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State of the art

Occult hepatitis B infection and transfusion-transmission risk

Hépatite B occulte et risques transfusionnels

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Abstract

Advances in serology and viral nucleic acid testing (NAT) over the last decades significantly reduced the risk of transfusion-transmitted hepatitis B virus (HBV). The combination of HBsAg testing and NAT efficiently prevents the majority of HBV transmission. However, a specific residual risk remains associated with extremely low viral DNA levels in blood donors with occult HBV infection (OBI) that are intermittently or not detectable even by highly sensitive individual donation (ID) NAT. Studies have reported HBV transfusion-transmission with blood components from donors with OBI that contained low amount of viruses (<200 virions). HBV transfusion-transmission seems to depend on a combination of several factors including the volume of plasma associated with the infected blood components transfused, the anti-HBV immune status of both recipient and donor, and possibly the viral fitness of the infecting HBV strain. Models based on clinical and experimental evidences estimate a residual transmission risk of 3–14% associated with OBI donations testing HBsAg and ID-NAT non-reactive. Anti-HBc testing has the potential to improve further blood safety but it may also compromise blood availability in settings with medium/high HBV prevalence. Pathogen reduction procedures might be considered.

Keywords: Hepatitis B virus; Blood safety; Transfusion-transmission; Occult HBV infection; Nucleic acid testing

Résumé

L'amélioration des performances des tests sérologiques et le développement des techniques de détection du génome viral ont réduit significativement le risque de transmission du virus de l'hépatite B (VHB) par transfusion. L'association du dépistage de l'AgHBs et du génome viral s'avère efficace pour prévenir la grande majorité des infections à VHB. Cependant, un risque résiduel transfusionnel lié aux donneurs porteurs d'une infection B occulte et présentant des niveaux extrêmement faibles d'ADN viral indétectables ou détectés de façon intermittente par les tests DGV unitaires les plus sensibles persiste, particulièrement dans les pays ne dépistant pas les anti-HBc. Des cas de transmission par des produits sanguins provenant de tels sujets et contenant de faibles quantités de virus (<200 virions) ont été rapportés. La transmission de l'infection B semble dépendre de plusieurs facteurs non-exclusifs tels que le volume de plasma associé au produit sanguin infecté transfusé, le statut immunitaire anti-HBV du receveur et/ou du donneur, et éventuellement les propriétés réplicatives de la souche virale infectante. Des modèles développés sur la base de données cliniques et expérimentales estiment un risque de transmission virale lié aux dons infectés par le VHB et échappant au dépistage de l'AgHBs et de l'ADN viral entre 3 % et 14 %. Le dépistage des anticorps anti-HBc en combinaison avec le DGV pourrait renforcer la sécurité transfusionnelle mais en compromettant la disponibilité des produits sanguins dans des zones de moyenne et forte endémie pour le VHB. Le recours à des méthodes de réduction des agents pathogènes dans les dons peut être envisagé.

Mots clés : Virus de l'hépatite B ; Sécurité transfusionnelle ; Transmission par transfusion ; Infection B occulte ; Détection du génome viral

1. Introduction

Despite the availability of a vaccine and the continuous development of antiviral treatments, persistent hepatitis B virus

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(HBV) infection remains a global major public health issue. It is estimated that more than two billion people worldwide have been in contact with the virus at some time in their lives and 257 million of them remain chronically infected [1]. HBV chronic infection is usually defined by detectable levels of HBV surface antigen (HBsAg) in the blood. The development of molecular diagnostic assays uncovered another form of active persistent/chronic HBsAg-negative HBV carriage identified as occult HBV infection (OBI) [2].

