Thomas C. Tsai, M.D., M.P.H.
Ashish K. Jha, M.D., M.P.H.
Harvard School of Public Health
Boston, MA
ajha@hsph.harvard.edu

Since publication of their article, the authors report no further potential conflict of interest.

1. Joynt KE, Jha AK. Characteristics of hospitals receiving penalties under the Hospital Readmissions Reduction Program. JAMA 2013;309:342-3.
2. Joynt KE, Jha AK. Thirty-day readmissions — truth and consequences. N Engl J Med 2012;366:1366-9.
3. Report to the Congress: Medicare and the health care delivery system. Washington, DC: Medicare Payment Advisory Commission, 2013 (http://www.medpac.gov/documents/Jun13_EntireReport.pdf).

DOI: 10.1056/NEJMc1313241

Resuscitation Fluids

TO THE EDITOR: Myburgh and Mythen (Sept. 26 issue)[1] suggest that it is difficult to justify using semisynthetic colloid solutions for fluid resuscitation in critically ill patients. However, although the adverse effects of colloids have been clearly shown, information on potential benefits remains sparse. Colloids are frequently used for resuscitation of patients with dengue shock syndrome, a potentially fatal complication of dengue characterized by substantial plasma leakage and hypovolemic shock.[2,3] At our hospital in Ho Chi Minh City, more than 200 children or young adults are admitted annually with dengue shock syndrome, of whom approximately 30 to 40% require resuscitation with colloid solutions to achieve cardiovascular stability but less than 1% die.[4,5] Given the huge global burden of disease[6] and the limited access to ventilatory support in many dengue-endemic areas, resuscitation with crystalloids alone might well result in increased global morbidity and mortality secondary to fluid overload and respiratory failure. This population of relatively young, previously healthy patients presenting with critical dysfunction of a single organ is markedly different from that seen in most critical care units; could you comment on what type of fluid to use for cases of dengue shock syndrome that have failed to respond to resuscitation with crystalloid solutions?

Trieu T. Huynh, M.D.
V. Chau Nguyen, M.D., Ph.D.
Hospital for Tropical Diseases
Ho Chi Minh City, Vietnam
Bridget A. Wills, M.D., D.M.
Oxford University Clinical Research Unit
Ho Chi Minh City, Vietnam
bwills@oucru.org

No potential conflict of interest relevant to this letter was reported.

1. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369:1243-51.
2. Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. N Engl J Med 2012;366:1423-32.
3. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization, 2009.
4. Wills BA, Dung NM, Loan HT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med 2005;353:877-89.
5. Lam PK, Tam DT, Diet TV, et al. Clinical characteristics of dengue shock syndrome in Vietnamese children: a 10-year prospective study in a single hospital. Clin Infect Dis 2013;57:1577-86.
6. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature 2013;496:504-7.

DOI: 10.1056/NEJMc1313345

TO THE EDITOR: The article on resuscitation fluids omitted mention of critically ill obstetrical patients, a special population at risk because of the increased cardiac output and reduced total peripheral resistance that restrict application of classical principles of fluid resuscitation.[1] Special conditions include postpartum hemorrhage and the aortocaval compression syndrome, preeclampsia, and the HELLP syndrome (hemolysis, elevated liver-enzyme levels, and a low platelet count).[2]

Although no randomized trials have been conducted, a recent review[3] proposes that large-volume crystalloid resuscitation may worsen obstetrical bleeding by increasing intravascular hydrostatic pressure and dislodging the fresh clots at sites of endothelial injury. Other authors suggest early use of blood products and the limiting of traditional fluid resuscitation with large volumes of crystalloid products to restrict further coagulopathy and bleeding.[4] Do the authors have any advice on special approaches to resuscitation in this population?

Nikolaos Vrachnis, M.D.
Dimitrios Zygouris, M.D.
Zoe Iliodromiti, M.D.
University of Athens Medical School
Athens, Greece
nvrachnis@hotmail.com

No potential conflict of interest relevant to this letter was reported.

