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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	
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研究報告の概要	使用上の注意記載状況・その他参考事項等
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。	

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。

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Current Safety of the Blood Supply in the United States

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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.

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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

Table 1.
Prevalence and Incidence of Major Transfusion-Transmissible Infections among the US Population and among US Voluntary Blood Donors*

Infection	Prevalence, pht		Incidence, phtpy	
	Population	Donors	Population	Donors
HBV (HBsAg)	420	77	27.9	1.3
HCV	1800	304	8.9	1.9
HIV	200	10	14.3	1.6

*From [1,6]. pht indicates per hundred thousand; phtpy, per hundred thousand person-years; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

for WNV RNA (see later). Despite the use of these tests, posttransfusion infections continue to be reported [7-9]. Essentially all of them have been identified as a result of focused lookback procedures. The frequency of these occurrences is very low, but the efficacy of reporting is questionable. Consequently, the risk of transfusion-transmitted infections is usually projected from evaluation of donor testing results.

A number of circumstances may contribute to posttransfusion infections, even when laboratory tests are used. These circumstances include laboratory error, infections with variant or mutant viruses that evade detection, and collection of blood during the window period. Busch analyzed the relative contribution of each of these factors and concluded that the major risk of posttransfusion infection is collection of blood during the test-negative window period [10].

The risk of residual infection from window-period donations can be calculated by simply multiplying the length of the window period by the incidence of new infection in the donor population. The window period for key transmissible infections has been defined either by direct observation of the period between exposure and development of the infection marker or by calculation from lookback cases. The window period estimates have been continuously corrected to reflect the use of tests of increasing sensitivity. The assessment of the effect of such tests has been done by examining closely spaced samples collected during seroconversion. Such panels of samples have been obtained from plasmapheresis donations.

The primary means of defining incidence rates among donors has been by direct observation of the frequency of new infections in large populations of regular donors. Thus many estimates of residual risk are applicable only to repeat donors. However, the incidence rates for infections among first-time donors also have been measured by careful use of modified or additional tests. For example, Janssen and colleagues used a less-sensitive anti-HIV test to measure the proportion of HIV-positive donors who were in the first 3 months of infection [11]. These observations allowed direct measurement of incidence. Somewhat similarly, Dodd and colleagues evaluated the frequency of donations that were positive for HCV RNA but negative for anti-HCV among first time donors [1]. Knowledge of the length of the RNA-only period again allowed estimation of the incidence rate for HCV. It was interesting that both of these studies showed that in US donor populations, the incidence of new infections among first-time donors is about 2.4-fold greater than that among repeat donors.

Table 2 shows an estimate of residual risk of retroviruses and hepatitis viruses among voluntary blood donors in the United States, both for repeat donors and for the overall donor population, which includes approximately 22.8% donations from first-time donors. In some cases (HBV and HTLV), there is no direct measure of incidence among first-time donors, so it has been assumed that the frequency is 2.5-fold greater than that for repeat donors. The impact of NAT also is shown in Table 2.

Since 1999, all donations in the United States have been tested by nucleic acid amplification methods for the presence of HCV and HIV RNA. Two commercial methods are in use, and most testing is performed on minipools of 16 or 24 samples, depending on the selected method. The yield of RNA-positive, antibody-negative samples has been 1 in 230,000 for HCV and 1 in 3.1 million for HIV [2]. As Table 2 shows, the impact of removing these donations from the blood supply has been reflected in an appreciable increment in blood safety. At the time of this writing, procedures for detecting HBV DNA in minipools have been evaluated, and data have been submitted to the US Food and Drug Administration in support of applications for licensure of these procedures. In at least one study, a small number of HBV DNA–positive yield samples were detected, but it is anticipated that HBsAg tests of increased sensitivity will offer a similar safety increment to DNA testing in minipools.

3. West Nile Virus

WNV is a good example of the unexpected emergence of an existing virus in a previously uninfected geographic locale. WNV is a flavivirus of the Japanese encephalitis serogroup. It is spread mainly by mosquitoes and, until the outbreak in the Americas, was endemic only in southern Europe, parts of Africa, and the Middle East. In these locations, the virus seems to be largely in equilibrium, although there have been a number of localized outbreaks of human disease. In these areas, the virus had never been considered to offer any threat to blood safety.

In 1999, WNV appeared for the first time in North America, in the form of a small but intense outbreak in New York City with 66 recognized human cases and 2 deaths. In the

Table 2.
Estimated Residual Risk of Infection from the American Red Cross Voluntary Blood Supply*

Infection	Residual Risk from	
	Repeat Donors	All Donors
HBV	1:205,000	1:144,000
HCV without NAT	1:276,000	1:199,000
HCV with NAT	1:1,935,000	1:1,390,000
HIV without NAT	1:1,468,000	1:1,048,000
HIV with NAT	1:2,135,000	1;1,525,000
HTLV	1:2,993,000	1:1,208,000

*Adapted from [1]. HBV indicates hepatitis B virus; HCV, hepatitis C virus; NAT, nucleic acid testing; HIV, human immunodeficiency virus; HTLV, human T-lymphotrophic virus.

