

Institution: The University of Oxford
Unit of Assessment: 1
Title of case study: <p style="text-align: center;">CLINICAL MANAGEMENT OF DENGUE FEVER</p>
Summary of the impact: <p>Research in the Oxford University Clinical Research Unit (OUCRU) in Vietnam have spent the past two decades defining effective management strategies for dengue, which is the most significant mosquito-borne viral disease in humans. Dengue affects an estimated 50 million people and kills over 22,000 patients (mainly children) worldwide each year. OUCRU research directly underpins the clinical practice guidelines worldwide for the treatment of dengue shock syndrome (DSS), including the World Health Organization's (WHO) 2009 Dengue Guidelines, leading to faster, more effective and safer resuscitation of affected individuals.</p>
Underpinning research: <p>Dengue haemorrhagic fever and dengue shock syndrome (DSS) are major causes of childhood morbidity and mortality. For many years, fluid resuscitation has been the leading treatment for DSS, as it helps to counteract plasma leakage from intravascular permeability, which leads to shock. In spite of the relative success of fluid resuscitation, the WHO reported in 2005 that fatality rates among children with DSS were still 2.5%¹, equating to approximately 550 children per year. As <i>Aedes</i> mosquitoes (found in tropical and subtropical regions) are responsible for the spread of dengue, over 70% of cases arise in Southeast Asia and the Western Pacific. In Vietnam alone there were 105,370 cases of dengue and 87 dengue related deaths in 2009.</p> <p>Without an effective vaccine or specific cure for dengue fever, researchers at the OUCRU in Vietnam have spent the past two decades investigating successful interventions for improved clinical management and outcomes.</p> <p>While WHO guidelines for the management of dengue were first published in 1975, by 1997 updates to these guidelines still identified the need for evidence-based recommendations for the management of DSS. In particular, concerns were raised regarding intravenous-fluid regimens for the management of moderate and severe shock.</p> <p>In 1999 OUCRU published the first randomised, double-blind trial, comparing the top four intravenous-fluid regimens for resuscitation of children with DSS². The University of Oxford group found that the two colloids used (dextran and gelatin) restored cardiac index, blood pressure, and normalised blood cells more rapidly than the two crystalloids (Ringer's lactate and "normal" saline). The trial also showed that out of the four fluids used, dextran provided the most rapid normalisation of blood cells and restoration of the cardiac index, without adverse effects².</p> <p>A subsequent trial from OUCRU compared the same four intravenous fluid regimens in the initial resuscitation of a larger group of Vietnamese children with DSS³. While all children survived, and there was no clear advantage to using any of the four fluids, researchers noted that the group receiving Ringer's lactate (a crystalloid) took the longest to recover. In an analysis of the pulse pressure of patients before and after fluid regimens, the trial also showed significant benefits from colloids among children presenting with lower pulse pressures³.</p> <p>Following these initial studies OUCRU addressed further specific aspects of DSS pathogenesis, including investigations into the characteristics of protein leaks in DSS⁴. A third larger scale resuscitation trial compared the top three performing fluid solutions for DSS⁵. Results from this trial indicated that Ringer's lactate should be used for aggressive initial resuscitation in children with</p>

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moderately severe shock, while both colloids work equally as well in patients with severe shock. A superior side effect profile also supported the use of hydroxyethyl starch as the preferred colloid over dextran⁵.

This research showed:

1. The benefits of aggressive early fluid resuscitation using isotonic crystalloid solution (Ringer's lactate) for children with moderately severe shock;
2. Equal survival rates for colloid and crystalloid regimens in patients with severe shock; and
3. The preferred use of colloids for rapid recovery in severe shock.

Following the publication of OUCRU's third trial in 2005, researchers from OUCRU Vietnam contributed to a pivotal paper, calling for a complete reassessment of the WHO's dengue classification and case definitions, to ensure better diagnosis and management of DHF and DSS⁶.

References to the research:

1. World Health Organisation, Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome in the Context of the Integrated Management of Childhood Illness, Discussion Papers on Child Health (2005). Available at http://whqlibdoc.who.int/hq/2005/WHO_FCH_CAH_05.13_eng.pdf (Accessed 2013) **WHO report showing fatality rates among children with DSS were 2.5% in 2005.**
2. Dung, N. M. *et al.* Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. *Clin. Infect. Dis.* **29**, 787–794 (1999). **Trial comparing the top four intravenous-fluid regimens for resuscitation of children with DSS.**
3. Ngo, N. T. *et al.* Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin. Infect. Dis.* **32**, 204–213 (2001) doi: 10.1086/318479. **Trial comparing the same four intravenous fluid regimens in the initial resuscitation of a larger group of Vietnamese children with DSS.**
4. Wills, B. A. *et al.* Size and charge characteristics of the protein leak in dengue shock syndrome. *J. Infect. Dis.* **190**, 810–818 (2004). doi: 10.1086/422754 **Study focusing on specific aspects of DSS pathogenesis, including investigations into the characteristics of protein leaks in DSS.**
5. Wills, B. A. *et al.* Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N. Engl. J. Med.* **353**, 877–889 (2005) doi: 10.1056/NEJMoa044057. **A third larger scale resuscitation trial comparing the top three performing fluid solutions for DSS.**
6. Deen, J. L. *et al.* The WHO dengue classification and case definitions: time for a reassessment. *Lancet* **368**, 170–173 (2006). doi: 10.1016/S0140-6736(06)69006-5. **Paper calling for a reassessment of the WHO's dengue classification and case definitions.**

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Details of the impact:

By identifying the best fluid replacement techniques for the management of severe shock, OUCRU has significantly improved clinical understanding and management of DSS globally. This research has improved international guidelines and clinical practice guidance in endemic countries, and has

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also directly influenced changes in the WHO's 2009 *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control*, and the WHO's 2012 *Handbook for Clinical Management of Dengue*. The impact on patients has been faster, safer and more effective resuscitation. The guidelines have simplified management for clinicians and helped to avoid unnecessary interventions.

