highlighting rarity of this infection in elderly. The average severity of illness, assessed by APACHE II or SOFA score was 9 and 4 respectively in patients who survived thereby providing clinician a tool for prognostication, family counselling and auditing their performance. In the era of increasing importance of cost effective care, length of stay (LOS) has become an important quality indicator and the average LOS of 4 days in survivors can be used as a benchmark of comparing ICU performance in managing Dengue fever. Acute undifferentiated febrile illness in tropical countries due to infections like malaria, dengue, leptospirosis, typhus, enteric fever usually presents with similar clinical features. Rarity of neurological (15%) and enteric symptoms (15%) on presentation in Dengue fever as described in the study may help in differential diagnoses of these infections on presentation, before confirmatory tests are obtained. Presence of thrombocytopenia, coagulopathy and liver injury was associated with worse survival, whereas lung injury was not, thus highlighting the importance on different outcome based on different organ involvement. Crude mortality of 38% in a relatively young population should be a warning to all of us to improve on our present care of this population in order to decrease mortality.

Cohort studies like this can identify areas for improvement and knowledge gap, which can only be improved by conducting basic, translational and clinical research in therapeutic and preventive aspects of this common menace. Guidelines for dengue management have been published by national<sup>[2]</sup> and international<sup>[3]</sup> organisations (WHO), to be utilised globally, predominantly in resource limited setting. The present study highlights the high mortality of severe Dengue even in urban setting, in a tertiary care ICU, thereby highlighting need of further research in this area specifically on the application of advanced haemodynamic monitoring tools for volume assessment and resuscitation. Utilising point of care ultrasound and assessment of inferior vena cava diameter and collapsibility, which is a common practice in sepsis resuscitation has also not been studied adequately in dengue sepsis. Type of resuscitation fluid needs to be reevaluated with more ready availability of balanced crystalloid to avoid hyperchloremic acidosis and renal impairment with chloride rich resuscitation which many Dengue patients are being subjected.<sup>[4-6]</sup> Moreover, use of colloids is recommended in guidelines, which in general sepsis patient are now contraindicated and may be even more detrimental in patients with coagulopathy. Use of point of care thromboelastography to elucidate quantitative and qualitative platelet defects and other haemostatic abnormalities will also help in rationalising the transfusion strategies in these patients.

The pathogenesis of thrombocytopenia needs to be better researched. A state of acquired thrombotic thrombocytopenic state due to defect in Von Willebrand's factor (Vwf) has been postulated as the mechanism for thrombocytopenia, which can be corrected with Fresh Frozen plasma infusion by replacing Vwf, which may become useful if there is

scarcity of platelets.<sup>[7]</sup> Massive capillary leak which is the hallmark of Dengue Shock Syndrome, needs to be better characterised. On one hand, fluid replacement is needed to maintain intravascular volume but it can also aggravate the pleural effusion and increases formation of ascites which can lead to abdominal compartment syndrome making it difficult to manage in these patients with bleeding diathesis. Macrophage activation syndrome with hyperferritinemia has also been found not uncommonly in severe dengue. Early identification of this entity with rising ferritin level needs to be studied, and the role of corticosteroids or other immune modulating drugs need to be studied. Use of other adjunctive modalities which are nowadays used in bacterial sepsis also need to be studied in severe dengue sepsis. These include, use of immunoglobulins, Vitamin C, corticosteroids, thiamine and extracorporeal cytokine removal devices.

There has been a long standing need for an effective vaccine for all strains of Dengue virus. CYD-TDV vaccine is licensed over 20 countries, but it is still not approved in India. The primary reason is that the vaccine is mainly effective in individuals who are previously infected with Dengue virus and are seropositive at the time of vaccination. For individuals who are seronegative at the time of vaccination, the risk of severe dengue is significantly increased.

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