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販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社)			

研究報告の概要

○B型肝炎ウイルス陽性となった供血者と血液の管理に関するヨーロッパの考え方

2005年7月21日、米国FDAの血液製剤諮問委員会(BPAC)の会合が開かれ、「核酸増幅検査(NAT)でB型肝炎ウイルス(HBV)陽性となった供血者と血液の管理」に関して勧告された。一部の血液センターでは、B型肝炎表面抗原(HBsAg)とB型肝炎コア抗原に対する抗体(HBc抗体)検査に加えてHBV NAT検査の実施を選択した。供血者のリエントリーについては基準の検討中である。

ヨーロッパ北西部ではHBVの有病率は低く(1%未満)南部では高い(5~15%)。南東部ではジェノタイプDが多く、北西部ではジェノタイプAが多く見られる。有病率の低い国では抗HBcスクリーニングが導入されており、有病率の高い南欧の国ではHBV NATが導入される傾向にある。感染の広がっていない国ではどちらも実施されていない。

HBVの感染ルートはほとんどが性感染や静注薬物乱用であり、HBV NATで検出されるのは、HBsAgが検出される前のウインドウ期の症例およびオカルト感染症例の双方である。人口移動によってHBVジェノタイプの種類が多様化し、感染リスクが高まることも指摘されている。

オカルトHBV症例の中で、HBs抗体陽性のものは感染しないが、HBs抗体陰性であれば感染性があると考えられる。HBV DNA、HBc抗体陽性でHBs抗体レベルが100IU/L以上の場合は供血を続けることができるというリエントリー・アルゴリズムが検討されている。HBs抗体陰性のオカルトHBVキャリアでは、DNA検査の結果に誤りがあったと証明されない限り、リエントリーは認められない。

効果的なHBV NATスクリーニングシステムと症例の積み重ねの経験のみが、この補完検査アルゴリズムが血液の安全性と供血者の管理の向上にとって最善、実用的、決定的なものであるかどうかを教えてくれるだろう。

報告企業の意見	今後の対応
B型肝炎ウイルス陽性となった供血者と血液の管理に関して、ヨーロッパではHBV DNA、HBc抗体陽性でHBs抗体レベルが100IU/L以上の場合は供血を続けることができるというリエントリー・アルゴリズムが検討されているとの報告である。	日本赤十字社では、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。HBV感染に関する新たな知見等について今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

MedDRA/J Ver.9.0J

COMMENTARY

A European perspective on the management of donors and units testing positive for hepatitis B virus DNA

On July 21, 2005, the US FDA's Blood Products Advisory Committee (BPAC) met to advise FDA on "Management of Donors and Units that Test Positive for Hepatitis B Virus (HBV) DNA by Nucleic Acid Tests (NAT)." The best and most complete record of the meeting is the transcript, slides, and accompanying material.[1]

With the approval of the COBAS Ampliscreen HBV test, some US centers have opted to test for HBV NAT in addition to hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc), which are both required for whole-blood donations (source plasma omits anti-HBc testing).[2] The algorithm does not change previous FDA deferral guidance, but the reentry of donors who may have a false-positive NAT test is under regulatory consideration. (Tables 1 and 2 in Reference 2 summarize the deferral algorithm for whole blood and source plasma.[2]) The algorithm follows three main principles:

1. Any HBsAg repeatedly reactive donor (initial screen positive with at least one of two repeat tests positive) that is confirmed by neutralization is permanently deferred.
2. Any NAT-positive and anti-HBc repeat-reactive donor (both lacking a licensed confirmatory test) is permanently deferred (two positive screening tests employing different laboratory methods).
3. Any NAT-positive HBsAg repeat-reactive donor without neutralization confirmation may be reentered.

Reentry can be evaluated at 6 months by the donation facility by retesting the screening panel (the NAT test would be single unit, not pooled) without a blood unit donation to protect against accidental release. If testing before the 6-month point has been performed for medical or donor notification, any NAT test positive permanently defers the donor.[2] If reentered, normal screening would be done on the next donation, thus providing two testing opportunities of the donor's blood following a deferral.

Based on the scientific data, BPAC unanimously agreed with FDA's proposal that

1. A donor of whole blood and blood components for transfusion who tests HBV NAT positive, anti-HBc nonreactive, and HBsAg nonreactive or HBsAg repeatedly reactive and/or not confirmed by neutralization may be reentered, if after a minimum period of 6 months, a sample from the donor tests negative for HBV DNA by individual-donation NAT, nonreactive for anti-HBc, and nonreactive for HBsAg.
2. A donor of source plasma for further manufacture into plasma derivatives who tests HBV NAT positive and HBsAg nonreactive or HBsAg repeatedly reactive and/or not confirmed by neutralization may be reentered, if after a minimum period of 6 months, a sample from the donor tests negative for HBV DNA by individual-donation NAT and nonreactive for HBsAg.

