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Newly Recognized Causes of Acute Lung Injury: Transfusion of Blood Products, Severe Acute Respiratory Syndrome, and Avian Influenza

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Transfusion of blood products and acute lung injury and acute respiratory distress syndrome

Clinical spectrum of lung injury secondary to hemotherapy

The development of lung injury from the transfusion of blood products occurs on a clinical spectrum, and therefore the proper recognition of lung injury must consider these possible scenarios. Transfusion-related acute lung injury (TRALI), in its classic and most recognized form, is the fulminant development of new lung injury in a patient who has just received or is receiving a blood-product transfusion. Often, severe respiratory failure develops, and frothy pulmonary edema fluid is suctioned from the endotracheal tube. This catastrophic and fulminant form of TRALI is easily diagnosed by most health care providers. Like most pathologic processes, however, TRALI extends on spectrum from mild to severe, and the milder forms of TRALI can go unrecognized even by highly trained and experienced health care providers. For example, TRALI in the stable patient on the general medical ward who is receiving packed red blood cells (PRBCs) for anemia and develops a mild decrease in oxygen saturation may go unrecognized, or the cause of the oxygen desaturation may be blindly assigned to volume overload. A recent retrospective study that tracked the recipients of blood products from a donor implicated in a case of TRALI exemplifies this point [1]. This highly motivated donor was linked to 15 cases of TRALI over a 2-year period, and many of the cases were associated with mild symptoms or mild oxygen desaturation. Most of these cases were not initially recognized as TRALI, nor were they reported to the blood bank as a potential adverse event. It is essential for the health care provider to maintain a high degree of vigilance for adverse reactions to blood products and to investigate thoroughly any oxygen desaturation temporally related to blood-product transfusion.

Another important category of potential lung injury related to blood-product transfusion is the worsening of pre-existing acute lung injury (ALI) by subsequent hemotherapy. It often is difficult to make a diagnosis of TRALI in critically ill patients who have existing ALI/acute respiratory distress syndrome (ARDS); however, if there is a sudden worsening of oxygenation and pulmonary compliance in a patient who is receiving or in the past 6 hours has received a blood-product transfusion (in the absence of signs of volume overload), a probable diagnosis of TRALI can be made. There are a few studies in the medical literature that support a contribution of blood-product transfusion to the worsening of pre-existing ALI/ARDS. Using the largest prospective study on the incidence of ALI in the pediatric population, Church and colleagues [2] retrospectively assessed the role of blood-product transfusions on the clinical outcomes of this patient population. These investigators discovered that the transfusion of fresh frozen plasma (FFP) was an independent risk factor for mortality in these pediatric ALI patients at 30 days. In an adult prospective investigation of the risk factors,

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incidence, and outcomes of ALI/ARDS at a single center, Gong and colleagues [3] reported that PRBC transfusion was independently associated with the initial development of ALI/ARDS and was an independent risk factor for mortality in ALI/ARDS, with a dose-dependent response.

Potential lessons also can be learned from the seminal Transfusions Requirements in Critical Care (TRICC) trial by the Canadian Care Trials Group [4]. In this randomized, controlled equivalency trial comparing restrictive and liberal transfusion thresholds, the patients transfused with a hemoglobin trigger of less than 7 g/dL had at least as good outcomes as the patients in the liberal transfusion arm. In an analysis of the ICU complications that developed in the two groups of patients, 32 patients (7.7%) in the restrictive transfusion group versus 48 patients (11.4%) in the liberal transfusion group developed ARDS during their ICU stay ($P = .06$). Unfortunately, it was not determined what proportion of these patients who had ARDS developed overt TRALI; however, it is provocative to consider that a proportion of ARDS may be preventable by adhering to lower transfusion thresholds. This potential benefit could result from the reduction of ALI/ARDS directly caused by the transfusion of blood products and ALI/ARDS resulting from the combination of blood transfusions and other causes (the two-hit model). In the TRICC trial, decreased infectious complications (eg, pneumonia, sepsis) did not seem to be a benefit of the restrictive transfusion group, and thus the decreased incidence of ALI/ARDS probably cannot be attributed to decreased transfusion-related immunomodulation. One other notable point to consider regarding the TRICC trial was the statistically significant decrease in pulmonary edema in the restrictive transfusion group. Pulmonary edema was listed as a cardiac complication, although it is unclear how rigorously noncardiogenic pulmonary edema was excluded. This decrease in pulmonary edema could potentially comprise both transfusion-associated circulatory overload and TRALI.

