

The medical team members may be frustrated or believe they've exhausted the workup studies, and they may prefer not to order any more. They may not be too keen on continuing the same antibiotics. The ICU team hungers for something new and preferably simple. As I review the differential diagnosis, with disclaimers as to why any given diagnosis does or does not adequately explain the fever, I get a feeling of *déjà vu*. The team has heard these ruminations from me and my colleagues many times, and I suspect that by now the discussion is minimally compelling or interesting academically.

This is not the multidimensional "great case" that FUOs were once advertised to be — the cases presented on chief-of-service rounds in which an expert diagnostician pontificates about the differential diagnosis of rare

or subtle disease complexes and their presentations. Given the nature of the illness in many of these patients, the conferences are more likely to be family conferences that include plans for palliative care. If the old FUOs were sometimes exhilarating, the FTMOs can be debilitating. Although some patients will recover and be discharged to lead full and active lives, many will either die or be sent to a long-term care facility.

We debate whether using antibiotics in apparently futile situations is ethical. After all, we may "create" some extremely resistant bacteria in one patient that could be transmitted to others. Alternatively, antibiotics may be life-saving. There are few directives, ethical guidelines, or clinical pathways to follow in these cases. As I mull over the options, I am disheartened by the knowledge that

whether I use or withdraw antibiotics (asking the team to observe the patient closely) or request more testing, I may simply be deferring the tough decisions for another day.

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From the Division of Infectious Diseases and Immunology, New York University School of Medicine, New York.

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## Should Blood Be an Essential Medicine?

Harvey G. Klein, M.D.

According to the World Health Organization (WHO), approximately 92 million units of blood are collected worldwide each year. Given that transfusions are generally credited with saving millions of lives, it may surprise clinicians to know that blood and blood components are not included on the WHO Model List of Essential Medicines.

The Model List, established in 1977, originally included about 200 active substances. It was meant to guide countries in providing access to cost-effective medicines that are vital for public health.<sup>1</sup> The list is revised every 2 years by a WHO expert committee. Medicines are designated as essential on the basis of their effi-

cacy and safety, availability, ease of use in various settings, comparative cost-effectiveness, and public health need. In many countries, the list forms the basis of national drug policies. Governments and health ministries often refer to it when making decisions regarding resource allocation and health care spending. The list does not include all efficacious medicines, the latest medicines, or even all medicines needed in a country. Rather, it helps to define the minimum medicine needs for a basic health system.

Although some protein concentrates (factors VIII and IX and immunoglobulins) are listed, no labile blood components are on the Model List. The reason for

their absence is unclear. Certainly, the lengthy, exhaustive process for applying for a listing can be discouraging; each component requires a separate detailed, complex application. Most medicines are proposed by manufacturers with a commercial interest in having their products listed. There has been no similar advocacy for blood components that are collected and prepared by not-for-profit organizations, until now.

There are compelling reasons to add whole blood and red-cell concentrates to the list. Blood transfusion originated as a medical practice requiring either surgical intervention to join donor to recipient or a licensed practitioner to draw and immediately infuse

blood. The development of anti-coagulant preservative solutions early in the 20th century and, later, sterile bottles and plastic blood bags permitted blood to be stored, which effectively distinguished the product that must meet defined standards from the medical practice of transfusion — a distinction that's critical to understanding why blood components are treated and regulated as drugs.

Is blood an essential medicine? Despite the dearth of randomized clinical trials, blood is clearly essential. Red-cell transfusion is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply. Despite well-publicized infectious and immunologic adverse events, red-cell transfusion has a therapeutic index exceeding that of many common medications.<sup>2</sup> In developed countries, most surgical procedures would not be undertaken without the availability of blood. The majority of units are transfused to support surgery, chemotherapy, stem-cell transplantation, and management of inherited disorders such as thalassemias and sickling syndromes. Blood is used differently in the developing world, where for logistic reasons, whole blood may still be the preparation of choice,<sup>3</sup> but a reliable supply of safe blood is crucial. Numerous deaths resulting from trauma, hemorrhage during childbirth, and the hemolytic anemia of childhood malaria are preventable. Too often, a reliable source of safe blood is lacking because of inadequate resources, infrastructure, oversight, or national will.

The question of whether blood is a medicine seems more contentious. Blood is certainly a substance used to treat, mitigate, or prevent disease. Whereas whole

blood and red cells differ from small-molecule pharmaceuticals in their unit-to-unit heterogeneity (batch variability), blood components are biologics that share many attributes with those medicines. Technical and regulatory developments during the past half-century have led to the manufacture of blood components for purity, potency, and safety. Blood donors are qualified as suppliers of raw material by rigorous selection and testing standards. Units undergo in-process quarantine; quality control to ensure that reagents, equipment, and methods perform as expected; temperature monitoring; batch release after suitability determination; and labeling for identity, content, expiration date, and intended use. Once issued, blood components are subject to standards for traceability, and many countries have developed hemovigilance systems that parallel pharmacovigilance systems.

