Safety in transfusion medicine

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Introduction

The transfusion of blood is an allogeneic transplant and, as such, is a medical procedure that carries intrinsic, irremovable components of risk:

- first and foremost, the biological risk, related to the genetic difference of the blood transfused;
- the risk of transmitting diseases;
- an intrinsic therapeutic risk, related to possible adverse events deriving from an interaction between the medical intervention and the individual's organic equilibrium;
- the risk of medical errors due to a wrong decision;
- the risk of technical and/or administrative errors due to the lack or mistaken application of procedural rules.

The process leading to a transfusion is long, complex and divided into many stages. Although, according to Italian legislation, the Transfusion Service is responsible for the whole process, numerous operative groups are involved and the parts of the process must, therefore, by integrated and co-ordinated in an organisation that establishes shared procedures, planned controls and continuous qualitative improvements.

Risk prevention in this biological and organisational setting, which, in a modern health care system involves about 1,000 more interventions than organ transplantation, is not simple.

In a process of risk assessment, different periods of potential risk and different factors can be identified in relation to the various stages of the transfusion process[1]:

1) risks of transmissible diseases from the donor (presence of viruses, bacteria, parasites in the donor's blood; presence of immunological disorders; presence of neoplastic diseases; presence of potentially pathogenic foreign substances);
2) risks related to the collection of the blood (possible bacterial contamination due to inadequate disinfection of the sampling site; possible administrative-type errors in unequivocal identification of the donor/exchange of biological samples);
3) risks related to the processing/storage of the blood (non-sterile processing, inappropriate storage, labelling errors);
4) risks related to the process of biological qualification (pre-analytic, analytic and post-analytic errors; intrinsic limitations of the methods used: sensitivity/ window period);
5) risks related to requests/assignation of the blood (administrative-type errors in identifying the patient and labelling the samples; medical errors in terms of therapeutic appropriateness of the transfusion);
6) risks associated with the unequivocal identification of the patient at the time of the transfusion;
7) risks from immunological interactions between the recipient and transfused unit due to donor-related factors (presence of undetectable antibodies against antigens in the recipient or the presence of particular genetic profiles predisposing to graft-versus-host disease reactions) or recipient-related factors (immunosuppression or the presence of antibodies against antigens on the transfused blood cells);
8) risks related to the patient's clinical condition (presence of heart failure, presence of autoimmune diseases).

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How to measure transfusion risk

It is difficult to measure transfusion risks. It is practically impossible to carry out prospective studies, since the relatively low probability of harmful events occurring in relation to transfusions means that a huge number of observations would be necessary in order to acquire significant data. It is equally unfeasible to use retrospective studies because of the inevitable impossibility of comparing data on events collected and recorded with different methods.

Currently the soundest method for assessing risk in this field is the use of haemovigilance systems based on *clinical case reporting*[2-4]. Such systems do, however, have clear limitations:

- first, because the presence of a risk does not necessarily mean that the recipient experiences a harmful or unexpected event;
- secondly, because the observation and the detection of events, according to organised and standardised models, presupposes very high levels of accuracy;
- thirdly, because when an unfavourable effect occurs some time after the transfusion, it can be difficult to detect and it can be even harder to determine the relation between the adverse event and the transfusion;
- lastly, because the systems can differ significantly from both a legal point of view (obligatory vs. voluntary) and a clinical point of view (stages of the process that are monitored: collection-transfusion vs. only transfusion; clinical severity of the events recorded: minor events vs. clinically relevant events; type of hazard recorded: real danger vs. hypothetical danger - near miss).

On this background, it has basically been necessary to renounce direct methods of measurement for some specific risks, falling back on indirect measurements estimated on the basis of epidemiological characteristics of a given population. For example, in order to assess the risk of transmission of viral infections, data on the prevalence and incidence of the most significant markers of infections in donors' blood are generally used to estimate, through complex mathematical models, the probability that a unit of blood containing a particular infectious agent is considered suitable for transfusional purposes despite all the precautions built into the validation procedures[5-7].