Definition of transfusion-related acute lung injury

The term ''transfusion-related acute lung injury'' was first coined in 1983 by Popovsky and Moore [5] and has been variably defined in the ensuing years. Recently, the field has been aided significantly by a consensus definition developed by a panel investigators convened by the National heart, Lung, and Blood Institute (NHLBI) [6]. Simply put, TRALI remains a clinical diagnosis, similar to the clinical definition used for ALI/ARDS [7]. In fact, if a patient meets clinical criteria for ALI/ARDS and has received a blood-product transfusion during the previous 6 hours (in the absence of another credible risk factor for ARDS), a clinical diagnosis of TRALI can be made. The blood bank and laboratory work-up of TRALI is an important component for the possible prevention of future TRALI from implicated blood donors, but it is not required to make a diagnosis of TRALI.

The use of the 6-hour window to implicate a blood-product transfusion in TRALI is not an arbitrary designation. The multitude of case reports in the medical literature confirms a close temporal association with the transfusion of blood products. In fact, it is common for TRALI to develop during the first 30 to 60 minutes of a transfusion [8]. Experimental evidence from animal models supports this temporal association. In at least four different animal models of TRALI using anti-neutrophil antibodies, anti–major histocompatibility class (MHC) I antibodies, and the plasma and lipid fractions from day 42 PRBCs and day 5 platelets, lung injury develops within 6 hours of challenge with these experimental agents [9]. In fact, in the MHC I antibody model, lung injury develops within 2 hours and often within 15 to 30 minutes [10]. The speed with which lung injury develops in a given patient is probably a complex interplay of host susceptibility and dose or titer of the injurious blood product.

The clinical diagnosis of TRALI is potentially complicated by the existence of other major risk factors for ALI/ARDS, clinical risk factors that often are present in critically ill patients receiving hemotherapy. The consensus definition of TRALI addresses this point by assigning a definite diagnosis of TRALI when no other ALI/ARDS risk factors are present and a probable diagnosis of TRALI when these other major risk factors are present [6]. The clinical course of these probable TRALI patients can be followed over time, and the credibility of the relationship of the risk factors to ALI/ARDS can be assessed. If hemotherapy remains the most credible risk factor for ALI/ARDS, a diagnosis of TRALI can be made.

The issue of massive transfusions as a risk factor for ALI/ARDS is a potential source of confusion in assigning the diagnosis of TRALI. Massive transfusion is defined as the replacement

by transfusion of more than 50% of a patient's blood volume over 12 to 24 hours [11]. Massive transfusion has been implicated as a major risk factor for ALI/ARDS in multiple studies and is probably the fourth most common cause of ALI/ARDS, accounting for approximately 20% of cases. Even with the experimental models of massive blood transfusion, it is not entirely clear how lung injury is produced by this insult. Because many of these patients, if not the majority, are involved in trauma, considerations include ischemia-reperfusion lung injury from shock and potentially a component of direct thoracic trauma. Older investigations using animal models of "shock lung" disproved the microaggregate or particulate theory of lung injury from transfusions but focused attention on the plasma fraction of blood products [9]. Is it possible that the development of ALI/ARDS from massive blood transfusion is a function of the cumulative risk of TRALI from individual blood products? This supposition may explain many of the cases; receiving multiple blood products places the patient at higher risk of receiving an incompatible product containing either a matched antibody or priming or activating bioactive lipids. If one considers the two-hit model of TRALI, then the underlying medical condition of the critically ill patient who is requiring multiple transfusions also places the patient at risk for TRALI. In summary, the certainty by which a diagnosis of TRALI can be made in a patient who has other risk factors for ALI or preexisting ALI is a complicated issue that may be aided by following the clinical course of the patient and also by focused laboratory investigation of implicated blood products.

Incidence and clinical outcomes

The most consistent incidence of TRALI reported in the medical literature is 1 in 5000 blood products transfused. [5]. This figure is probably a significant underestimation given the evidence for the under-recognition and underreporting of TRALI [1]. The new consensus definition and the recent proliferation of case reports and clinical reviews of TRALI should aid in the greater recognition and reporting of this condition in the future. In addition, the NHLBI has recently funded a Specialized Centers of Clinically Oriented Research (SCCOR) grant to the University of California, San Francisco and the Mayo Clinic, Rochester to conduct a prospective observational cohort study on the incidence and outcomes of TRALI at these two medical centers. This study promises to yield the largest cohort of TRALI patients in the medical literature and should provide a reliable estimate of the incidence of TRALI.