BPAC did not propose or approve any alternative approaches that the FDA should consider.[1] This commentary will provide a European viewpoint, with the *Guidelines for the Blood Transfusion Services in the UK*, 7th Edition, cited as a background reference.[3]

COMMENTARY: THE HBV DNA SITUATION IN THE EUROPEAN UNION

HBV epidemiology in Europe is characterized by a northwest to southeast shift in infection prevalence and genotype distribution. There is a low prevalence of HBV in the northwest (<1%) and higher in the south (5-15%), with genotype D more prevalent in the southeast and genotype A in the northwest.[4] As a result of the differences in prevalence, approaches to transfusion safety vary. In countries of relatively low prevalence such as France, Germany, or Ireland, anti-HBc screening has been introduced; in other countries, such as Greece, Italy, Spain, and Portugal, with higher prevalence, screening for anti-HBc would defer an unacceptable number of donors and blood banks are inclined to implement HBV-NAT. In most low endemic countries, neither anti-HBc nor NAT has been implemented for a variety of reasons including lack of cost-efficiency.

To date, there is no consensus in the EU or at national levels regarding HBV NAT except in Poland, where it was made mandatory in 2005 to test in either individual plasma samples or pools of no more than 24 donations, depending on the test manufacturer. Although not mandatory in Germany, Austria, and Luxembourg, some blood

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banks in these countries have implemented HBV NAT in pools of various sizes, utilizing in-house or commercial assays, in which the loss of sensitivity is often compensated by a concentration step by ultracentrifugation.

The CE marking of the GenProbe/Chiron TMA triplex for HCV, HIV, and HBV genomes in 2004, called Ultrio, has somewhat modified the blood centers' attitude with regard to HBV NAT, particularly in those areas of southern Europe where HBV infection is prevalent but anti-HBc testing impractical. In these countries, HCV NAT is mandatory and HIV NAT rapidly spreading. A desire to ensure blood safety suggested more attention to HBV and the cost increase from the duplex (Procleix) to the triplex (Ultrio) appeared to be acceptable.

The epidemiology of HBV in southern Europe has changed with the widespread use of HBV vaccination, either in infants or in older children, beginning in the mid-1980s. These infant immunization programs have not yet significantly affected blood donors. HBV infection routes are mostly sexual or through intravenous drug abuse. As a result, the intended targets of HBV NAT are both incident cases in the pre-HBsAg window period and HBsAg-negative late stages of chronic or recovered infection (occult HBV infection is defined as a carrier of HBV DNA without detectable HBsAg irrespective of the anti-HBc and anti-HBs status).[5] In both cases, but more so in occult infection, DNA levels are very low, defeating the pooling strategies designed for HCV and HIV NAT. The proponents of HBV DNA screening also point out that the increasing influx of workers from areas of high HBV endemicity and their families will progressively diversify the spectrum of HBV genotypes and increase the risk of HBV in the donor pool. Overall, while centers in Germany, Austria, and Luxembourg continue pool testing, individual blood centers of southern Europe have mostly chosen individual donation screening (80%) or testing on small pools of eight samples (20%). No data have been published yet since screening started in 2005. Unpublished data suggest, however, that occult HBV infections are considerably more frequent than window-period cases. Health authorities in the EU and in individual countries are probably awaiting these data to define a policy that is likely to be heterogeneous depending on member state epidemiology.

In the European discussion forum, the position taken by the FDA is interesting but applies to donated blood screened for anti-HBc. The European situation more frequently tests donors without anti-HBc, although screening for anti-HBc is being considered as a strategy to avoid NAT and still be able to defer occult HBV carriers with detectable levels of anti-HBc. Dealing with three assays (HBsAg, anti-HBc, and HBV DNA) has the considerable advantage of assuming that two positive markers would be confirmatory and direct the permanent deferral of the donor. In European countries where NAT will be implemented without anti-HBc, the issue raised by the BPAC panel of an absence of licensed confirmatory HBV DNA assay will not be a factor since both Ultrio and Roche COBAS Ampliscreen HBV DNA are CE-marked. Either assay can be used for screening; the alternate can be used for confirmation.

