

Balancing evidence and public opinion in health technology assessments: The case of leukoreduction

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Leukoreduction, filtering white blood cells from transfusion blood, effectively avoids leukocyte-related complications of blood transfusion. The technology has proven its relative cost-effectiveness for specific patient populations. With the advent of variant Creutzfeldt–Jakob disease, a transmittable spongiform encephalopathy caused by mad cow disease (bovine spongiform encephalopathy), the hard hit United Kingdom introduced universal leukoreduction for all patients as a precaution for transmission of prions in 1999. This costly policy was followed by many other countries, in the absence of much evidence of an actual health problem or of a more than presumed effectiveness of leukoreduction in preventing prion transmission. The core problem proved to be legal. The blood banks are legally accountable for blood safety. This accountability is absolute, based on avoidance of all possible risks, regardless of costs. This strategy leads to inefficiencies in health care: (i) blood safety management is guided by available rather than cost-effective technology, and (ii) private insurance premiums for civil liability are sharply increasing, while they are in no way related to the expected returns and the high and increasing blood safety. A rational safety policy is to be optimal, taking into account costs and effects of the safety procedures. This issue will need an open discussion with the general public of the real risks and a clear and unambiguous definition of proportionality in the precautionary principle, based on the European law.

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Leukoreduction, leukodepletion, leukofiltration, or deleukocytation are all synonyms of a technology by which leukocytes (white blood cells) are removed from donated blood. Leukoreduction is performed to avoid complications associated with blood transfusion (4). Leukocytes are allogeneic immunoreactive cells and have no clinical benefit for the recipient. Leukoreduction is proven effective in several patient populations, such as cytomegalovirus-seronegative patients (5;7;8;12;22), immunocompromised patients (6),

patients with human leukocyte antigen (HLA) immunization (10;23;25), patients with hematologic or hemato-oncologic affections who require frequent transfusions, patients with congenital or acquired hematologic anemia, and patients who have suffered from febrile nonhemolytic transfusion reactions (19). In these patient groups, leukoreduction is also cost-effective relative to no leukoreduction (17).

Extension of leukoreduction to all patient populations, that is, universal leukoreduction, recently has been introduced in many European countries. The main reason for this introduction was the much feared transmission of variant Creutzfeldt–Jakob (vCJD) disease by blood transfusion. vCJD is a human transmittable spongiform encephalopathy, a devastating and invariably fatal disease, caused by

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infectious proteins (prions). The causative prion is the same as the one that causes bovine spongiform encephalopathy (BSE) or mad cow disease (11). The decision for universal leukoreduction of all blood products was first taken in the United Kingdom in 1999. The rationale was reasonable precaution, facing large uncertainties about a potentially devastating epidemic with a likely possibility of transfusion transmissions. This policy was taken over by many countries between 2000 and 2003, while the vCJD epidemic in the United Kingdom developed without taking massive proportions. In the rest of the world, only France observed more than two cases.

In this study, we scrutinize the justification for implementing universal leukoreduction in countries outside the United Kingdom, with special attention to the case of Belgium. We critically review the medical and economic rationale for universal leukoreduction, their relative importance in the decision making, and try to identify potential areas for improvement in the current blood transfusion safety policy.

BLOOD SAFETY

In countries where blood is donated by unpaid voluntary donors, as in Belgium, blood can be considered very safe, thanks to the selection based on good health and altruistic behavior. The risks of viral transmission by means of blood transfusion vary from 1 in 200,000 for hepatitis B virus to 1 in 1 million for hepatitis C virus and 1 in several million for human immunodeficiency virus (20;21). Mortality caused by blood-transmitted viral infections is even lower, on the order of one in several million blood units. The majority of the adverse events related to blood transfusion result from administrative errors (15). Between 1 in 12,000 and 1 in 20,000 adverse events have been reported to be due to avoidable administrative errors in the United States and the Netherlands, respectively (1). This rate represents approximately 70 percent of all adverse events related to blood transfusion.