Medical providers are required to report fatalities related to TRALI to the Food and Drug Administration (FDA). During the past few years the FDA has received between 8 and 21 reports per year of fatal TRALI, and TRALI has now emerged as the primary cause of transfusion-associated mortality, surpassing infectious complications and ABO mismatch [12,13]. The United Kingdom's Serious Hazards of Transfusion Annual Report for 2004 evaluated 23 cases that had been reported as TRALI events and concluded that 13 cases were either highly likely or probable TRALI, and 4 of these cases were possible TRALI [14].

The clinical outcomes of patients who have TRALI differ considerably from the outcomes of patients who have all causes of ALI/ARDS. One of the largest case series in the TRALI literature reported the clinical outcomes of 36 patients at the Mayo Clinic in the mid-1980s, predating the use of low tidal volume ventilation in the management of patients who have ALI/ARDS [15]. In this investigation, three quarters of the patients required mechanical ventilation, and the vast majority of the patients had rapid clearance (<96 hours) of the pulmonary edema. Two of the 36 patients died, yielding a mortality of 6%. The rapid clearance of the pulmonary edema and mortality differ considerably from all-cause ALI/ARDS, which has an estimated mortality of 30% to 40% [16].

Implicated blood products in transfusion-related acute lung injury

All plasma-containing blood products have been implicated in TRALI. This list includes whole blood, PRBCs, FFP, whole blood platelets, and apheresis platelets, with less frequent associations with intravenous immunoglobulin and cryoprecipitate. Controversy exists concerning which blood product is most commonly implicated in TRALI, but the two blood products with the largest plasma fraction, FFP and platelets, are probably the top offenders. In the reports of TRALI fatalities reported to the FDA, FFP was the most commonly implicated product, followed by red blood cells, platelets, and cryoprecipitate [13]. The association of platelets with TRALI is supported by a single-center investigation

reporting that whole blood platelets caused TRALI in 72 of 90 cases [17].

Pathogenesis of transfusion-related acute lung injury

Classically, the pathogenesis of TRALI has been explained by the passive transfusion of a plasma-containing blood product with a HLA class I/II or neutrophil antibody that recognizes specific HLA or neutrophil antigens in the recipient. Numerous case reports and case series have documented the presence of these antibodies and the matching antigens in the recipient, and in animal models MHC I and anti-neutrophil antibodies have produced acute lung injury [8,10,18,19]. In rarer circumstances, roles can be reversed, and recipient antibodies can react with antigens on donor leukocytes. In the FDA's report on fatalities secondary to TRALI, anti-HLA I antibodies were the most frequently implicated antibody, followed by anti-granulocyte and anti-HLA II antibodies [13]. In an anti–MHC I mouse model that reproduces many features of clinical TRALI, lung injury was produced secondary to the recognition of endothelial-bound MHC I antibody by circulating neutrophils and their Fc gamma receptors [10]. In another experimental model of TRALI, evidence was presented that a mouse monoclonal anti-neutrophil antibody directly activated human neutrophils, leading to lung injury [19]. Common to all antibody models, however, is the central role of the neutrophil in producing disease, either from direct antibody activation or indirectly through Fc gamma receptor activation. Other investigators have shown that monocytes may be important in TRALI pathogenesis [20].

Although the antibody theory of TRALI is supported by both clinical and experimental evidence, solid clinical data and animal models also implicate biologically active lipids that accumulate in older cellular blood products [21–23]. These biologically active lipids, thought to be breakdown products of cellular membranes from stored blood products, can prime and activate neutrophils in vitro. Cellular blood products (PRBCs, platelets) have been shown to accumulate these lipids over time, and the plasma and lipid fractions from these older blood products have been used to produce pulmonary edema in isolated, perfused rat lung models. Older blood products have been implicated in TRALI cases [17] but recently, red blood cell storage time was not associated with the development of new ALI/ARDS [24].

A phenomenon that has not been adequately explained is the inconsistent development of lung injury even when a recipient is transfused with a matched HLA or neutrophil antibody. For example, a retrospective study of TRALI involving an antibody to a neutrophil antigen expected to be present in more than 90% of recipients produced TRALI in only a minority of patients transfused with this antibody [1]. This lack of a consistent relationship between antibody-antigen matches and TRALI has been explained by host susceptibility and specifically by the two-hit model of TRALI. This hypothesis states that the recipient must have an underlying medical condition that contributes to immune priming and that with the transfusion of HLA or neutrophil antibody or biologically active lipids (or both), TRALI is produced. Evidence supporting this hypothesis includes the frequent occurrence of TRALI in the ICU or operating room and epidemiologic associations with cardiopulmonary bypass and hematologic malignancies [17]. In addition, the biologically active lipid model involves a necessary systemic endotoxin-priming step to produce ALI [22,23]. Host susceptibility factors such as genetic polymorphisms also may be contributing factors.