Moreover, in countries where anti-HBc testing is introduced, it is common practice to measure the anti-HBs titer to determine the recovery status of the donor. In Germany, an algorithm is being considered to reinstate HBV NAT–negative anti-HBc–positive donors on the basis of an anti-HBs titer. Among occult HBV cases, those with anti-HBs (recovered) are unlikely to be infectious while those without anti-HBs (anti-HBc only) may be infectious. Examples of HBV transmission by transplanted livers from anti-HBs–positive donors, however, suggest caution when anti-HBc– and anti-HBs–positive blood components, even with titers of greater than 100 IU per L, are transfused to immunodeficient recipients. Nearly 50 percent of the transfused blood in Western Europe is given to recipients with some level of immunodeficiency. As a result the proposed algorithm being anti-HBc instead of HBV NAT is that every anti-HBc–positive sample be tested for both anti-HBs and HBV DNA. Donors HBV DNA–positive would be permanently deferred but those DNA negative with anti-HBs levels of at least 100 IU per L could continue donating. This prudent attitude is not necessarily endorsed by all European blood services or regulatory agencies. Where HBV NAT is implemented, detection and titration of anti-HBs would be useful to counsel donors, an anti-HBs titer of at least 100 IU per L strongly suggesting noninfectivity (see Fig. 1). This algorithm is hypothetical and to our knowledge not implemented anywhere in Europe.

For occult HBV without anti-HBs (anti-HBc only or DNA only), reentry is not an option unless the DNA result can be proven erroneous. We remain concerned that these donors may be infectious. There are a few reported cases of infectivity by transfusion and many of infectivity by transplanted organs from donors with the anti-HBc–only profile. Some cases might carry anti-HBs at the viral surface without detectable circulating anti-HBs, and those might be revealed by dissociation procedures. Others, and probably the most frequent, correspond to the tail end of chronic carrier state at the nonreplicative phase and are more likely infectious. This area remains problematic, and detailed characterization of the virus and solid clinical data are critically needed.

Although contamination has been raised as a source of difficulty for interpretation of positive tests, going back to the original units was not recommended. In Europe, it is likely that both returning to the collected unit and accessing the mandatory archived samples will be authorized. In Europe, unlike the United States, it is mandatory that a sample from all tested blood donations be kept for 2 years or more, depending on the country. This sample is

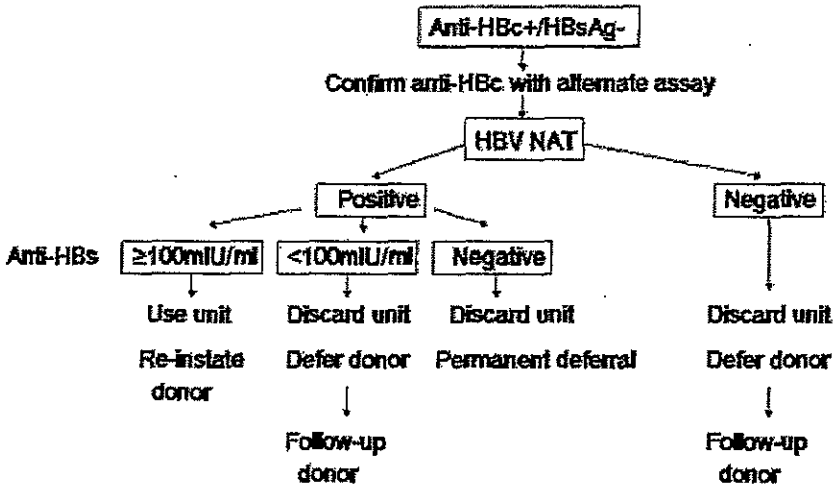

Fig. 1. Proposed European algorithm for blood donors anti-HBc–positive and HBsAg-negative.

intended for studies related to potential or emerging infectious agent transmission by transfusion. The alternative method of HBV diagnosis confirmation provided by the comparison of sequences will be difficult to implement for two reasons: one is that even in the most variable pre-S-S region, identical sequences within the same genotype are often found; the second is that when dealing with a low viral load, this method has a high failure rate.

The last and probably the most relevant issue is that a sample from an individual with a very low viral load might well be negative 6 months after deferral due to fluctuation of DNA level in occult infections.[6] Reinstatement of a NAT-positive donor on the basis of a negative result in a second test of the index donation or in a follow-up sample at 6 months tends to become "a lottery." Many Mediterranean blood banks that use HBV NAT on individual donations have started to confirm NAT reactivity not only with alternate assays, but also with duplicate or multiple repeat NAT screening tests. This procedure enables them to minimize the risk of missing low-level HBV DNA carriers and alerts them in time to save the unit for HBV resolution testing, which involves nucleic acid extraction from larger plasma volume and serological assays (N. Lelie, personal communication).

On both sides of the Atlantic, only experience with efficacious HBV NAT screening systems and the accumulation of yield case data will tell whether a given supplementary test algorithm is optimal, practical, and critical for improving blood safety and donor management.

