In this study, AHF lot B was derived solely from plasma tested by a high-titer B19 NAT screening procedure and had no detectable B19 DNA. In contrast, AHF lot A was mostly derived from unscreened plasma. The transmission case might not have occurred had B19 NAT screening been performed. That is, if donations with high levels of B19 DNA had been identified, the high-titer plasma pool for the implicated lot, 10^7 geq per mL, would not have existed. A B19 transmission by a similar S/D-treated, immunoaffinity-purified, AHF product to a seronegative child with mild hemophilia A, who had not been previously infused with any blood product, has been documented.[16] As in most reported cases, however, sequencing analysis was not performed and the amount of B19 DNA infused was unknown.

Little is known regarding the correlation between a product's infectivity and its B19 DNA content. The B19 infectious dose in susceptible individuals, that is, presumably seronegative persons, would be expected to vary depending on whether the product contained anti-B19 IgG antibodies. For example, pooled plasma, S/D-treated, had levels of anti-B19 IgG[11,29] approximately 40 IU per mL in every product lot because each pool of plasma represented up to 2500 plasma donations. Only those seronegative volunteers infused with a 200-mL dose of product lots containing greater than 10^7 geq per mL B19 DNA were infected, whereas those infused with an equal volume of lots containing less than 10^4 geq per mL did not seroconvert.[29,30,32]

In a separate transmission case, a seronegative child was infected by infusing a dry heat–treated FVIII concentrate, which contained 4×10^3 geq per mL B19 DNA, over a period of 52 days.[17] The total infectious dose for this case was equivalent to 4×10^6 geq of B19 DNA from a product whose anti-B19 content, if any, was unknown. In our study, the seronegative recipient was infected by receiving a total of 2×10^4 geq of B19 DNA from a product that contained no detectable B19 IgG.

In conclusion, we have confirmed B19 transmission in a recipient of a S/D-treated high-purity AHF product derived from mostly B19 NAT unscreened plasma. The seronegative recipient became infected after receiving 2×10^4 geq (or IU) of B19 DNA present in the product.

Therefore, to safeguard the viral safety with respect to B19, minipool screening by B19 NAT should be implemented to reduce the level of potentially infectious B19 virus in the resulting products, especially those without the presence of anti-B19.

ACKNOWLEDGMENTS

We thank J.S. Finlayson, PhD, for critical review of the manuscript and Donald Baker, PhD, of Baxter BioScience for providing not only the information regarding NAT screening status relevant to implicated AHF lots but also relevant plasma pools for analysis. In addition, we appreciate the staff of the Dartmouth Hitchcock Hemophilia and Thrombosis Center for assistance with collecting data for this project and Mary Hitchcock Memorial Hospital for identification of the specific implicated lots of AHF.

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医薬品　研究報告　調査報告書

識別番号・報告回数		第1報	報告日	第一報入手日 2005年3月10日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥濃縮人アンチトロンビンIII		研究報告の公表状況	International J of Hematology 80(2004) 301-305 Current safety of the blood supply in the United States	公表国 米国	
販売名（企業名）	アンスロビンP-ベーリング (ZLB ベーリング株式会社)					

研究報告の概要

問題点（現在の米国での血液供給の安全性）

米国で実施している血液製剤の安全対策に関する総説論文である。米国において、献血ドナーを注意深く選択し、スクリーニングの問診、NAT などの各種ウイルスのテストを実施した結果、HIV と HCV 感染は献血 1500 万件ついて 1 件に減少している。
しかしながら、新興感染症であるシャーガス病、バベシア症、マラリア、WNV と vCJD に注意しなければならない。
バベシア症は、ダニによる感染である。米国で輸血によるバベシア症の感染は約 50 件の報告がある。日本は 1 件の報告がある。献血時のスクリーニングテストはなく、問診等も効果がない。輸血感染による致命的な症例はないが、高齢者、免疫低下患者、無脾症患者は危険性がある。
マラリアは、米国で年間 1-2 例の輸血感染がある。献血時の問診で渡航歴の危険性の高いドナーは排除しているが、最近の感染例はこの問診時に問題があったためである。
シャーガス病は、ラテンアメリカでは一般的な寄生虫(T. cruzi)疾患であり、米国で4件、カナダで2件の確定した感染報告がある。現在米国でT. cruzi抗体のテストはない。献血時にシャーガス病であるか問診されるだけである。臨床研究によると、輸血を受けた総計120,000人の心臓手術患者でT. cruziが感染した例はない。
WNVのNAT導入により、約1000件のWNV-RNA陽性の献血ドナーを見つけ、感染の伝播を防いでいる。WNVの低titerやミニプールNAT検出レベル以下の場合、検出できず感染する恐れがあるが、確定された感染例はない。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
採血国である米国の血液供給を脅かす情報を入手した為、報告する。 シャーガス病は、T. cruzi による感染症で、大きさが約 20 ミクロンであり、本剤を含む弊社の血漿分画製剤における製造工程、特に滅菌ろ過(0.22 ミクロン等)で十分除去できるものである。また輸血からの感染報告は存在するが、血漿分画製剤からの感染の報告はない。また 63℃、30 分の加熱で死滅する報告がある。 マラリアも同様に、血液製剤の製造過程で寄生虫は除去される報告がある。 シャーガス病、マラリア、バベシア症に関して、弊社の血漿分画製剤は滅菌濾過等により安全である。 WNVも、製造工程中で60℃10時間の液状加熱で不活化されるので、本剤では特に問題ないと考える。	今後ともvCJDなどの新興感染症に関する情報収集に努める所存である。