Clinical manifestations, diagnosis, and management of transfusion-related acute lung injury

Patients who develop TRALI often develop dyspnea, tachypnea, and hypoxia. Both hypotension and hypertension have been reported in patients who have TRALI, as has hyper- and hypothermia. In mechanically ventilated patients or at the time of endotracheal intubation, frothy pulmonary edema fluid is sometimes elaborated in fulminant TRALI cases. The same criteria used by clinicians and researchers to diagnose other causes of ALI/ARDS are used to make a diagnosis of TRALI [7]. Chest imaging reveals bilateral pulmonary opacities in a pattern consistent with noncardiogenic pulmonary edema (Fig. 1). Adjunctive tests that aid in a TRALI diagnosis include echocardiography, serial white blood cell counts, and the protein analysis of undiluted pulmonary edema fluid [8]. Echocardiography can aid in the work-up by helping exclude volume overload and cardiogenic dysfunction. Often, patients who have fulminant TRALI have evidence of low cardiac filling pressures. Measurement of

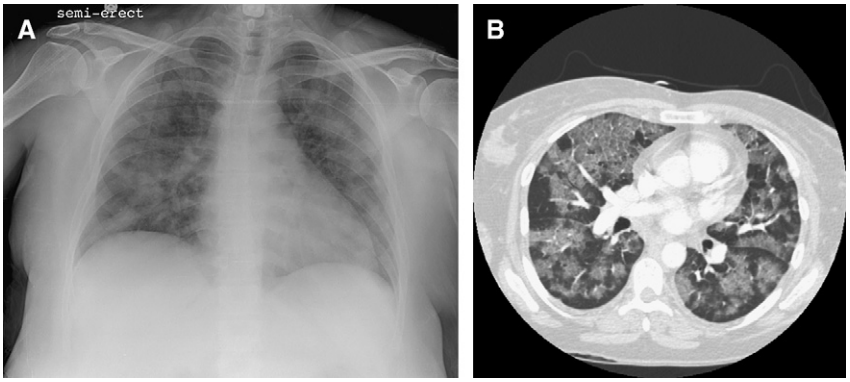

Fig. 1. (*A*) Anterior-posterior chest radiograph in a 43-year-old woman recovering from knee surgery who developed respiratory distress and hypoxia during a PRBC transfusion. Bilateral pulmonary opacities are present. (*B*) Chest CT in the same patient revealing bilateral ground-glass opacities and interstitial septal thickening. CT was done 24 hours after the chest radiograph in Fig. 1A.

brain natriuretic peptide may also be an adjunctive test that can be helpful. There are several case reports of leukopenia and neutropenia temporally associated with the onset of pulmonary edema in TRALI [25–28]. This laboratory finding often is dynamic, with leukocyte counts recovering a few hours after the initiation of TRALI. There is even one case report of leukopenia heralding the onset of TRALI [29]. The mouse MHC I antibody model of TRALI also has documented this phenomenon, which speaks to the association of leukopenia with disease pathogenesis [10]. Other causes of ALI/ARDS (eg, pneumonia, sepsis) also might produce leukopenia, so this finding is not specific to TRALI. Thrombocytopenia and decreased complement have been reported also, but much less frequently. Finally, if present, the measurement of the protein concentration of undiluted pulmonary edema fluid and a matched plasma sample can be helpful in documenting a permeability pulmonary edema and thus helping exclude transfusion-associated circulatory overload or cardiogenic pulmonary edema [30].

There is no unique or specific treatment for TRALI, but the proper recognition of this syndrome leads to provision of the same supportive care given to any patient who has ALI/ARDS. Additionally, correctly identifying TRALI allows one to avoid potentially injurious interventions, such as diuretics, in these patients, who often are volume depleted. Paradoxically, these patients, who sometimes have severe pulmonary edema, may require intravenous fluids to support blood pressure. Colloid and vasopressors may be required in some instances. Corticosteroids have no role in the treatment of TRALI patients. It is important to consider that most patients who have TRALI improve fairly rapidly, and overall mortality is low; thus, with patience and the avoidance of any unnecessary blood-product transfusions, most patients will do well.