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別紙様式第2-1

No. 26

医薬品 研究報告 調査報告書

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研究報告の概要

○遡及調査からみた残存リスクの評価

HBV、HCV、HIVについて、2000年2月から2004年1月までの4年間の遡及調査と、従来のヘモビジランスの結果から、日本での輸血感染症の実態を報告する。遡及調査は、主に複数回献血者において感染症マーカーが陽転した場合に前回の血液のサンプルを個別NATで精査するもので、HBVについては50プールNAT、HBsAg、HBcAbのいずれかの陽転例約1万6千人について前回の保管検体を調べた。全体で1.01%が個別NATで陽性であった。HBcAbの有無でこれを分類すると、その60%はHBV感染既往者(オカルトキャリアー)、40%がウインドウピリオドのドナーによるものであった。これらの個別NATのみ陽性の血液を輸血された患者63人の輸血前後の情報を集めると、感染が確認された患者は12人のみであった(感染確率19%)。感染を起こした血液をHBcAbの有無で分類すると、ウインドウ期由来の血液は22本のうち11本が感染を起こした(感染確率50%)のに対し、キャリア由来の血液は33本のうち1本のみが感染を起こした(感染確率3%)。前者の感染性は後者の10倍以上高いことになる。感染を起こした製剤と起こさなかった製剤とで、含まれるHBVのコピー数には違いはなかった。赤血球製剤もFFPと同じく高い感染性を有していた。感染を起こした患者が免疫抑制状態にあるという傾向は認められなかった。1年間に頻回献血者の血液の輸血で起こるHBV感染は、キャリア血液によるもの0.7~0.9例、ウインドウ期の血液によるもの7.1~9.7例と推察される。医療機関からの従来の副作用報告によるものをあわせると、日本では輸血によるHBV感染が1年に約19例起こることが予想される。感染性をもつオカルトキャリアによる頻回の献血がこれからの問題となる。輸血によるHCV感染は4年に1例、HIVは2年に1例起こるものと推定される。

報告企業の意見	今後の対応
輸血用血液製剤のHBV、HCV、HIVについて、2000年2月から2004年1月までの4年間の遡及調査と、医療機関からの副作用報告による感染例をあわせると、日本では輸血によるHBV感染が1年に約19例、HCV感染は4年に1例、HIV感染は2年に1例起こるものと推定されるとの報告である。なお、HBV感染のリスクは、以前13~17例と推計していたが、今回の推計は直近のデータ数も含めたものである。	日本赤十字社では、「血液製剤等に係る遡及調査ガイドライン」(平成17年3月10日付薬食発第0310009号)に基づき、輸血感染症の調査を行っている。HBV/HCV/HIV感染に関する新たな知見等について今後も情報の収集に努める。次世代NAT試薬についての評価、検査方法の改良に向けた開発・検討を進める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(2)

シンポジウム4　輸血感染症の実態とその対策

SY4-1　遡及調査からみた残存リスクの評価

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HBV，HCV，HIVについて，2000年2月から2004年1月までの4年間の遡及調査と，従来のヘモビジランスの結果から，日本での輸血感染症の実態を報告する．遡及調査は，主に複数回献血者において感染症マーカーが陽転した場合に前回の血液のサンプルを個別NATで精査するもので，HBVについては50プールNAT，HBsAg，HBcAbのいずれかの陽転例約1万6千人について前回の保管検体を調べた．全体で1.01%が個別NATで陽性であった．HBcAbの有無でこれを分類すると，その60%はHBV感染既往者(オカルトキャリアー)，40%がウィンドウピリオドのドナーによるものであった．これらの個別NATのみ陽性の血液を輸血された患者63人の輸血前後の情報を集めると，感染したことが確認された患者は12人のみであった(感染確率19%)．感染を起こした血液をHBcAbの有無で分類すると，ウィンドウ期由来の血液は22本のうち11本が感染を起こした（感染確率50%）のに対し，キャリア由来の血液は33本のうち1本のみが感染を起こした(感染確率3%)．前者の感染性は後者の10倍以上高いことになる．感染を起こした製剤と起こさなかった製剤とで，含まれるHBVのコピー数には違いはなかった．赤血球製剤もFFPと同じく高い感染性を有していた．感染を起こした患者が特に免疫抑制状態にあるという傾向は認められなかった．1年間に頻回献血者の血液の輸血で起こるHBV感染は，キャリア血液によるもの0.7～0.9例，ウィンドウ期の血液によるもの7.1～9.7例と推察される．医療機関からの従来の副作用報告によるものをあわせると，日本では輸血によるHBV感染が1年に約19例起こることが予想される．感染性をもつオカルトキャリアによる頻回の献血がこれからの問題となる．輸血によるHCV感染は4年に1例，HIVは2年に1例起こるものと推定される．