Notwithstanding their limitations, the haemovigilance systems have been found to be precious instruments both for measuring overall transfusion risk and for analysing the individual risks, demonstrating a sufficiently clear hierarchy of risk and, in this way, laying the basis for a global strategy of risk management.

For example, some significant information can be extracted easily from the last two annual reports available from the haemovigilance system in the United Kindgom[8,9]. In 2004 and 2005 there were between 500 and 600 notifications of unfavourable events that were potentially relevant from a clinical point of view; this is a frequency of about 1 event every 10,000 blood components transfused. In the same years there were, respectively, four and five deaths definitely caused by transfusion, with the frequency being about 1 death per million blood components transfused. As far as concerns the 500 to 600 notified adverse events, more than 80% were related to errors of various types that led to the transfusion of a blood component that should not have been transfused to that particular patient; on the other hand, just under 20% of the adverse events were related to immunological problems. Fewer than 0.2% of the notified adverse events involved bacterial contamination of the blood component.

With regards to the assessment of risk of transmission of viral diseases, using the data on prevalence and incidence of the most significant markers of infections in Italian blood donors, the residual transfusion risk can be estimated to be one infection per 1.4×10^6 units for human immunodeficiency virus (HIV), one per 0.2×10^6 units for hepatitis C virus (HCV), and one per 1.6×10^6 units for hepatitis B virus (HBV)[10].

On the basis of this documented evidence it does, therefore, seem very reasonable to agree with those who consider that transfusion of blood components is a safe medical procedure and that the lion's share of the risks associated with this procedure is due to errors, whether of a technical or administrative type. Besides errors, immunological risks are still important. Problems related to bacterial contamination of blood products seem to be less relevant, although worthy of note. The risk related to possible transmission of viral infections now seems to be almost negligible.

Risk management: real risk and perceived risk

As a result of this risk assessment, it would seem that risk management should be focused primarily on

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strategies to minimise errors and secondarily on the prevention of immunological reactions, while it could be limited, with regards to the problems of infections, to maintaining the measures of control currently in use and to careful monitoring of possible new pathogens. This order of priority has not, however, been followed at either a national or international level over the last few years.

The problem of risk assessment in Transfusion Medicine is not as straightforward as it is in other areas of health care: various factors, the most significant being past experience, have led to perceived risk being attributed a very important role, and sometimes a predominant one, compared to real risk (or, at least, the risk measured with a scientific method), in the transfusion sector.

Over the last 30 years, numerous research articles have been published on the subject of perceived risk in the context of health care: the overwhelming majority of authors have shown that the risk perceived by society is very poorly or not at all related to probabilities calculated using data derived from evidence, but is, rather, based on a multifactorial cognitive set in which feelings, reason, media influence, trust in institutions, and many other psychological elements are inextricably linked[11].

As far as concerns Transfusion Medicine specifically, it is clear and well justified that the so-called scandal of infected blood and the transfusion-related transmission of HIV and HCV to thousands of patients throughout the world in the 1980s have left scars in the conscience of international civil society and have, consequently, severely influenced the perception of risks related to the transfusion of blood.

The most recent studies on this subject[12-16] are all concordant in emphasising that the fear of catching HIV or, at any rate, a severe infection, is still the main worry of people who must receive a transfusion; that the risk of catching an infection through a transfusion is greatly overestimated; and that, nevertheless, there is still much concern about the safety of transfusions, despite the awareness of the great progress made in this field.

This is demonstration of the peculiarity of Transfusion Medicine and of the paradox underlying the process of risk assessment of transfusions, which condition management strategies: transfusion therapy is safe –it is safer than it has even been –and yet the conventional notions of safety in health care and the parameters that usually form the basis for acceptability of clinical risk are not considered acceptable for Transfusion Medicine. There is a very strong demand for *absolute* safety in this field[17].