Prevention of transfusion-related acute lung injury

TRALI is best prevented by avoiding unnecessary blood-product transfusions using evidence-based transfusion triggers. Use of erythropoietin [31] and recombinant factor VII may help reduce transfusion requirements in selected populations. Most experts agree that if a blood donor is implicated in a TRALI case, that donor and the donor's existing blood products should be removed permanently from the donor pool. Given the incidence of HLA sensitization in multiparous females [32] and the association of TRALI with FFP transfusion, the United Kingdom has excluded all women from donating FFP, directing their donations instead to plasma-poor blood products [14]. In addition, platelet pools are suspended in male plasma as much as possible. There has not been ample time to determine the benefit of this regulatory action on the incidence of TRALI; however, the number of highly likely or probable TRALI cases decreased from 22 in 2003 to 13 cases in 2004. (The FFP policy was implemented in October 2003.) Given time delays in the work-up of TRALI cases and the long shelf-life of stored FFP, the true impact of the male-only FFP policy change will not be known until

the next reporting years. Leukoreduction of PRBCs is now an almost universal blood bank procedure, but it is unlikely that it will significantly reduce the incidence of TRALI, because recipient antibody recognition of antigens on donor leukocytes is a rare mechanism in TRALI.

Severe acute respiratory syndrome

Clinical importance and epidemiology of severe acute respiratory syndrome

The severe acute respiratory syndrome (SARS) burst on the international scene in 2002 and 2003 causing much concern because of its rapid, global dissemination and fears of a pandemic. From late 2002 to mid-2003, more than 8000 people developed probable SARS in many different countries across five continents, with the predominance of cases in China, Hong Kong, Viet Nam, Taiwan, Singapore, and Canada. Approximately one in four patients who had SARS become critically ill, with ALI occurring in 80% of these patients (16% of all patients). In fact, ALI is the most common organ-system dysfunction in SARS patients. Of the patients who become critically ill with SARS, approximately 50% die, with mortality rates increased in the elderly [33].

Much has been learned about the epidemiology of SARS since its emergence in the Guangdong Province of China. Remarkably, through collaborations with multiple laboratories in different countries, a novel coronavirus was identified as the causative agent of SARS just 4 to 5 months after the initial reports of the SARS outbreak [34,35]. A similar coronavirus was also isolated from wild animals (eg, Himalayan palm civets, raccoon dogs) sold in the ''wet'' markets in Guangdong Province, supporting a zoonotic origin of this novel virus [36]. The incubation period for SARS seems to range between 2 and 10 days, although longer incubation times have been documented. Unlike influenza, in which transmissibility peaks soon after the onset of clinical symptoms, SARS is transmitted most efficiently after 10 days of illness. The primary route of transmission is contact (direct or indirect) with respiratory droplets or fomites. Fecal–oral spread also may play a role, given the presence of SARS coronavirus in stool specimens and the presence of watery diarrhea in many affected patients. The spread of SARS seems to involve so-called ''super-spreaders'' who disproportionately infect many persons, and it also prominently involves transmission in the health-care setting [37].

Pathogenesis of severe acute respiratory syndrome

A Clinical SARS Working Group, comprised of experts from Canada and the United States, determined that patients admitted to ICUs with respiratory failure secondary to SARS met the established clinical definition of ALI/ARDS [33]. Lung pathology obtained from SARS nonsurvivors reveals a pattern of disease that is indistinguishable from other causes of ALI/ARDS, namely diffuse alveolar damage [38].

Much has been learned about the potential cellular and molecular mechanisms of lung injury secondary to SARS coronavirus infection. For example, the tropism of the SARS coronavirus for the lung and the gastrointestinal tract can be explained by the epithelial distribution of its cellular receptor, ACE-2, which is found on the surface of alveolar type I and II epithelial cells and also on small bowel enterocytes [39,40]. Therefore, the severe pulmonary damage observed in SARS can be explained by viral–alveolar epithelial cell interaction.

Diagnosis, management, and prevention of severe acute respiratory syndrome

SARS presents clinically with a nonspecific viral syndrome of fever, myalgia, chills, fatigue, and cough; upper respiratory symptoms (eg, rhinorrhea, sore throat) are often absent. Watery diarrhea can be present in some patients. Severely affected patients develop shortness of breath, tachypnea, and tachycardia. Routine laboratory investigation often reveals lymphopenia, thrombocytopenia, and elevated transaminases. Chest imaging is nonspecific with high-resolution CT being abnormal in nearly all patients showing ground-glass attenuation and focal consolidation with some cases of pneumomediastinum [37].