(14)

Progress in Hematology

International Journal of
HEMATOLOGY

Current Safety of the Blood Supply in the United States

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Received August 16, 2004; received in revised form May 24, 2004; accepted September 3, 2004

Abstract

In common with other developed countries, the United States has placed a great deal of emphasis on blood safety. As a result of careful donor selection and the use of advanced tests, including nucleic acid testing (NAT), the risk of transmission of human immunodeficiency virus and hepatitis C virus has been reduced to about 1 in 1.5 million donations. NAT for hepatitis B virus has not been introduced, but nevertheless the risk is low. Attention recently has been focused on emerging infections. NAT for West Nile virus was implemented within 6 to 8 months of recognition of the need to prevent transfusion transmission of this newly introduced virus. Approximately 1000 potentially infectious donations were identified and removed from the blood supply during the 2003 season. Other emerging infections attracting attention include Chagas' disease, babesiosis, malaria, and variant Creutzfeldt-Jakob disease.

Int J Hematol. 2004;80:301-305. doi: 10.1532/IJH97.04123

Key words: Blood transfusion; HIV; Hepatitis C; Hepatitis B; Emerging infections

1. Introduction

In the United States, blood safety depends on selection of voluntary donors, extensive use of screening questions, laboratory testing, and maintenance of deferral registries. These processes are highly regulated and are managed under voluntary quality systems such as the standards of the American Association of Blood Banks (AABB). Over the years, there has been a process of continuing improvement, particularly in testing. This process has resulted in a very low frequency of residual infectivity from the blood supply, at least for hepatitis and retroviral infections. The recent introduction of nucleic acid testing (NAT) has had a major impact on safety [1-3]. At the same time, a number of new threats to blood safety have appeared and necessitated additional donor deferral and/or testing measures [4]. Notable among these new infections have been West Nile virus (WNV) and variant Creutzfeldt-Jakob disease (vCJD).

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2. Current Risk of Hepatitis Viruses and Retroviruses

The original approach to controlling transfusion-transmitted hepatitis and, later, acquired immunodeficiency syndrome (AIDS) involved careful questioning of donors about their medical history and risk behaviors. The majority of these questions are still in place, despite the use of tests of increasing sensitivity. Overall, however, very few donors are deferred as a result of these questions, but there is good evidence that almost 2% of donors may fail to report deferrable risk behaviors during the donation process [5]. Nevertheless, both the prevalence and incidence of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection among donors is much lower than that attributable to the general population (Table 1) [6]. It seems likely that the majority of infected and at-risk individuals do not donate as a result of the use of a voluntary donor population along with broad public education.

In the United States, the following tests are performed on all blood donations: antibodies to hepatitis B core antigen (anti-HBc), hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (anti-HCV), antibodies to HIV-1 and HIV-2 (anti–HIV-1/2), antibodies to human T-lymphotrophic virus I (HTLV-I) and HTLV-II (anti–HTLV-I/II), serologic test for syphilis, and minipool NAT for HIV and HCV RNA. In addition, all donations are tested by investigational NAT

next 2 years, a similar number of cases were seen, but surveillance studies revealed that the virus was spreading to a larger area each year. The major amplifying hosts were a number of bird species, and significant avian mortality occurred. At that stage in the epidemic, there was little concern about the risk of transfusion transmission of WNV, although a risk estimate was published for the initial outbreak [12]. In 2002, however, there was an enormous outbreak of human cases, totaling 4156 with 284 deaths and affecting the majority of the continental United States. Of most concern, 61 potential cases of transfusion-transmitted WNV infections were reported, and of these 23 were confirmed [13]. In all cases in which samples of the implicated donations were available, it was found that readily detectable levels of WNV RNA were present.