Like other medicines, blood has its defined medical indications and recognized adverse effects and may be administered only by doctor's order or prescription. International product standards for manufacture of blood components underscore the need for supplier qualification, trained personnel, quality-system essentials, and validation of equipment, facilities, and processes.<sup>4,5</sup> Common to all blood-component regulations are requirements to assure that blood components meet product standards through controls on manufacturing, and the WHO recently published guidance for Good Manufacturing Practices for blood establishments.

In many jurisdictions, blood is already regulated as a drug. In the United States, blood and other biologics became subject to regulation as medicines under the

Food, Drug, and Cosmetic Act in 1938 and subject to licensing in 1944. In Canada and Germany, blood and blood components are regulated as biologic medicines; in Japan, they are regulated under the Pharmaceutical Affairs Law; and in Australia, blood-component manufacturers are licensed to ensure that products meet Council of Europe standards. Blood is listed in several national formularies, including the U.S. Pharmacopeia.

Adding whole blood and red cells to the Model List of Essential Medicines would boost awareness of the global need for blood and of blood's role in protecting the public health. Listing would underscore governments' responsibility for sustainable funding of a safe, adequate, accessible blood supply. It would call attention to the importance of appropriate regulatory oversight of blood collection, processing, testing, and distribution to ensure safety and quality, as well as the need for adherence to guidelines for clinical use. Finally, listing would emphasize the need to ensure that blood is cost-effective and affordable. The last three benefits are particularly relevant for low- and middle-income countries.

Concern has been expressed that including blood on the Model List might erode principles related to volunteerism and altruism and increase the cost of blood, but I don't believe that would happen. Designating blood as a medicine should neither introduce blood sales and donor payment in countries where they don't exist nor accelerate commercialization of blood in countries where they do. On the contrary, listing on a WHO-sponsored document should emphasize the desirability of voluntary, non-remunerated blood donation and the not-for-profit

status of blood-collecting organizations — policies that the WHO endorses and that were stressed again in a 2011 World Health Assembly resolution. These principles can also be established within a country through legislation or policy and can be achieved within a biologics manufacturing environment.

Additional concerns are that treating blood as a medication might increase costs and interfere with the function of blood systems that have grown up outside the oversight of health ministries and other regulatory agencies. The immediate direct costs of introducing regulated manufacturing systems are high, but indirect savings from improved patient outcomes and donor safety, though harder to calculate, are substantial. Furthermore, the manufacture of blood components that meet set quality standards might allow costs to be recovered through provision of separated plasma suitable for fractionation.

Finally, national investment in and oversight of blood systems, far from being disruptive, have led to improved availability and quality of blood for transfusion.

The Expert Committee on Selection and Use of Essential Medicines will hold its biennial meeting in April 2013. An application to include whole blood and red cells on the next Model List has been submitted and posted on the WHO website ([www.who.int/selection\\_medicines/committees/expert/19/en/index.html](http://www.who.int/selection_medicines/committees/expert/19/en/index.html)) for public comment. Patient advocacy groups, professional associations, national blood services, regulatory agencies, and others should review and comment on this application. Adding blood to the Model List would encourage governments to invest in infrastructure and the governance of blood systems and increase their efforts in blood-donor recruitment and blood collection, which should lead to the provision of safe and cost-effective therapy, prevent

deaths and disabilities from blood shortages, and improve health globally.

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From the Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, MD.

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## The Patient Experience and Health Outcomes

Matthew P. Manary, M.S.E., William Boulding, Ph.D., Richard Staelin, Ph.D., and Seth W. Glickman, M.D., M.B.A.

Do patients' reports of their health care experiences reflect the quality of care? Despite the increasing role of such measures in research and policy, there's no consensus regarding their legitimacy in quality assessment. Indeed, as physician and hospital compensation becomes increasingly tied to patient feedback, health care providers and academics are raising strong objections to the use of patient-experience surveys. These views are fueled by studies indicating that patient-experience measures at best have no relation to the quality of delivered care and at

worst are associated with poorer patient outcomes. Conversely, other studies have found that better patient experiences — even more than adherence to clinical guidelines — are associated with better outcomes. Which conclusion is correct? We believe that when designed and administered appropriately, patient-experience surveys provide robust measures of quality, and our efforts to assess patient experiences should be redoubled.

Critics express three major concerns about patient-reported measures, particularly those assessing "patient satisfaction." First,

they argue that patient feedback is not credible because patients lack formal medical training. They believe that patient-satisfaction measures actually capture some aspect of "happiness," which is easily influenced by factors unrelated to care. Articles in the popular press have even suggested that employing singing, costumed greeters would raise patient-experience scores. However, Jha and colleagues found that overall satisfaction with care is positively correlated with clinical adherence to treatment guidelines.<sup>1</sup> One explanation for this correlation is that patients base their satisfac-