The diagnosis of SARS relies on consideration of key epidemiologic data in a patient who has a viral syndrome or idiopathic respiratory failure. Because the clinical syndrome, routine laboratory testing, and chest imaging are nonspecific, diagnosis relies on detection of the SARS coronavirus in clinical specimens. Real-time polymerase chain reaction (PCR) is used to test samples from multiple potential sites, including the upper and lower respiratory tracts, stool, urine, and plasma. The virus concentrates in the lower respiratory tract and is present in low quantities

early in the disease course; thus negative results early in the clinical course, especially from upper respiratory specimens, should be interpreted with caution. The standard diagnostic test for SARS is seroconversion, but this testing is rarely helpful prospectively.

The evidence-based management of SARS has been reviewed by the NHLBI/Centers for Disease Control and Prevention/National Institute of Allergy and Infections Diseases Clinical SARS Working Group [33]. Generically, because SARS produces a clinical syndrome consistent with other causes of ALI/ARDS, respiratory failure should be managed in a similar fashion, with a pressure-limited, low tidal volume strategy. The roles of antiviral agents (eg, ribavirin and interferon-α) and corticosteroids are controversial and suffer from the lack of quality data. Anecdotal and small case series have supported the role of corticosteroids for severe cases [41], and thus, in the absence of placebo-controlled trials, steroid therapy should be considered, especially in patients who have clinical deterioration.

Several factors contributed to the halt of SARS transmission and its current disappearance from the clinical landscape. The involvement by the World Health Organization in issuing a global health alert, the quarantine of infected and exposed individuals, and, importantly, the ban on the sale of wildlife in the wet markets of Guangdong, China all helped to stop the spread of this potential pandemic. Phase I trials are now in progress on vaccine strategies that could prove to be important should SARS re-emerge on the global scene [42].

Avian influenza (H5N1)

Clinical importance and epidemiology of H5N1 infection

Influenza pandemics have been marked by the emergence of epizootic strains of influenza for which there is no immunologic memory in humans. The Spanish influenza (H1N1) pandemic of 1918 killed an estimated 40 to 50 million people worldwide. Subsequent pandemics in 1957 (H2N2) and 1968 (H3N2) also killed many thousands. Attention and trepidation are now focused on the H5N1 epizootic strain and its potential to cause worldwide disease and mortality. The H5N1 virus first emerged in 1959 in chickens in Scotland and now is causing a pandemic among chickens in Southeast Asia [43]. According to World Health Organization statistics accessed on June 5, 2006, 224 humans have been infected with H5N1 virus in 10 different countries, and 127 have died, yielding a mortality of 57%, many of which are children and young adults [44]. Almost all the persons infected with H5N1 have been linked epidemiologically with exposure to sick birds or, in a very small number of cases, to exposure to another human who had H5N1 infection. It is unknown just how widespread and lethal a pandemic of H5N1 infection would be, but the Congressional Budget Office estimates that 200 million people could be infected in the United States alone.

H5N1 disease pathogenesis

The H5N1 influenza A subtype contains a new H5 hemagglutinin to which humans have little immunity. The hemagglutinin molecules attach to epithelial cells and macrophages in the lungs by interaction with cell-surface sialic acid residues. A true influenza pandemic can develop only if the avian H5N1 virus can spread efficiently from human to human, a scenario that has occurred only rarely thus far. Recent reports might help explain why the avian H5N1 virus currently is inefficient in human-to-human infection. It seems that established human influenza viruses (eg, H1N1) and avian flu viruses target different regions of the human respiratory tract. Human flu viruses preferentially recognize sialic acid residues in the proximal respiratory tract (trachea and bronchi), whereas H5N1 infects alveolar type II cells, macrophages, and the nonciliated cuboidal epithelium of the terminal bronchi [45,46]. This differential tropism may help explain the clinical presentation of ALI/ARDS in humans infected with H5N1, and perhaps more importantly, it may help explain why H5N1 is not transmitted efficiently among humans: human influenza is transmitted easily from its proximal location in the respiratory tract, whereas H5N1 is a more deeply seated infection. There is even some concern from animal models of H5N1 infection that viremia can lead to fecal shedding of the virus and the potential for fecal–oral transmission.