These observations led to rapid development and implementation of NAT for WNV. The decision to move toward such testing was made in September 2002, and tests were fully in place before the start of the 2003 WNV season in July. During 2003 there were 9388 human cases of WNV disease with 246 deaths. The cases occurred over an even broader geographical area than that affected in 2002. Blood collectors identified approximately 1000 WNV RNA–positive donations (a rate of about 1 in 5000), preventing many potential infections among blood recipients. In some localities, the frequency of finding RNA-positive donors was extremely high (for example, 1 in 47 in parts of Nebraska) [14]. As a result of concerns that NAT in minipools did not detect all RNA-positive donations and the eventual demonstration of recipient infections attributable to such low-titer samples, limited single-donation testing was implemented in some areas of highest incidence of WNV infection. It was clear that this approach did detect some otherwise undetectable, potentially infectious samples. The practice of performing resource-limited single-donation testing of this type continued into the WNV season in 2004. During 2003, 6 confirmed cases of transfusion-transmitted WNV were reported. All seemed to be attributable to donations with very low titers of WNV, below the levels detectable by minipool testing. As of this writing, however, there has been no authenticated case in which transmission has been attributable to a blood unit with detectable levels of WNV immunoglobulin M (IgM), although it is known that IgM and WNV RNA may coexist for a time. Thus the unexpected emergence of WNV and the finding of its transmissibility by transfusion posed a significant challenge in 2002 [15]. Rapid development and implementation of NAT clearly had a significant impact on the problem, although it has not proven possible to entirely eliminate the risk.

4. Other Infections

4.1. Syphilis

All donations are tested for syphilis with treponemal tests, nontreponemal tests, or both. There has been no reported case of transfusion syphilis in the United States for well over 40 years. It is possible that this outcome is a result of continuing testing, and it has not proven possible to eliminate the requirement for such testing [16]. In recent studies, however, Orton and her colleagues did not find treponemal DNA and/or RNA in 169 blood donor samples with confirmed positive serological test results for syphilis [17]. Thus the potential for detection of an infectious sample appears to be low.

4.2. Malaria

Malaria is probably the infection most frequently transmitted by transfusion. However, such transmission is a rarity in the United States with only 1 or 2 cases annually [18]. Approximately 1000 cases of imported malaria are diagnosed each year in the United States. This number is small compared with the numbers in, for example, Western Europe. There is a comprehensive effort to exclude at-risk donors by careful questioning about their travel history. Many of the recent cases of transfusion transmission of malaria appear to be attributable to failures in the questioning process. Although endemic malaria has been eliminated from the United States, there is concern about the occurrence of epidemiologically unexplainable cases, most recently in Virginia and Florida. At least some of such cases are attributable to mosquito-borne transmission from migrant workers or travelers, but it is clear that a questioning strategy would be ineffective in identifying such secondary cases if the individuals were to present to give blood. This is a situation that deserves future scrutiny.

4.3. Chagas' Disease

It is well-established that Chagas' disease (caused by the protozoan parasite *Trypanosoma cruzi*) is transmitted by blood transfusion. In Latin America, where human infection is endemic, it is estimated that a recipient of parasitemic blood has a 12% to 50% chance of being infected. Because infection is often lifelong, population movements from endemic areas lead to the presence of infected and potentially infectious individuals in nonendemic areas such as the United States. There have been a total of 6 well-authenticated transfusion transmitted cases of *T cruzi* infection in the United States (4 cases) and Canada (2 cases) [4]. These cases are thought to be a substantial minority of the cases that might occur, because the disease is not readily diagnosed, nor is it often suspected. One of the recognized cases was identified only as a result of careful follow-up of a patient inadvertently given a transfusion of seropositive platelets [19]. Essentially all cases were traced to donors who had been infected early in life in areas of endemicity. There is currently no testing for *T cruzi* antibodies in the United States, and donors are asked only if they have had Chagas' disease. This measure is very insensitive [20]. Seroprevalence studies have shown that in areas with a high proportion of migrants from Latin America, as many as approximately 1 in 7500 donors may be in the seropositive state, and approximately 60% of these donors actually have parasitemia, as demonstrated by polymerase chain reaction analysis and or parasite culture [4]. It is thought that the national seroprevalence rate may be between 1 in 40,000 and 1 in 25,000, suggesting a potential for a few hundred infections each year. Lookback studies, however, did not identify any infected recipients within a group of 19 patients who received blood

been shown that a rapid response to a newly emerging, transfusion-transmissible agent is possible, as in the case of WNV.

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