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NON-INFECTIOUS SERIOUS HAZARDS OF TRANSFUSION

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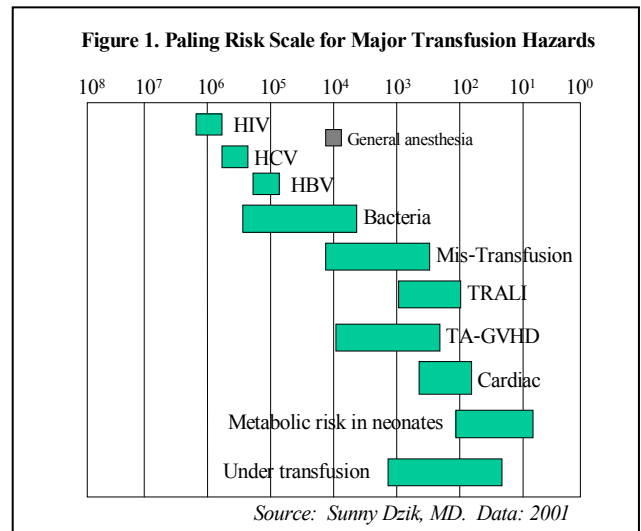
Safe transfusion therapy is a basic requirement for advanced medical care. In order to establish priorities for improving safe transfusion for patients, it is essential to distinguish transfusion safety from blood safety. Blood safety refers to the safety of the product. In contrast, transfusion safety refers to the safety of the overall process of transfusion from donor to recipient.¹

Blood safety is not matched by increases in transfusion safety. Enormous progress has been made in blood safety during the last few decades. Donor restrictions and high performance viral screening assays have virtually eliminated viral transmission by blood transfusion in the developed world. For example, the risk of hepatitis or HIV from transfusion has declined by approximately 10,000 fold.

In contrast, during the same period there has been little change in the risk of non-infectious hazards. Some result from medical errors made during the collection of a patient sample or during blood administration. Data suggest that the rate of medical errors occurring in hospitals is increasing and a labor shortage in hospital laboratories also decreases patient safety. For example, a recent study from a prestigious university program documented that from 1993 to 1999 the number of errors rose from 1238 to 2052 per year.² It is particularly alarming that errors involving patient samples quadrupled from 112 (10% of total errors) in 1993 to 434 (20% of total) in 1999. The Institute of Medicine report, *To Err Is Human*, has called attention to the enormous morbidity and mortality associated with hospital-based errors. These errors have been largely ignored by government agencies focused on blood safety. For example, the Canadian Krever Commission selectively applied the precautionary principle only to infectious risks of transfusion, but not to the very real non-infectious hazards of transfusion.³ Thus, while blood product safety has been a remarkable achievement, emphasis on product safety diverted attention from transfusion safety.

Hemovigilance programs and the risk of transfusion. Hemovigilance programs are national systems for reporting adverse events and provide one objective means to assess current risks of transfusion. In reports of adverse occurrences in the United Kingdom, mis-transfusion accounted for over 50% of adverse events and non-infectious hazards of transfusion accounted for over 95%.⁴ Similar data generated from hemovigilance programs in France and Canada suggest that innovations to address non-infectious hazards should be given high priority.

Viewed from the perspective of risk per individual unit, non-infectious hazards overwhelm current infectious risks. Figure 1 shows current estimates of the risks of an individual unit of blood using the Paling scale. These data demonstrate two important findings. First, the confidence interval of the risk estimate is much more precise for infectious hazards compared with non-infectious hazards. The precision of infectious risk estimates has



resulted from studies conducted in the last decade. Similar studies for non-infectious hazards have not been conducted. Secondly—and more importantly—the graph shows the extent to which patients are at greater risk from non-infectious serious hazards of transfusion. For example, estimates of the per-unit risk of mis-transfusion errors may exceed the risk of viral infection by as much as 10,000 fold.

Examples of non-infectious hazards of transfusion:

Mis-transfusion of blood. Mis-transfusion can be summarized as a failure to give “the right blood product to the right patient at the right time for the right reason.” At its worst, mis-transfusion results in major ABO incompatible transfusions. Despite dramatic improvements in overall medical care in the past half-century, the morbidity (renal damage) and mortality associated with ABO hemolytic transfusion reactions has not improved much over that observed decades ago. For example, transfusion errors comprised 2.7 % of all sentinel events reviewed by the Joint Commission on the Accreditation of Hospitals from January 1995 through March 2002,⁵ although these and other data from the US based on passive reporting may underestimate the true frequency of mis-transfusion. An active audit of transfusions at three university hospitals in Belgium observed numerous unreported mistakes. Overall, the incidence of serious error was 1 in 400 units and the rate of reported errors underestimated the true rate by 30 fold.⁶