Diagnosis, management, and prevention of H5N1 infection

Children and young adults seem to be disproportionately affected by H5N1 infections, with median ages of affected individuals ranging from 9.5 to 22 years [47]. H5N1 infection has typical influenza-like symptoms but prominently involves

the lower respiratory tract and often is accompanied by a watery diarrhea. Like SARS, lymphopenia, thrombocytopenia, and increased transaminase levels are often present. The most common radiographic findings are multifocal consolidations, and progression to respiratory failure occurs in the majority of hospitalized individuals within 48 hours of admission. Diagnosis relies on consideration of the appropriate epidemiologic context in conjunction with reverse transcriptase PCR of respiratory samples, with pharyngeal samples having a higher yield than nasal specimens.

From what is currently known, the treatment of H5N1 infection does not deviate substantially from the treatment of severe human influenza infections. Supportive care for patients who have H5N1-associated ALI/ARDS should include a pressure-limited, low tidal volume ventilatory strategy. For antiviral treatment, some data indicate that many of the H5N1 strains isolated from humans are resistant to the adamantanes [48], to which the current circulating human influenza strains also have recently become highly resistant. The H5N1 strains isolated from humans have proven susceptible to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), although there have been case reports of isolates resistant to oseltamivir [49]. Prophylaxis of health care workers and postexposure prophylaxis would be essential elements of the response to a pandemic, provided that adequate supplies of neuraminidase inhibitors are available. The potential role of corticosteroids in the treatment of influenza-associated ALI/ARDS is not known.

Like the primary focus in the annual influenza season, prevention of H5N1 infection is justly receiving a great deal of attention. Researchers from throughout the world are racing to develop a vaccine that is highly effective, has low side effects, and can be mass produced in a short period of time. Multiple strategies are being used to produce an immunogenic vaccine. A recent report used two doses of an inactivated subvirion H5 vaccine administered intramuscularly to humans and showed that, at the highest dose of the vaccine administered, approximately half of the patients developed neutralizing antibody titers [50]. The 50% effectiveness of this vaccine contrasts with the 70% to 90% effectiveness of human influenza vaccines in current use. It has been proposed that the use of an adjuvant may increase H5 vaccine effectiveness, because new hemagglutinin proteins in humans may be poorly immunogenic. Other groups are testing live attenuated influenza vaccines and also adenovirus-based immunization strategies, which can elicit a strong T-cell immunity response.

Summary

TRALI, SARS, and H5N1 influenza are recently described causes of ALI/ARDS from which much has been learned, but many questions remain unanswered. The biggest impact on decreasing the incidence of TRALI will be from adherence to evidence-based transfusion guidelines and potentially from regulatory action that limits exposure to blood products or donors that have been consistently implicated in TRALI. The outcomes of recent initiatives by the United Kingdom limiting exposure to female plasma will be followed closely to determine if similar action should be taken in the United States. With the threat of SARS temporarily under control, attention is intensely focused on the pandemic threat of H5N1 influenza, which has the potential to overwhelm existing critical care resources for the treatment of respiratory failure. Undoubtedly, new infectious and noninfectious causes of ALI/ARDS will emerge in the future, mandating vigilance by health care providers, providing a challenge to public health officials and clinical and basic science investigators, and requiring transparent communication among the members of today's global society.

References

[1] Kopko PM, Marshall CS, MacKenzie MR, et al. Transfusion-related acute lung injury: report of a clinical look-back investigation. JAMA 2002; 287(15):1968–71.

[2] Church GD, Matthay MA, Flori HR. Blood product transfusion is independently associated with mortality in pediatric acute lung injury. Proc Am Thorac Soc 2005;2:A244.

[3] Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med 2005;33(6):1191–8.

[4] Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340(6):409–17.