In recent years the impact of perceived risk has been further increased by the appearance of new, re-emergent and migrant pathogens which, although only marginally affecting the safety of blood products, have nevertheless caused the spread of new, worrying diseases, such as the variant form of spongiform encephalopathy (mad cow disease), SARS, west Nile virus, avian 'flu, and Chikungunya fever. This has renewed the public's opinion that pathogens, previously unknown, or considered harmless or, at any rate, limited to only very distant parts of the planet, could be spread rapidly and dramatically through transfusions.

Since, in a democratic society, the public's perceptions influence policy choices, this risk perception has affected risk management policies with respect to both the allocation of resources and the priority of interventions. This has led to criticisms from people who complain of inappropriate use of resources to prevent completely hypothetical transfusion risks, thus neglecting real risks in other areas of health care, as well as from other people who are perplexed by the allocation of resources to reduce already minimal transfusion risks (those related to the transmission of diseases) rather than directing them to resolve other equally serious but much more frequent transfusion risks (those related to errors).

The precautionary principle

The most important consequence of this public feeling, which is so widespread in the western society, has undoubtedly been the extension of the so-called "precautionary principle" from environmental protection to the safeguarding of public health, particularly with respect to transfusion safety. The extension of this principle was first formalised in various international declarations, then by the regulations of some European countries, and finally by the European Commission on 2 February, 2000[18].

The precautionary principle arose in the 1970s within the setting of European environmental movements with the declared aim of preventing the introduction of measures and/or technology even only hypothetically capable of producing environmental damage. The principle was formalised in the closing

declaration of the United Nations Conference on the Environment and Development held in Rio de Janeiro in 1992[19] with the statement "...Where there are threats of serious or irreversible damage, lack of scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

Since then, despite the numerous and for certain aspects not unreasonable criticisms (the principle leads to over-regulation, it deprives society of technological innovations, it creates unjustified fears about completely hypothetical risks, it minimises the importance of scientific research, etc.), the precautionary principle has become the inescapable basis of all environmental policy choices.

The broadening of the principle to encompass public health in general and blood transfusion in particular was made in France immediately following the so-called scandal of infected blood:

- in 1992, the precautionary principle was included in the proposed new law on transfusion presented to the French parliament[20];
- in 1994 and 1998, two successive pronouncements by the French State Council made the precautionary principle the cornerstone of safety in health care[21,22].

Since then, the principle has appeared in various other public declarations regarding transfusion policies in Europe and outside of Europe[23], and does, in fact, condition the major choices on the supply, qualification and distribution of blood for transfusion purposes.

As expressed, the principle does, however, have substantial margins of ambiguity making it difficult to apply to public health[24].

In particular, while the application of the precautionary principle to the environmental sector translates into the introduction of measures which are, by definition, without risk, its application in Transfusion Medicine involves the introduction of measures which in themselves are of potential risk and which do, therefore, necessitate a careful evaluation of the advantages and risks deriving from their introduction. In other words, the application of the precautionary principle in Transfusion Medicine, leading to an evaluation of opposite and competing risks, must be undertaken in the context of risk management: the alternative is the real possibility of creating risks that are equally as serious as those intended to be prevented[25].

There is no lack of examples:

1) at the beginning of the 1990s, in full respect of the precautionary principle, Peru stopped adding chlorine to drinking water: it was subsequently recognised that this was one of the co-causes of the spread of cholera and the decision was revoked[26];
2) at the end of the 1990s, again in full respect of the precautionary principle, South Africa banned the use of DDT: this decision was then identified as the cause of the increased number of cases of malaria and the ban was lifted[27].

From the above it is clear that in order to enable a balanced application of the precautionary principle to the area of health care, it is essential to have a better definition of the nature of the concepts expressed by the principle, the ways of applying the recommendations and, finally, the structural and formal characteristics of the consequent provisions.

The European Commission responded clearly to these needs in its Communication on the precautionary principle, adopted on 2 February, 2000.

