

Finding Adolescents and Young Adults With Transfusion-Associated Hepatitis C

Looking Forward to Looking Back

A SMALL PROPORTION OF INDIVIDUALS WITH chronic hepatitis C virus (HCV) infection are children. Although transmission from mothers infected with HCV is currently the primary way in which children are infected, receipt of blood or blood products prior to routine HCV testing had been a common method of acquisition. The first HCV testing was introduced into blood banks in 1990 and a more sensitive assay was introduced in 1992. Receipt of blood or blood products prior to 1992 is considered a risk factor for HCV infection that warrants testing. This recommendation has been made by both the Centers for Disease Control and Prevention¹ and the American Academy of Pediatrics.²

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Children who have been multiply transfused with either blood or blood products prior to 1992, such as those with thalassemia^{3,4} or hemophilia,⁵ have infection rates ranging from 50% to 95%. Children with past transfusion exposure, such as those who had been treated for childhood malignancies,^{6,7} those who had been treated with hemodialysis^{8,9} or extracorporeal membrane oxygenation,¹⁰ or those who had undergone surgery for congenital heart disease,¹¹ have an intermediate anti-HCV seroprevalence of 10% to 20%. In general, the risk of HCV acquisition from blood transfusion increased with the number of units of blood or blood products received.^{8,10} The risk from blood transfusion associated with neonatal intensive care in this country has not been quantified. Because the risk of HCV infection from transfusion of blood, blood products, and organ transplantation has been reduced to a negligible degree, children infected this way are now adolescents and young adults.

Children and adolescents do not donate blood and do not undergo routine blood tests, such as measurement of liver enzymes, during primary care. In many instances, clinicians caring for children are unaware of risk factors such as a remote history of transfusions. Thus, children infected with HCV are unlikely to be identified without being targeted for specific diagnostic testing. These facts raise several important clinical questions for medical providers to older children and adolescents. What is the magnitude of the problem of undiagnosed transfusion-associated HCV in this population? What current programs exist for detecting these infected individuals? What are the risks of chronic HCV over the lifetime of these young individuals? What is the benefit of early

diagnosis? What screening program should be implemented, and how much would it cost?

In this issue of the ARCHIVES, Cagle et al¹² have attempted to begin to tackle some of these questions. Looking at a pediatric population with a relatively high rate of blood transfusion, ie, children who had been cared for in a neonatal intensive care unit (NICU) for more than 2 days, they have conducted a "lookback" and notification program to ascertain the prevalence of HCV infection and the frequency with which at-risk individuals recognized their risk by knowing they had received transfusions. The prevalence of HCV infection was 3% in their overall cohort. Half of those at risk were unaware of their history of blood transfusion. Based on these data, Cagle and colleagues recommend that patients cared for in a NICU before 1992 be tested for HCV.

Data from the National Vital Statistics System indicate that between 1980 and 1989, approximately 1.2% of live-born infants weighed less than 1500 g. Based on birth rates for that decade, 40 000 to 50 000 newborns per year were born at less than 1500 g. Many of these very low-birth-weight infants spend some time in a NICU, and a large proportion (approximately one third in the study by Cagle and colleagues) receive at least 1 blood or blood product transfusion. This translates roughly to 12 000 to 15 000 newborns who receive transfusions per year. If the HCV infection rate was approximately 3%, as in the Alaskan group described by Cagle and colleagues, 360 to 450 newborns acquired HCV each year in the NICU. With rough calculation and some extrapolation, this means that more than 500 000 individuals from the period between 1980 and 1992 would need to be identified and tested to detect about 4500 to 5000 infected persons, depending on the survival rate. These children will now be aged 14 to 26 years, an age group with typically very little physician contact outside of acute illnesses or trauma.

There are no programs currently in effect to identify these adolescents and young adults. In 1998, under guidance of the Food and Drug Administration, a targeted lookback program was established in blood banks. In this program, individuals who received blood from donors who later tested positive for anti-HCV were notified and tested. A significant limitation was the lack of electronic records prior to 1988 in many centers. Approximately 16 000 at-risk recipients had been notified by the time of an interim report.¹³ Although compliance with the recommendations was relatively high, it was estimated that only 0.5% of persons who had acquired HCV by transfusion were newly identified by this method.¹³ The cost of this program has not been reported.

Hepatitis C virus infection has few clinical manifestations during childhood, and the natural history is benign in many cases during the first 2 decades after infection.¹⁴ The proportion of children who will eventually have significant morbidity from HCV acquired early in life has not been clearly established. Although spontaneous viral clearance may occur, the large majority remain infected for many years.¹⁵ Also, it is clear that liver disease does occur in some children and adolescents with chronic HCV, and several studies^{16,17} have demonstrated a correlation between the duration of infection and the degree of hepatic fibrosis. This indicates that although the course may be protracted, it may be progressive. Progression of liver disease may be accelerated by long-term alcohol consumption, other infections, obesity, or hepatotoxic medications. Identification of individuals infected with HCV in the early stages presents an opportunity for counseling to minimize these other factors as well as to prevent transmission to others. In addition, there are data suggesting that therapy is more effective in the early stages of chronic HCV infection.¹⁸ Also, young people may have better tolerance of the rigorous treatment regimen. For these reasons, there are obvious benefits to detecting chronic HCV in adolescents and young adults who were infected near the time of birth.

Logistic feasibility must be considered. The study by Cagle and colleagues is a labor-intensive multistep lookback program for children and adolescents treated at 1 centrally located NICU. The targeted individuals lived in 1 state, Alaska. A significant proportion of the subjects were cared for in an integrated state program, and even in that more easily traced cohort, only 43% of notified subjects were screened by this HCV program. In the private sector cohort, only 20% of those notified returned the HCV questionnaire. Without electronic records that link blood bank records to current demographics, blood banks and hospitals have no straightforward way of identifying and contacting every person transfused prior to 1992, especially given the general lack of electronic records. With this in mind, it would be virtually impossible to design a program that would be efficient at honing in on this highly selected group of adolescents and young adults who were transfused early in life.

No screening program can be discussed without consideration of the cost. Cagle and colleagues have calculated that the cost of notification of each of their subjects at risk was \$105. Their study involved identification and notification of individuals from only 1 NICU. Of 651 notices sent (at a cost of about \$68 355 by their estimate), 26 individuals (35%) eventually participated in the data collection and 6 cases of HCV were identified. There is no way to extrapolate from this what the cost of attempting to find and notify 500 000 persons from NICU records during the period between 1980 and 1992 might be, even if logistically feasible, but it appears that it could be prohibitive. If 35% of notified persons responded and completed testing, this would mean testing in 175 000 persons. The cost of the tests themselves, the follow-up of results, notification and counseling of those found to be infected, etc, would need to be calculated. This could be considered in light of a recent study¹⁹ that estimated the direct medical cost burden of HCV infection in children over a 10-year period to be \$168 million to \$404 million.

What makes the most sense then? Primary care providers such as pediatricians, internists, family care physicians, and gynecologists need to be reminded that there are, no doubt, young patients in their practices with unrecognized HCV infection. Simply asking patients whether they have a history of blood transfusions is not enough, especially when those transfusions may have been administered in the newborn period. As Cagle and colleagues have indicated, it may be most prudent and cost-effective to be alert to this risk and to test all individuals aged at least 14 years who had been treated in a NICU for HCV as they are recognized.

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