Medical Advantages of Leukoreduction

Leukoreduction has proven to be highly effective in the prevention of adverse blood transfusion reactions in selected patient populations, such as patients with recurrent nonhemolytic febrile transfusion reactions, HLA alloimmunization (10;25), platelet refractoriness (24), and cytomegalovirus (12;22). Weak and controversial evidence exists on the benefits of leukoreduction for surgical patients; leukoreduction may lower the rate of postoperative infections in this population (2,24,26).

Universal leukoreduction has the theoretical advantage that it may also avoid the transmission of unknown or known (but for which no testing is currently performed) leukocyte-associated viruses. The clinical relevance of this risk reduction remains debatable. The United Kingdom decided

to implement universal leukoreduction to reduce the risk of transfusion-transmitted vCJD (14). The introduction of a universal leukoreduction policy in the United Kingdom was reasonable, given the threatening risk suggested by the BSE epidemic in the 1990s. In the United Kingdom, the epidemic of BSE took much larger proportions than outside the United Kingdom. Until April 2004, 151 cases of vCJD were identified, of which 141 were in the United Kingdom (13). France has known six cases (and a seventh suspect case) over the past 10 years, or 1 in 10 million people. Belgium as of yet has not seen one case of vCJD. Although it is uncertain whether leukoreduction is effective in the prevention of vCJD by means of blood transfusion in human beings, animal models have shown that the TSE load in the blood is lowered by 42 percent after leukoreduction (9). From a medical point of view, if there are arguments in favor of universal leukoreduction outside the United Kingdom, at least that argument cannot be the prevention of vCJD transmission, a very unlikely event outside the United Kingdom.

ECONOMICS OF LEUKOREDUCTION

Unit Costs of Leukoreduction

The incremental cost of leukoreduction relative to no leukoreduction is approximately €25 per unit (US: €21–€29; UK: €26; NL: €23) (3;16;18). This is also the difference in reimbursement for a unit of leukoreduced and a unit of nonleukoreduced blood in Belgium. The unit cost of leukoreduction may still decrease in the future, for example, through industrial competition for cheaper filters or economies of scale at larger output volumes.

Aggregate and Net Costs of Universal Leukoreduction

Perspective of the Blood Banks. In 2003, approximately 35 percent of the red blood cell concentrates and 100 percent of the platelets were leukoreduced in Belgium, mainly for patients for which leukoreduction has proven clinical benefits. Universal leukoreduction would suggest a budget increase for the blood banks of approximately €7.71 million per year to cover the costs.

However, universal leukoreduction also induces benefits of a very different kind to the blood banks. Under the current law, blood banks are accountable for blood products. As a consequence, they risk huge damages whenever patients experience transfusion-related complications. Blood banks are generally insured against this risk. The insurance premiums, however, are often not in proportion to the efforts blood banks make to increase blood safety and quality. The societal clamor for zero risk may be a more important determinant for the level of the premium than the objective risk. Between 1998 and 2004, the insurance premiums paid by the Belgian blood banks rose 228 percent. The sharpest increase came in 2000, not by chance the year after the introduction of

universal leukoreduction in the United Kingdom. Belgian blood banks, who are insured by a British insurance company, saw their insurance premiums rise, although their objective risk had not changed.

Universal leukoreduction might reverse this upward trend in insurance premiums, although this is highly speculative: the price setting of insurance premiums is not driven by objective elements. Universal leukoreduction may also induce savings in logistics: simplified stock control, standardization of procedures, learning by experience, and industrial competition for cheaper filters will reduce long-term average costs.

PERSPECTIVE OF THE HEALTHCARE PAYER

From the perspective of the Belgian healthcare payer, the incremental direct cost of universal leukoreduction relative to selective leukoreduction would be €7.71 million per year. This amount excludes the potential direct savings generated by the avoidance of leukocyte-related complications in patients who do not receive leukoreduced blood in a selective leukoreduction policy. It is impossible to estimate these direct savings without speculating far beyond available evidence of the clinical effectiveness in populations at low risk of leukocyte-associated blood transfusion complications.