In fact, this Communication:

- describes the nature of the precautionary principle: "the precautionary principle is part of a structured approach to the analysis of risk and is particularly relevant to the management of risk";
- defines the setting for its application: "it regards cases in which scientific findings are insufficient, inconclusive or uncertain and the preliminary scientific evaluation indicates that there are reasonable grounds for concerns that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the European Community";
- explains the attributes that any measures taken must have, stating that any actions undertaken must be:
  - proportional to the level of chosen protection but not aimed at reaching zero risk;
  - non-discriminatory in their application and consistent with similar measures already adopted in equivalent situations for which there is consolidated scientific evidence;
  - based on a careful examination of the potential benefits and costs of the action or lack of the action;
  - maintained for as long as the scientific data remain incomplete, imprecise or inconclusive;

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- subject to continuous review, in the light of new scientific data;
- put into act after decisions made with complete transparency and with the direct involvement of all the interested parties.

The Communication does not offer benchmarks for the degree of evidence necessary to activate the processes related to the precautionary principle or to scale its application: it states, unambiguously, that the judgment of the acceptability or not of a given health care risk is eminently one of policy, in which scientific evidence and social situations must be balanced.

Concluding remarks

Within this scenario, the overall reference frame in which to place the issue of safety in Transfusion Medicine becomes clear: the reasons underlying the risk management choices over the years, which have sometimes been criticised in the light of the principles of evidence-based medicine, cannot be challenged but the foundations for implementing a management plan and minimising risk in our discipline are equally evident.

The transfusion of blood products is definitely already a safe medical practice, but one of the priority requests of civilised society is yet higher levels of safety. Consequently, attempts must be made to improve the safety of transfusion and these efforts must be extended to all stages of the transfusion process: both those stages that scientific evidence indicates objectively as most at risk and those that society considers most at risk.

It must, therefore, be our paramount duty to focus attention and resources on the prevention of medical and clerical errors that, as we have seen, are responsible for the vast majority of adverse events of potentially clinical relevance.

Improving professional training, establishing professional standards, spreading guidelines, and revitalising the Hospital Committees for the Good Use of Blood should be key features of any project to prevent medical errors, while standardisation, automation extended to every working stage and integration of the transfusion process, in the wider context of health care procedures in hospitals, will be fundamental for the prevention of clerical errors.

In second place, attention and resources should be dedicated to problems related to immunological risks: particular dedication should be given to resolving scientifically proven and measured risks, but no less attention should be given, at least in our country, to potential risks such as the immunodepression induced by the transfusion of leucocytes which, in compliance with the precautionary principle, has led many European countries and Canada, unlike Italy and the USA, to generalised filtration of blood.

Last, but not least, attention should be given to preventing the risk of infections: this certainly means maintaining the risks related to the viruses of greatest transfusion impact at their current minimal levels, but, still more, implies protecting the blood supply from new, re-emerging and migrant pathogens, which could profoundly alter the current epidemiological picture. The interventions should, also in this case, be made at several levels and in various directions: from re-considering the mechanisms of the donor's history taking and clinical evaluation, to promotion of regular blood donations: from the use of ever more sensitive screening tests to the development of technologies for pathogen inactivation. I would like to make one further observation to conclude: I previously emphasised that a transfusion should, nowadays, be considered a very safe medical procedure even though there is still room for further lowering of the risks and I highlighted the strength of the demand for safety from society and how the judgement on the acceptability or not of a given health care risk is based strongly on policy decisions, in which scientific evidence and social considerations must be balanced.

Given the foreseeable further progress in transfusion safety, we are probably reaching the time for a rethink of the concepts of transfusion risk, of the limits between certainty and uncertainty of the result, and of the level of acceptability of the risk. "*How safe is safe enough?"* is a question that many people in the western world are now asking: I do not believe that the answer lies in the utopian and deceptive request for zero risk. It is, however, clear that an acceptable response must originate from a highly scientific and ethical background, which, with transparency and intellectual honesty, involves all the interested parties: society, institutions and professional figures. The SIMTI is already available to help in this difficult but fascinating project.

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