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Hydroxyethyl starch solutions and patient harm

Published Online February 9, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30255-1

To the Director General of WHO,

On Jan 26, 2018, the European Medicines Agency (EMA) suspended the marketing authorisations of hydroxyethyl starch (HES) solutions across the European Union.[1] These intravenous solutions are often used for plasma volume replacement following acute blood loss. Evidence from high-quality, investigator-initiated clinical trials in kidney donors, patients with sepsis, and in critically ill patients has shown that HES use is associated with serious adverse effects with no patient benefits.[2] Results from experimental and clinical studies strongly suggest that the toxicity of HES is attributed to tissue storage and coagulopathy.[3] HES-induced coagulopathy increases the risk of bleeding and the need for blood products in patients with sepsis, intensive care patients, and those undergoing major surgery.[4]

The EMA based the decision not only on evidence of harm, but also on the fact that the 2013 decision to restrict the use of HES to non-septic patients with haemorrhagic shock was not being observed in many countries. HES solutions continued to be used in prohibited populations.

We know that WHO guidelines for the prevention and treatment of post-partum haemorrhage[5] recommend that crystalloids are used in preference to colloids for the resuscitation of women with post-partum haemorrhage. Nevertheless, during the WOMAN trial[6] we became aware that many women with post-partum haemorrhage receive colloids and, most often, HES. We are concerned that the suspension of HES use in Europe will lead to intensification of efforts to market HES in low-income and middle-income countries, and that this will mean vulnerable patients, particularly women with obstetric bleeding, will bear the highest burden as a consequence. This is a major global health issue, which the WHO is uniquely positioned to address.

We seek the support of WHO to protect patients by banning the use of HES solutions worldwide.

JB was a member of the first advisory panel (PRAC) convened by the Medicines and Healthcare Products Regulatory Agency to advise the European Medicines Agency on the continued licensing of intravenous hydroxyethyl starch solutions. SF reports non-financial support from Baxter Healthcare, and financial support from Bristol-Myers Squibb, outside the submitted work. JM reports non-financial support from Baxter Healthcare and Fresenius Kabi, grants from CSL Bioplasma and National Health and Medical Research Council, and Fresenius Kabi, outside the submitted work. AP reports grants from CSL Behring, Ferring, and Fresenius Kabi, outside the submitted work. KR is a board member of the Global Sepsis Alliance, International Sepsis Forum, and Sepsis Foundation, and has received consultancy fees from Adrenomed and reimbursement from the International Sepsis Forum for participation in colloquia, and has stocks in InflaRx NV. All other authors declare no competing interests.

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EMA recommendation to suspend HES is hazardous

Published Online February 9, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30254-X

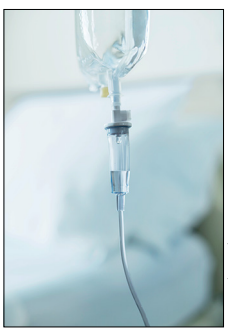
This online publication has been corrected. The corrected version first appeared at thelancet.com on March 8, 2018

In 2013, the European Medicines Agency (EMA) restricted the use of solutions containing hydroxyethyl-starch (HES) in critically ill patients with sepsis, burns, and impaired kidney function while maintaining authorisation for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient.[1] On Jan 12, 2018, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended the suspension of HES from the European market.[2] On Jan 26, the EMA's Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) approved this recommendation by 15 to 13. This decision was based on findings from two drug utilisation studies highlighting that HES solutions are still given to patients with sepsis,[3] and after auditing of stakeholders and the ad-hoc expert committee.