Transfusion-related acute lung injury (TRALI). TRALI is an immune-mediated lung injury syndrome, which in its worst form is life-threatening and indistinguishable from adult respiratory distress syndrome. The actual incidence is uncertain and many cases undoubtedly are attributed to other causes. Over a two-year period in a general hospital, Clarke *et al* reported that 46 of 2,430 transfusions of platelets (2%) were associated with respiratory reactions.⁷ A more recent study observed frequent oxygen desatu-

ration among recipients of fresh frozen plasma (FFP) donated by multiparous females.⁸ Mild to moderate cases of TRALI may result in less overt lung injury that nevertheless prolongs ventilator time. In the last three years, TRALI and hemolytic transfusion reactions have resulted in more deaths reported to FDA than all infectious hazards combined.

Circulatory overload and cardiac toxicity of blood transfusion. True estimates of the frequency of cardiac overload and cardiac toxicity from transfusion are uncertain, since the condition is enormously under-reported. A report from Mayo clinic estimated the frequency at 1 in 708 recipients.⁹ In an important randomized controlled study, patients in intensive care units were transfused according to either a liberal transfusion strategy (to maintain hematocrit at >30%) or a restrictive strategy (hematocrit >21%).¹⁰ A secondary analysis of complications in the two groups demonstrated that those in the liberal transfusion group had a statistically higher rate of cardiac and pulmonary complications.

Metabolic risk to neonates. Metabolic complications are common in neonates who receive transfusion therapy. Hypoglycemia may occur when very low birth-weight infants are transfused. In one study, 10 of 16 (64%) premature infants receiving packed RBCs required supplemental glucose within the first two hours of transfusion because of a blood glucose level <40 mg/dL or clinical signs of hypoglycemia.¹¹ Among pediatric recipients of exchange transfusion, severe metabolic risks are real, even if under-reported. Jackson reviewed 140 exchange transfusions among 106 neonates and found that 34% of infants developed significant hypocalcemia during exchange.¹² One in twenty infants (5%) had abnormal EKG changes and one had a cardiac arrest. The frequency of death or severe morbidity was even higher among the subset of very ill premature neonates.

Inadequate or inappropriate transfusion. Inadequate transfusion has not been extensively studied and remains a risk for a subset of patients. A small study among patients with extensive vascular disease documented a high frequency (80%) of post-operative cardiac ischemia as the hematocrit fell below 30%¹³ and a more recent study correlated adverse outcomes with low admission hematocrits.¹⁴ More research is needed to identify clinical indicators that are better than the hematocrit for guiding the decision to transfuse. Many transfusions of FFP are likely to be completely inappropriate. However, the fault does not rest with clinicians but rather with the absence of any randomized trials designed to determine the indications for transfusing FFP.

Improving transfusion safety with new technology. Solutions to the problems of transfusion safety could come from both technological advances and the deployment of new personnel.

The use of transponder technology, wireless communications and advanced bar code reading could decrease the frequency of mis-labeled patient samples and mis-transfusion. Similar technologies are already widely used in the postal system and in tracking of manufacturing inventories in the commercial sector. Inexpensive wireless chip technology could be used to monitor the status, location, and destination of blood units the same way in which the "black box" carried on commercial aircraft are used to monitor the airplane. Microsensors that can record and report tissue oxygen levels currently are used in a research setting and would represent an exciting area for clinical application as a new means for deciding when to transfuse RBCs. With proper funding, existing systems of computerized patient data retrieval could be used to provide more sophisticated feedback to clinicians on medical decision-making and proper blood utilization.

Improving transfusion safety with new people. A second key to improving transfusion safety now being discussed by transfusion medicine specialists is the development of a new professional position, the Transfusion Safety Officer (TSO), charged with improving processes leading to transfusion. TSO positions are being developed in Canada and Europe.¹⁵

Can we afford improved transfusion safety? Compared with recent expenditures for blood safety, improvements in transfusion safety are likely to be highly cost-effective. Hand-held scanners could be implemented at a cost of less than \$4 per transfusion and automation and widespread use would reduce this cost even more. If one FTE TSO were required for each 20,000 red blood cells transfused, the incremental cost per transfused component would be <\$2/unit. These costs are trivial compared with those for universal leukoreduction or pathogen inactivation.

Time to make transfusion safety our top priority. Recent evidence documents that hospital-based non-infectious hazards of transfusion carry a risk to patient safety that is many thousand fold greater than the infectious risks. New solutions that can reduce non-infectious risks are available. If we are to improve outcomes for our patients, then government, manufacturers and health professionals need to place a higher priority on enhancing overall transfusion safety.

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