A second potential source of savings of universal leukoreduction is the reduction in financial resources flowing to private insurers in the form of insurance premiums, although this is, as explained earlier, still rather speculative. Belgian blood banks are financed from the federal healthcare budget per unit of blood concentrate. From their budget, the blood banks have to pay the insurance premiums for civil liability. Part of these premiums return to the society in the form of damages, of which a small proportion returns to the healthcare sector for the treatment of the adverse blood transfusion reactions. A final part is absorbed by the insurance company in the form of profits. As there is no relationship between the insurance premiums and the expected healthcare costs of transfusion-related adverse reactions—premiums are more guided by the public perception of risk than by objective risk—a large sum is flowing away from the healthcare system. These resources are lost to the healthcare sector and are no longer available for the improvement of health.

The inefficient use of scarce health care resources is mediated by the current regulations. The European Directive 2002/98/EC that sets the standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components states that “In order to safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures during their (blood and blood components) collection, processing, distribution, and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elim-

ination of transfusion transmissible pathogenic agents.” The wording “all precautionary measures” suggests that blood banks should abandon efficient use of scarce resources and strive for maximal blood safety. It also opens the door for opportunistic interpretation and legal charges. The potential danger is that blood safety management will become more and more guided by available technology rather than by objective need and efficiency.

SOCIETAL PERSPECTIVE

The value for money of universal leukoreduction from the societal perspective depends on its costs and its effects relative to selective leukoreduction. Although leukoreduced blood is of better quality than nonleukoreduced blood, generalization of leukoreduction to patient groups at low risk has not proven its effectiveness. The incremental effectiveness will be low anyway, as the baseline risks are already low. As for the societal costs, universal leukoreduction generates both additional costs related to the procedure and savings related to the more efficient use of resources at the blood banks.

For blood safety policy, the public perception of blood transfusion risks may be more important than the objective cost-effectiveness of blood safety interventions. A socially acceptable and economically justified blood safety policy should take both the objective risks and the social perception of risks into account. A short-sighted perspective, in which risk reduction is pursued only for the sake of stabilizing insurance premiums or for reducing public fear, is insufficient. Economic evaluations on this matter run the risk of being isolated and neglected in policy making because their importance does not outweigh the importance of the exaggerated public fear. To avoid this problem, frank and open discussion of uncertainty and policy implications is crucial. Expert knowledge and lay knowledge need to be integrated to assess what uncertainty levels and opportunity costs are considered socially acceptable. This strategy means that the general public should be actively involved in the decision-making process about blood safety. Such involvement implies an adequate communication of the true risks of blood transfusion but also the consequences of any decisions, both in terms of clinical effects and in terms of opportunity costs within the healthcare sector. This concept supports the development of policies that take into account socially acceptable levels of risk as well as opportunity costs.

CONCLUSION

From the perspective of the blood banks, there are clear economic arguments in favor of universal leukoreduction: reduction in legal charges, potential reduction in or stabilization of insurance premiums for civil liability, more standardization of procedures, and simplified logistics. From the perspective of the healthcare payer, universal leukoreduction suggests an incremental cost at unknown and likely low benefits. The

insurance premiums rise not in any reasonable proportion to the increasing blood safety. Most of these resources seem wasted to the healthcare sector.

The general public expects maximal blood safety, reflected in the European Directive 2002/98/EC. This expectation is irrational, certainly given the already extremely high blood safety, but the public opinion cannot be disregarded in decisions about blood transfusion safety. Blood safety is best served by voluntary unpaid donors, and their trust is to be maintained.

There are few medical or economic arguments for the introduction of universal leukoreduction instead of selective leukoreduction in Belgium. The central problem is legal accountability, underpinned by a societal desire for zero risk. This irrational demand is matched by the offer of the industry, driving up the costs of blood, given for free by voluntary blood donors. If the accessibility of blood transfusions decreases, the voluntary blood donor might turn away, endangering blood safety much more. We will need to improve communication with the public, explaining how inefficiency gains few benefits in one sector (here blood safety) but wastes large opportunities elsewhere. The law should be changed accordingly, to encourage a precautionary policy based on proportionality and reasonableness. Blood banks should be held accountable for optimal blood safety, not for all risks possible and imaginable.

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