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Alternative strategies in assuring blood safety: An Overview

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ABSTRACT

Assuring transfusion safety is an essential element of health care in all countries, requiring government commitment, national policy and a legal framework. Fundamental safety strategies include selection of low risk donors, Good Manufacturing Practices in preparation of blood components, and appropriate clinical use including avoidance of unnecessary transfusions. Hemovigilance, including surveillance for known adverse events and sentinel reporting of unexpected adverse events, enhances safety through benchmarking to promote best practices and by enabling rapid responses to new threats. Preventing transmission of infectious diseases is a principal safety concern. Selection of low risk donors includes use of screening questions to elicit risk factors known to be associated with transmissible infections. Laboratory testing for specific infectious disease markers is an established strategy for interdicting contaminated donations. The sensitivity, specificity, and operational convenience of laboratory testing have improved over time and newer technologies are imminent. Donor screening and laboratory testing, while highly effective in reducing risk, cannot eliminate all risk from known agents and must be developed de novo to address emerging infections. In contrast, pathogen reduction technologies offer the possibility for robust inactivation of a broad spectrum of blood transmissible agents and provide an added safeguard against newly emerging infectious threats of most types. Current pathogen reduction methods also inactivate leukocytes, adding safety benefits similar to leukocyte removal and product irradiation. However, to date, concerns about the safety and efficacy of cellular blood components treated by pathogen reduction have prevented approval of these technologies in the U.S. and Canada. FDA is promoting clinical and basic scientific studies to clarify these issues and would consider alternative approaches to assuring blood safety if pathogen reduction technologies are proven to be safe and effective.

1. Introduction

Newer technologies including gene based pathogen detection and pathogen reduction systems have expanded the possible approaches to assuring blood transfusion safety. However, each of the alternative strategies has benefits and limitations. The choice of a best approach therefore depends upon a clear understanding of these methods and how their characteristics will affect safety and cost in the setting of use. This paper discusses the relative merits of alternative strategies.

2. The transfusion safety paradigm

Safety of blood transfusion depends upon three fundamental elements: maximizing the safety, efficacy and availability of blood products, optimizing patient blood management, and hemovigilance.

2.1. Assuring safe and effective products

In any region, providing an adequate supply of safe and effective blood products for transfusion is a complex undertaking that requires a comprehensive system operating under regulatory oversight and quality management. The basic requirements of an effective blood system include government commitment and support, a national blood policy and plan, and a legal framework [1]. Within that system, organized recruitment of healthy low risk donors and laboratory testing for evidence of infectious diseases are the cornerstones of safe blood. Blood collection and processing need to follow documented Standard Operating Procedures consistent with current Good Manufacturing Practices. Standardization, documentation and quality control are needed in all areas including donor management, laboratory testing, aseptic collection and processing of components, labeling and tracking, cold chain, compatibility testing, reconciliation of unit assignment with a patient identifier, and bidirectional traceability (unit to patient and patient to unit). Adequate education, training and supervision of staff are essential. Ideally, the blood service should meet

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standards for external accreditation and the quality assurance program should include external audits.

Selection of healthy low risk donors is accomplished by use of donor deferral criteria. These criteria are based on medical, behavioral and geographical factors that are epidemiologically associated with transfusion transmissible diseases and are amenable to accurate history taking in the donor setting. This safety strategy reduces collection of infectious units that otherwise would enter the quarantine inventory and might be released due to false negative tests or by release error. Since donor deferral precedes any phlebotomy, the strategy also serves to protect blood center staff against possible infectious exposures. Additionally, donor deferral conserves resources by averting collection of units that must later be discarded as a result of positive laboratory tests.

2.2. Patient blood management

Transfusion carries risk even with the safest possible products. This observation leads to the concept of protecting patients by avoiding unnecessary transfusions. While simple in concept, this approach requires very sophisticated clinical management. Evidence-based "transfusion triggers" are difficult to define and vary with the clinical situation. Hence, optimal patient management lies in exercise of medical judgment with avoidance of transfusion as an automatic default. For example, some patients can be managed with colloid and crystalloid to correct hypovolemia when physiological tolerance of anemia is expected. Avoidance of transfusion also can be achieved by preventive recognition and treatment of conditions likely to result in a need for blood. Examples include pre-operative correction of anemia and coagulopathy. In the operative setting, blood loss can be minimized in a number of ways including blood sparing surgery, intra-operative and post-operative blood cell salvage and normovolemic hemodilution. Pre-operative autologous donation can reduce or avoid allogeneic blood exposures.