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

from donors subsequently found to have seropositive results. A study of cardiac surgery patients receiving a total of approximately 120,000 transfusion products did not identify any new transmissions of *T cruzi* [21]. It is possible that in an environment in which component therapy is the rule, most transmissions actually come from platelets rather than red blood cells.

4.4. Babesiosis

Babesia organisms are small, intraerythrocytic protozoan parasites. Their natural hosts are mammals, and they are transmitted by ticks. Humans are accidentally infected as a result of a bite from an infected tick. In the United States, the predominant species is *Babesia microti*, which is endemic in the Northeast coastal area and in parts of the upper Midwest (Wisconsin and Minnesota). Other species have been found on the West Coast and in Missouri and Kentucky. Approximately 50 cases of transfusion-transmitted babesiosis have been reported in the United States. However, seroprevalence studies show that approximately 1% of blood donors are antibody-positive in endemic areas of Connecticut and as many as 60% of these individuals may have parasitemia and transmit the infection to recipients of their blood. The overall infection risk in Connecticut has been estimated at 1 per 1800 units of red cell concentrates [4]. It is interesting that there has been a single report of transfusion transmission of *Babesia* organisms in Japan [22]. No routine test is currently available, and epidemiologic or risk questions are ineffective in identifying infectious donors. In most cases, the disease is readily treatable. However, some fatal transfusion-transmitted cases have occurred. Elderly, immunocompromised, and asplenic patients are at most risk.

4.5. Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies (TSEs) are progressive, uniformly fatal, degenerative neurologic diseases that occur in mammals and humans. The prototypic human TSE is Creutzfeldt-Jakob disease (CJD), which occurs with a worldwide annual incidence of about 1 per 1 million. The TSEs are thought to be caused by prions, or conformational variants of a normal protein. It is thought that the pathologic form of the prion can catalyze the same conformational change in the normal protein, thus replicating the infectious agent. The prions are themselves infectious, and CJD has been iatrogenically transmitted by the use of neurosurgical instruments, by transplantation of dura mater prepared from infected donors, and by the use of pituitary-derived human growth hormone. A particular feature of the infectious agent of TSEs is its resistance to inactivation. For many years, there has been concern that CJD might be transmissible by blood transfusion, but at the time of this writing, there has been no evidence of such transmission.

Over the past 15 years, a new TSE, bovine spongiform encephalopathy, has emerged among cattle, particularly in the United Kingdom, where hundreds of thousands of cases occurred [23,24]. The disease also has been reported from many countries and has a global distribution, probably as a result of export of cattle feed and live cattle. The disease arose as a result of a policy of feeding meat and bone meal to cattle, allowing recirculation of the infectious agent. The infectious agent has been transferred to human populations as a result of consumption of meat and meat products from affected animals. The resulting human disease is a clinically and pathologically distinct TSE termed variant CJD (vCJD) [25]. As of the middle of 2004, almost 150 deaths had been attributed to vCJD, the majority of which occurred in the United Kingdom. Because of its natural history, distribution in the body, and results of animal model studies, it was feared that vCJD might be transmissible by transfusion. At the time of this writing, 2 likely cases of such transmission have been reported, both in the United Kingdom [26,27]. As of this writing, it is not possible to characterize the actual risk of further cases, although the risk is likely to be very low. A number of precautionary measures have been taken to reduce the risk. In particular, in countries outside the United Kingdom, persons who have spent time in the United Kingdom or in other European countries are deferred from donation.

4.6. Bacteria

The most frequent microbial adverse events in transfusion medicine are septic reactions due to bacterial contamination of platelet products. A US national surveillance study showed a rate of confirmed septic events of approximately 10 per 1 million platelet transfusions, and approximately 20% of these events were fatal [28]. In contrast, a prolonged study in a single hospital showed a frequency of patient reactions of approximately 1 per 15,000 units transfused [29]. Although it was generally accepted that the risk of such reactions increased with the length of storage (which is up to 5 days in the United States), the national study reported that deaths occurred at a median of 2.5 days of storage, perhaps as a result of the presence of fast-growing bacteria [28]. In a number of countries, procedures to evaluate platelet contamination by automated culture have been implemented. In the United States, in March of 2004 the AABB started requiring methods for limiting and detecting bacteria in platelets. Almost all apheresis platelets are evaluated by automated culture, but this practice has not proved possible for whole blood–derived platelets, which are generally evaluated by surrogate methods with lesser sensitivity. Overall, apheresis platelets are yielding reactive culture results at a rate of about 1 per 2000, but one half or more of such findings are falsely positive. It seems likely that these measures will prevent the transfusion of at least a proportion of bacteria-contaminated platelets.

5. Summary

Overall, the risk of infection from blood transfusion is very low in the United States, significantly less than 1 in 1 million for HCV, HIV, and HTLV. The risk of HBV infection may be somewhat higher, although there are essentially no contemporary reports of posttransfusion hepatitis B. In contrast, it appears that the risk of infection by other agents (particularly certain parasites) may be much greater. It has

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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