We, attendees of the EMA ad-hoc expert meeting held in London on Dec 18, 2017, recommended to the PRAC against suspending HES. This was because, firstly, in 2013, results from an international, industry-independent trial[4] (involving 2857 patients with acute hypovolaemia in intensive care) found no difference in 28-day mortality between crystalloids and colloids (relative risk [RR] 0·96, 95% CI 0·88 to 1·04; p=0·26), significantly lower 90-day mortality in the colloids group (0·92, 0·86 to 0·99; p=0·03), and more vasopressor-free days (mean difference 1·04, 95% CI −0·04 to 2·10; p=0·03) and ventilator-free days (1·10, 0·14 to 2·06; p=0·01) by day 28. The study found no evidence that colloids increased risk of acute kidney injury (AKI) or any other serious adverse event. Analyses of long-term outcomes from the CHEST trial[5] reported no difference in mortality between patients who received HES and patients who received saline at 6 and 24 months, as well as a comparable mean number of quality-adjusted life-years gained. Results from a systematic review[6] of 32 trials and 16 647 patients showed that administration of colloids did not increase mortality in critically ill, trauma, and surgical patients (odds ratio [OR] 0·99, 95% CI 0·92 to 1·06). In surgical patients, colloids did not increase the risk of AKI (p=0·43) or renal replacement therapy (p=0·66). In trauma patients, the OR of AKI was 0·46 (95% CI 0·23 to 0·92) in favour of colloids. Thus, there is no evidence to support suspending HES. Secondly, three ongoing trials (EudraCT numbers 2016-002176-27, 2016-002-163-30, and 2014-005575-84) are comparing HES to crystalloids (two upon request by the PRAC and one funded by the French Agency for Medicines and Health Products), and will inform practice in trauma and in patients having abdominal surgery. Thirdly, the PRAC has not considered our warning that suspending HES might result in serious unmet medical needs when crystalloids are not sufficient, which is a very common situation in acutely ill and perioperative patients. The clinical and economic effects of this recommendation have not been provided. There are insufficient data on balanced crystalloids, gelatins, dextrans, or albumins to promote their use as alternate fluid therapy, particularly in surgical, obstetrical, and trauma patients.[6] HES solutions are also widely used in combination with albumin as plasma replacement during plasmapheresis.[7] Their withdrawal from the European market will increase the use of albumin—a product derived from pooled human plasma—and lead to cost issues and shortage of albumin in many countries. Fourthly, the retrospective drug utilisation studies have serious limitations—eg, absence of appropriate answers when filling in the electronic forms, forcing incorrect answers and erroneous classifications of non-adherence. Notably, results from the two drug utilisation studies already mentioned show that adherence to recommended daily treatment dose and duration was satisfactory, and actual doses and durations were substantially lower than in studies showing increased AKI and mortality.[6] Thus, we recommended reappraising existing drug utilisation studies and launching new studies that are better designed.

Finally, the PRAC has not considered the following recommendations to enhance consumers' adherence: appending the statement "crystalloids alone are not considered sufficient" with "in patients treated with crystalloids", clarifying the degree of hypovolaemia as acute blood loss of at least 500 mL, including an additional warning on primary containers (such as do not use in sepsis or in critically ill patients), distributing with every bag of HES a chart to fill in and a patient-completed medication form, and a registry prospectively collecting safety data. For these reasons, we strongly believe that the EMA recommendation to suspend HES is not scientifically grounded and is potentially hazardous to patients.

DA was the primary investigator of the CRYSTAL trial, which was funded by the French Ministry of Health. TF-B reports speaker fees from MSD, outside the submitted work. TS reports personal fees from Masimo and Edwards, outside the submitted work; is chair of Scientific Subcommittee 14 (Monitoring, Equipment and Ultrasound) of the European Society of Anaesthesiologists; and is chair of the Cardiovascular Dynamics section of the European Society of Intensive Care Medicine. MK reports lecture fees from the Finnish Red Cross Blood Service. CZ declares no competing interests.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Universal health coverage is needed to deliver NCD control

President Vázquez and Tedros Ghebreyesus (Sept 23, p 1473)[1] rightly highlight the urgent global need for fiscal, trade, environmental, and political actions against non-communicable diseases (NCDs). Sania Nishtar suggests that scope exists for a new NCD agency because such diseases "have exploded around the world".[2] However, hyperbole around NCDs is unhelpful. Premature NCD mortality (ie, mortality in individuals aged 30–69 years) is estimated to be decreasing across all sociodemographic quintiles (figure). Simultaneously, middle and late adult age groups are facing rapid demographic expansion worldwide, partly due to health and development successes that are extending life expectancy. The biological risk of NCDs increases with age. Therefore, as populations age, the prevalence of NCDs increases, and subsequently demand for treatment and the number of NCD-related deaths increase.