[5] Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive

transfer of antileukocyte antibodies. Am Rev Respir Dis 1983;128(1):185–9.
[6] Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med 2005;33(4):721–6.
[7] Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818–24.
[8] Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest 2004; 126(1):249–58.
[9] Looney MR, Matthay MA. Animal models of transfusion-related acute lung injury. Crit Care Med 2006;34(5 Suppl):S132–6.
[10] Looney MR, Su X, Van Ziffle JA, et al. Neutrophils and their Fcγ receptors are essential in a mouse model of transfusion-related acute lung injury. J Clin Invest 2006;116(6):1615–23.
[11] Nathens AB. Massive transfusion as a risk factor for acute lung injury: association or causation? Crit Care Med 2006;34(5 Suppl):S144–50.
[12] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44(12):1774–89.
[13] Holness L, Knippen MA, Simmons L, et al. Fatalities caused by TRALI. Transfus Med Rev 2004; 18(3):184–8.
[14] Serious hazards of transfusion. Available at: www.shot-uk.org (2004). Accessed June 5, 2006.
[15] Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985;25(6):573–7.
[16] Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353(16):1685–93.
[17] Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood 2003;101(2):454–62.
[18] Seeger W, Schneider U, Kreusler B, et al. Reproduction of transfusion-related acute lung injury in an ex vivo lung model. Blood 1990;76(7):1438–44.
[19] Sachs UJ, Hattar K, Weissmann N, et al. Antibody-induced neutrophil activation as a trigger for transfusion-related acute lung injury in an ex vivo rat lung model. Blood 2006;107(3):1217–9.
[20] Kopko PM, Paglieroni TG, Popovsky MA, et al. TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. Transfusion 2003;43(2):177–84.
[21] Silliman CC, Paterson AJ, Dickey WO, et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. Transfusion 1997;37(7):719–26.
[22] Silliman CC, Voelkel NF, Allard JD, et al. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. J Clin Invest 1998;101(7):1458–67.
[23] Silliman CC, Bjornsen AJ, Wyman TH, et al. Plasma and lipids from stored platelets cause acute lung injury in an animal model. Transfusion 2003;43(5): 633–40.
[24] Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. Transfusion 2004;44(10):1468–74.
[25] Ausley MB Jr. Fatal transfusion reactions caused by donor antibodies to recipient leukocytes. Am J Forensic Med Pathol 1987;8(4):287–90.
[26] Leger R, Palm S, Wulf H, et al. Transfusion-related lung injury with leukopenic reaction caused by fresh frozen plasma containing anti-NB1. Anesthesiology 1999;91(5):1529–32.
[27] Nakagawa M, Toy P. Acute and transient decrease in neutrophil count in transfusion-related acute lung injury: cases at one hospital. Transfusion 2004;44(12):1689–94.
[28] Yomtovian R, Kline W, Press C, et al. Severe pulmonary hypersensitivity associated with passive transfusion of a neutrophil-specific antibody. Lancet 1984;1(8371):244–6.
[29] Church GD, Price C, Sanchez R, et al. Transfusion-related acute lung injury in the pediatric patient: two case reports and a review of the literature. Transfus Med 2006, in press.
[30] Yost CS, Matthay MA, Gropper MA. Etiology of acute pulmonary edema during liver transplantation: a series of cases with analysis of the edema fluid. Chest 2001;119(1):219–23.
[31] Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 2002;288(22):2827–35.
[32] Densmore TL, Goodnough LT, Ali S, et al. Prevalence of HLA sensitization in female apheresis donors. Transfusion 1999;39(1):103–6.
[33] Levy MM, Baylor MS, Bernard GR, et al. Clinical issues and research in respiratory failure from severe acute respiratory syndrome. Am J Respir Crit Care Med 2005;171(5):518–26.
[34] Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348(20): 1953–66.
[35] Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003; 348(20):1967–76.
[36] Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 2003; 302(5643):276–8.

[37] Peiris JS, Yuen KY, Osterhaus AD, et al. The severe acute respiratory syndrome. N Engl J Med 2003; 349(25):2431–41.
[38] Franks TJ, Chong PY, Chui P, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Hum Pathol 2003;34(8):743–8.
[39] Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4.
[40] Lau YL, Peiris JS. Pathogenesis of severe acute respiratory syndrome. Curr Opin Immunol 2005; 17(4):404–10.
[41] Yin-Chun YL, Chun-Wing LA, Yuk-Lin LF, et al. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. J Infect 2006.
[42] Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med 2004;10(12 Suppl):S88–97.
[43] Fauci AS. Emerging and re-emerging infectious diseases: influenza as a prototype of the host-pathogen balancing act. Cell 2006;124(4):665–70.
[44] World Health Organization. Avian influenza. Available at: www.who.int/csr/disease/avian_influenza/en/. Accessed June 5, 2006.
[45] van Riel D, Munster VJ, de Wit E, et al. H5N1 virus attachment to lower respiratory tract. Science 2006; 312(5772):399.
[46] Shinya K, Ebina M, Yamada S, et al. Avian flu: influenza virus receptors in the human airway. Nature 2006;440(7083):435–6.
[47] Beigel JH, Farrar J, Han AM, et al. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005; 353(13):1374–85.
[48] Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353(13):1363–73.
[49] Moscona A. Oseltamivir resistance—disabling our influenza defenses. N Engl J Med 2005;353(25): 2633–6.
[50] Treanor JJ, Campbell JD, Zangwill KM, et al. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N Engl J Med 2006;354(13):1343–51.