WHO 2009 Guidelines

WHO guidelines for the management of dengue were first formulated in 1975 and subsequently updated in 1986, 1994, and 1997. While these guidelines recommended immediate treatment with crystalloid solutions for dengue shock, and colloid treatment for persistent shock, a lack of evidence and any significant updates since 1975 led to increasing concern that the recommendations were outdated and ineffective. In particular, there was debate among clinicians regarding the use of crystalloids versus colloids.

OUCRU ended this debate by performing the first three randomised blind trials, investigating the effect of different crystalloid and colloid fluid regimens on the outcome of DSS. This work provided key evidence for the WHO's 2009 Dengue guidelines for the management of DSS.

The following recommendations were published in the 2009 WHO *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control*, directly citing OUCRU's three fluid trials^{2,3,5} as key evidence:

*"The action plan for treating patients with compensated shock is as follows... Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour."*⁷

*"Based on the three randomized controlled trials comparing the different types of fluid resuscitation regime in dengue shock in children, there is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome^{2,3,5}. However, colloids may be the preferred choice if the blood pressure has to be restored urgently..."*⁷

*"Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock."*⁷

Ministry of Health Malaysia 2010 Guidelines

The 2009 WHO updates led a number of local health ministries to revise their own clinical practice guidelines. The Ministry of Health Malaysia and Academy of Medicine Malaysia revised its *Management of Dengue Infection in Adults, Clinical Practice Guidelines* in 2010, directly citing the three key papers from OUCRU⁸.

*"To date, only three randomised controlled trials studying different types of fluid regime in DSS in children aged from 5 to 15 years of age are available^{2,3,5}. Our recommendations are extrapolated from these studies. These studies showed no clear advantage of using any of the colloids over crystalloids in terms of the overall outcome. However, colloids may be preferable as the fluid of choice in patients with intractable shock in the initial resuscitation."*⁸

WHO Handbook for Clinical Management of Dengue 2012

The WHO released a revised *Handbook for Clinical Management of Dengue* in 2012⁹, emphasising the importance of early aggressive resuscitation. OUCRU's three key papers on fluid replacement regimens were cited directly in this handbook⁹.

*"All patients (infants, children and adults) with hypotensive shock should be managed more vigorously... Colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock^{2,3,5}."*⁹

UpToDate Clinical Guidelines 2013

OUCRU Vietnam's three papers on fluid replacement regimens are also cited in *UpToDate*, an evidence-based clinical decision support system, which is authored by physicians to help clinicians make the right decisions at the point of care. Last updated in 2013¹⁰, the following recommendations appear on the *UpToDate* page for the *Prevention and Treatment of Dengue Virus Infection*.

"There has been debate as to whether crystalloids or colloids should be used for volume replacement in critically ill patients. Three randomized, blinded trials have investigated the effect of different fluid regimens on outcome^{2,3,5}. The largest of these studies was a double-blind randomized comparison of three fluids for initial resuscitation of 512 Vietnamese children with dengue shock syndrome⁵.... This trial established that Ringer's lactate was a safe, effective, and inexpensive alternative in initial resuscitation of patients with moderate shock. In patients with severe shock, dextran and starch colloid solutions performed similarly, although dextran was associated with more hypersensitivity reactions."

Sources to corroborate the impact:

7. WHO Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. New Edition 2009. WHO Chapter 2. Page 50 (2009). Available at http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf (Accessed 2013). **WHO Dengue management recommendations, directly citing OUCRU's three fluid trials as key evidence for management procedures.**
8. Ministry of Health, Malaysia and Academy of Medicine, Malaysia. *Management of Dengue Infection in Adults*. (2010) Available at <http://www.moh.gov.my/attachments/5502> (Accessed 2013). **Revised Management of Dengue Infection in Adults, Clinical Practice Guidelines, directly citing the three key papers from OUCRU.**
9. World Health Organisation Handbook for Clinical Management of Dengue. *apps.who.int* (2012). Available at http://apps.who.int/iris/bitstream/10665/76887/1/9789241504713_eng.pdf (Accessed 2013) **WHO revised Handbook for Clinical Management of Dengue emphasising the importance of early aggressive resuscitation. OUCRU's three key papers on fluid replacement regimens are cited.**
10. Rothman, A. L., Srikiatkachorn, A. & Kalayanaroj, S. Prevention and treatment of dengue virus infection (2013) In *UpToDate* Basow, DS (Ed), *UpToDate*, Waltham, MA, 2013. (Accessed 2013) Website accessible to subscribers only (available on request). http://www.uptodate.com/contents/prevention-and-treatment-of-dengue-virus-infection?source=search_result&search=dengue+virus+infection&selectedTitle=2%7E43. **OUCRU's three papers on fluid replacement regimens are cited in UpToDate's guidelines on Dengue management.**