Global successes against infectious and external causes of death postpone eventual mortality into age groups in which NCDs are the primary risk. Therefore, because everyone will die of something eventually, and the individual chance of an NCD causing death increases with age, the number of NCD-related deaths is likely to increase. Thus, NCDs will never be eradicated. However, the WHO 25×25 strategy[4] and Sustainable Development Goal 3.4[5] wisely target premature NCD mortality. Decreases in premature NCD mortality probably reflect decreased exposure to risks, improved disease management, and healthier lifestyles. NCD risk factors need to be reduced further and improvements in clinical care and health promotion are needed to successfully decrease the burden of NCDs. One consequence of galvanising political will for universal health coverage—as championed by Tedros and WHO—will be improved action against NCDs. Establishing a separate NCD agency would add confusion to this central aim.

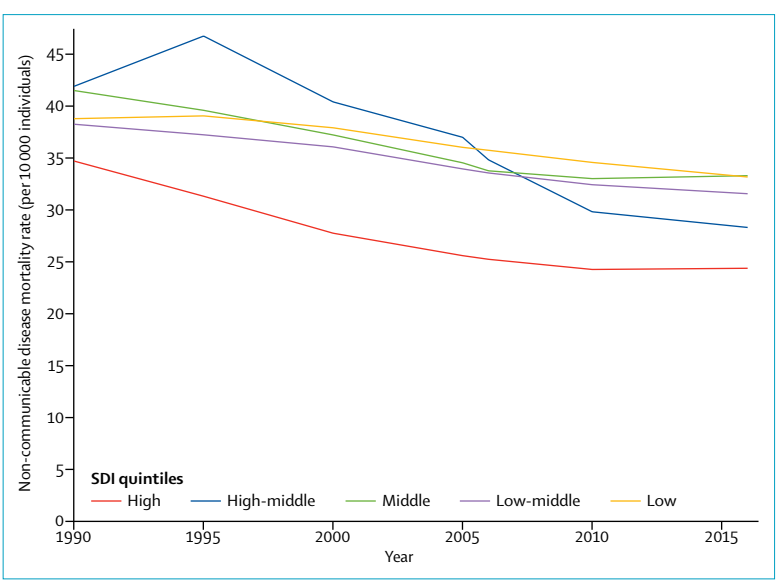

Figure: **Global Burden of Disease[3] estimates of mortality due to non-communicable diseases in the 30–69 year age group between 1990 and 2016**
SDI=Socio-Demographic Index.

I declare no competing interests.

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Women helping women prevent HIV in resource-limited settings

Almost a third of the total HIV-infected population in Nepal are women, and this female population is the fastest growing HIV-infected population in the rural areas of Nepal.[1] Along with illiteracy and poverty, gender inequality and an inability to successfully negotiate safer sex with their partners have been noted as reasons for the increase in the burden of HIV among women.[2] Realising that they are at risk of HIV infection because of sociocultural factors, women in rural areas of Nepal are helping to prevent HIV at the local level; however, their role in HIV prevention is often unrecognised. In this Correspondence, I want to highlight how local women, individually or in groups, are helping each other to prevent HIV in rural areas of Nepal.

Firstly, across Nepal women have formed non-partisan groups to meet every month and discuss the empowerment and mobilisation of women and the alleviation of poverty.[3] These groups also discuss and learn