2.3. Hemovigilance

A third element of transfusion safety is hemovigilance, which consists of organized prospective monitoring and reporting of the outcome of transfusions (and other hemotherapies). Conceptually, hemovigilance can be divided into two activities, namely surveillance and sentinel monitoring. Surveillance is the comprehensive reporting of known adverse events and reactions under a framework of fixed definitions. Combined with denominator data on the overall number of transfusions, surveillance reporting permits the monitoring of trends and the detection of geographical and temporal clusters. These data permit recognition of system deficiencies, local benchmarking against best practices and meaningful assessment of the outcome of interventions. In contrast, sentinel monitoring is the detection and reporting of unexpected adverse events and reactions. Sentinel hemovigilance facilitates the identification of new threats and enables rapid system level responses. The use of standardized terminology, such as for case definitions, imputability and severity, improves data quality and allows data from different sources to be aggregated or compared. Although it is not operationally a part of blood collection and use, hemovigilance plays a critical role in the assessment and progressive improvement of the blood system. For this reason, it needs to be regarded as an essential function.

3. Effectiveness of the conventional blood safety strategy

Donor selection, laboratory testing for infectious diseases and aseptic processing and storage constitute the conventional approach to maximizing blood product safety. In the U.S. and other countries, these methods, which include nucleic acid testing for HIV and HCV, have lowered the major risks from viral infections to levels that cannot be measured directly. In the U.S., current risks have been estimated at 1 in 1.5–1.8 million per unit for HIV and HCV, and 1 in 174,000–269,000 for HBV [2]. In contrast, the risk of bacterial contamination of platelets is less well controlled. The American National Red Cross reported for the period of 2004–2006 that the rate of clinical sepsis ranged between 1:41,000 and 1:193,000 with a fatality rate of approximately 1:500,000 despite interventions including screening with bacterial cultures [3].

3.1. Value of donor questioning

Donor selection by the use of questionnaires is intended both to protect the health of the donor and to lower the risk of collecting an infectious unit. Deferral of candidate donors based on risk factors for transmissible infections prevents the collection of contaminated units that might otherwise be released from inventory through error. Additionally, risk factor screening compliments laboratory testing by avoiding collections in the "window period" of recent infection when laboratory tests may be negative and serve as an added precaution against procedural failures that can result in falsely negative tests. In urgent situations, where testing and/or pathogen reduction are infeasible, donor selection criteria may be the only safeguard. The same is true for controlling the risk of variant Creutzfeldt–Jakob disease since no screening tests currently exist. Donor selection criteria sometimes have surrogate value. For example, for donors in a non-endemic area, deferral based on a history of malaria exposure in an endemic area might prevent transfusion risk from an emerging disease in the malaria endemic area.

Compared with laboratory testing, donor screening by the use of questionnaires suffers serious limitations of sensitivity and specificity. Low specificity is especially problematic because it can result in a significant loss of healthy donors and can undermine public confidence in the blood system. Also, validation of donor questions is often lacking. Few validation studies of donor questions have been done mainly due to the difficulty in performing adequately powered studies in deferred donors. Recently, investigators at the American National Red Cross demonstrated a strong correlation of admitted risk factors for hepatitis with markers of hepatitis infection in deferred donors. However, they were unable to demonstrate a comparable association of infectious disease markers with donor responses to other risk questions. It is unresolved whether the absence of a demonstrated association was due to lack of value of the other questions or due to the limited study size [4]. This problem is aggravated by the fact that donor questions often are introduced without objective validation. While empirical use of donor questions may be a prudent response to an emerging threat, their use can remain unexamined scientifically even after effective testing is introduced.

3.2. Value of donor testing

Laboratory testing for markers of infectious diseases has profoundly improved blood safety in recent decades. Donor testing can be highly cost-effective, though this depends on the prevalence of infections in donors, the performance characteristics of the tests and their costs. Additionally, testing contributes to individual and public health through the notification of infections in donors, permitting donor education, treatment and the exercise of preventive measures against secondary spread. Also, when linked to demographics, marker rate data obtained through testing provide epidemiological information that can be used to identify