1. Chesnutt AN. Physiology of normal pregnancy. Crit Care Clin 2004;20:609-15.
2. Nelson-Piercy C, Mackillop L, Williams DJ, Williamson C, de Swiet M, Redman C. Maternal mortality in the UK and the need for obstetric physicians. BMJ 2011;343:d4993.
3. Ickx BE. Fluid and blood transfusion management in obstetrics. Eur J Anaesthesiol 2010;27:1031-5.
4. Pacheco LD, Saade GR, Costantine MM, Clark SL, Hankins GD. The role of massive transfusion protocols in obstetrics. Am J Perinatol 2013;30:1-4.

DOI: 10.1056/NEJMc1313345

TO THE EDITOR: In the article by Myburgh and Mythen on resuscitation fluids, trauma, which is the leading cause of death among young, productive persons, was not addressed.[1] The authors do not mention prehospital settings, where fluid resuscitation is routine.

We have recently introduced plasma as the resuscitation fluid of choice for hemorrhaging trauma patients in the prehospital setting, a use not discussed in the article. This is unlike its use as a supplement to blood-product transfusion in hospital settings.[2] In fact, plasma (i.e., in lyophilized form) as a volume expander meets the requirements suggested by the authors for the "ideal" resuscitation fluid, although of course not without disadvantages. Our initial experience indeed supports it as an improved resuscitation fluid.[3] Could the authors comment on this special case?

Elon Glassberg, M.D., M.H.A.
Roy Nadler, M.D.
Yitshak Kreiss, M.D., M.H.A., M.P.A.

Israel Defense Forces Medical Corps
Ramat Gan, Israel

No potential conflict of interest relevant to this letter was reported.

1. Injuries and Violence Prevention Department. The injury chart book: a graphical overview of the global burden of injuries. Geneva: World Health Organization, 2002.
2. Glassberg E, Nadler R, Rasmussen TE, et al. Point-of-injury use of reconstituted freeze dried plasma as a resuscitative fluid: a special report for prehospital trauma care. J Trauma Acute Care Surg 2013;75:Suppl 2:S111-S114.
3. Glassberg E, Nadler R, Gendler S, et al. Freeze-dried plasma at the point of injury: from concept to doctrine. Shock 2013;40:444-50.

DOI: 10.1056/NEJMc1313345

TO THE EDITOR: In addition to the issues reviewed by Myburgh and Mythen, clinicians should consider the allergenic properties of resuscitation fluids, particularly in the management of anaphylaxis, a common clinical setting in acute medicine in which large volumes of fluids leave the circulation and enter the interstitium. Colloids and hyperosmolar solutions are known to trigger both anaphylactic and anaphylactoid reactions through different mechanisms.[1] Complement activation and activation of the bradykinin cascade as well as IgE-dependent mechanisms have been implicated in reactions induced by gelatin-based or starch-based colloids, and IgE-independent degranulation of mast cells and basophils has been shown on exposure to hyperosmolar solutions.[2,3] Moreover, it was recently reported that sensitization to gelatin contained in red meat represents a risk factor for gelatin colloid allergy, because most patients who are allergic to red meat are sensitized to gelatin, and a subgroup will be clinically allergic to both.[2]

Therefore, World Allergy Organization guidelines recommend infusion of isotonic or normal saline during anaphylaxis, because colloids (mainly gelatins) and hyperosmolar solutions may themselves cause histamine release and worsen the ongoing reaction.[4]

Emanuel Della-Torre, M.D.
Mona-Rita Yacoub, M.D., Ph.D.
Giselda Colombo, M.D.

San Raffaele Hospital
Milan, Italy
dellatorre.emanuel@hsr.it

No potential conflict of interest relevant to this letter was reported.

1. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms: a French multicenter prospective study. Ann Fr Anesth Reanim 1994;13:301-10. (In French.)
2. Mullins RJ, James H, Platts-Mills TA, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-α-1,3-galactose. J Allergy Clin Immunol 2012;129(5):1334.e1-1342.e1.
3. Gullikkson M, Palmberg L, Nilsson G, Ahlstedt S, Kumlin M. Release of prostaglandin D2 and leukotriene C4 in response to hyperosmolar stimulation of mast cells. Allergy 2006;61:1473-9.
4. Simons FE, Ardusso LR, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol 2011;127(3):587.e1-22–593.e1-e22.

DOI: 10.1056/NEJMc1313345

THE AUTHORS REPLY: These letters highlight aspects of resuscitation fluids in specific patient populations for which evidence is limited and

that are unlikely to be studied in randomized, controlled trials.

Huynh et al. raise the role of colloids in children with severe dengue shock syndrome, which is characterized by a transient capillary permeability leak syndrome. There is limited evidence that semisynthetic colloids are more effective than crystalloids in restoring hemodynamic stability.[1] Given the evidence of harm associated with hydroxyethyl starch (HES) solutions in patients with severe sepsis, their role in dengue must be questioned. Although albumin has an unsubstantiated beneficial effect in sepsis,[2] there is no evidence to recommend its use in the dengue shock syndrome. Furthermore, the availability of albumin is usually restricted in regions where dengue is prevalent.

Vrachnis et al. highlight the selection of resuscitation fluids in critically ill obstetrical patients. When hypovolemia is primarily due to severe hemorrhage, resuscitation with fresh blood and blood-component therapy is the mainstay of fluid resuscitation. HES solutions are not recommended for use in pregnancy; for this reason, these patients were excluded from the Crystalloid versus Hydroxyethyl Starch Trial.[3]

Glassberg et al. discuss the role of lyophilized plasma in the early resuscitation of persons with traumatic hemorrhage. The selection of resuscitation fluids under field situations requires pragmatic considerations that primarily relate to the availability and stability of fluids in addition to the efficacy and safety of hemodynamic resuscitation. On the basis of current evidence, crystalloids are the fluids of choice in these patients,[4] and the use of new and emerging fluids such as lyophilized plasma in these patients requires validation in a randomized, controlled trial.

Della-Torre et al. highlight the association between semisynthetic and hyperosmolar solutions and the development of hypersensitivity reactions. These fluids, particularly gelatin solutions,[5] should not be used for the treatment of anaphylaxis, which often involves administration of large volumes of fluid.

The administration of these fluids with excessive volumes of asanguinous fluids may be associated with the development of clinically significant interstitial edema in patients with capillary permeability leak syndromes such as sepsis, dengue, pregnancy, and anaphylaxis. The efficacy and safety of restrictive fluid-resuscitation strategies in these patients as well as in those with trauma or burns require evaluation in randomized, controlled trials to determine both the appropriate type and dose of resuscitation fluids in critically ill patients.

John A. Myburgh, M.B., B.Ch., Ph.D.

University of New South Wales
Sydney, NSW, Australia
jmyburgh@georgeinstitute.org.au

Michael G. Mythen, M.D., M.B., B.S.

University College London
London, United Kingdom

Since publication of their article, Dr. Myburgh reports that his institution (the George Institute for Global Health) has received travel expenses from Baxter Healthcare, and Dr. Mythen reports having received an honorarium from Edwards Lifesciences and an honorarium and accommodation from Deltex Medical and sponsorship for the Acute Dialysis Quality Initiative. No further potential conflict of interest relevant to this letter was reported.

1. Wills BA, Dung NM, Loan HT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med 2005;353:877-89.
2. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 2011;37:86-96.
3. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901-11.
4. American College of Surgeons Committee on Trauma. Advanced trauma life support for doctors. 2012 (http://www.facs.org/trauma/atls/index.html).
5. Ford SA, Kam PC, Baldo BA, Fisher MM. Anaphylactic or anaphylactoid reactions in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2001;15:684-8.

DOI: 10.1056/NEJMc1313345

Survey of Oncologists about Shortages of Cancer Drugs

TO THE EDITOR: It is becoming increasingly difficult for patients with cancer to receive the lifesaving treatments they need. Generic chemotherapy agents that are routinely used for the curative treatment of common and aggressive cancers have been vulnerable to shortages in the United States since 2006.[1] One retrospective analysis confirmed that drug substitutions forced by