HBV transmission involves direct exposure to infected blood or organic fluids containing infected blood. Before 1970, it is estimated that HBV transfusion-transmission occurred in ∼6% of multi-transfused patients. Over the last four decades, blood safety has been continuously improved by the constant development of sensitive and specific serologic assays to detect the HBV surface antigen (HBsAg) and anti-HBc antibodies against the HBV Core antigen (anti-HBc) in blood donations. Global implementation of nucleic acid testing (NAT) for HBV DNA in 2004–2008 significantly reduced further the residual risk of HBV transfusion-transmission by reducing the diagnostic pre-seroconversion window period and by detecting occult HBV infection/carriage [3]. Yet, HBV transmission remains the most frequent transfusion-transmitted viral infection. The residual risk of HBV transfusion-transmission appears to be mainly related to blood donations negative for HBsAg but containing extremely low levels of viral DNA potentially infectious that may escape detection by the currently most sensitive NAT assays.

2. Reducing the risk of HBV transfusion-transmission

2.1. Blood donor selection

Recruitment of voluntary non-remunerated donors and risk behavior-based selection of donors prove essential for blood safety. These processes reduce the risk for transfusion-transmissible infections (TTIs) by temporarily or indefinitely deferring high-risk and therefore potentially infectious candidate donors. The pre-donation evaluation usually consists of a self-administrated written questionnaire about a range of risk exposures for TTIs and a confidential interview with a medical counselor. Effectiveness is shown by the significant lower prevalence of TTIs observed among eligible donors compared to the general population, but it also strongly depends on both donor education and accurate and truthful risk behavior disclosure. However, post-donation interviews revealed that 22% to 28% of infected donors subsequently admitted risk exposures that would have result in permanent deferral [4,5]. Reasons behind donor questionnaire noncompliance can be complex varying from deliberate (e.g., test seeking, social discomfort, disagreement with deferral criteria, misunderstanding of the pre-donation screening purpose since donations are tested further) to genuine (e.g., misinterpretation of questions, failure of recall, erroneous no-risk belief associated with temporally remote exposure). A recent study reported a 10% rate of non-compliance in HBV-infected blood donors from the Netherlands that was mainly associated with male-to-male sex risk factor, whereas the main infective risk exposure identified in the whole donor population with confirmed HBV infection was to originate or to be related to a HBV endemic country [4,5].

2.2. HBsAg testing

HBsAg testing remains the first-line of HBV screening in blood donors. Commercial enzyme immunoassays (EIAs), including enzyme linked immunosorbent assays (ELISAs), and chemiluminescent immunoassays/chemiluminescent enzyme immunoassays (CLIAs/CLEIAs) are the most commonly used assays for blood screening. These assays are currently implemented on (semi)-automated testing platforms combining high throughput and high analytical sensitivity ranging between 5 and 50 mIU/mL. HBV genotypes and mutations associated with structural changes and/or with reduced synthesis or secretion of HBsAg may negatively affect the analytical and clinical performance of HBsAg detection [6]. The formation of circulating immune complexes between HBsAg and hepatitis B surface antibodies (anti-HBs) may also cause detection failure when they are not or poorly displaced by the HBsAg capture antibodies used in the manufactured assays.

The high cost and considerable equipment requirements of these commercial HBsAg assays may limit their use in resource-limited settings. Over the last decade, several reliable and sensitive rapid diagnostic tests (RDTs) have been successfully developed that do not require laboratory infrastructure, are easy to perform with minimal training, and provide conclusive results within a few minutes [7].

2.3. Anti-HBc testing

Antibodies to the HBV core protein (anti-HBc) are associated with HBV natural infection and remain detectable throughout the entire course of chronic infection at least in immunocompetent individuals. They also persist for life after recovery even when anti-HBs become undetectable and can be the only serological marker, associated or not with low levels of viral DNA, in rare long-standing chronic infection. However, anti-HBc assays show mediocre specificity despite continuous improvements and the lack of proper confirmatory tests necessitates retesting reactive samples with an alternative assay to discriminate true from false-positive samples [8]. Despite these limitations, anti-HBc screening has been implemented in HBV low-endemic countries where donor definitive deferral was considered sustainable in terms of donation wastage, but it adds to the already considerable list of donor exclusion. Introducing anti-HBs testing in anti-HBc only positive donations has been considered to mitigate donor lost in countries that have a slightly elevated HBV prevalence like Japan where donations with high anti-HBs titers ($\geq$ 200 IU/L) presumably non-infectious are considered acceptable for plasma fractionation, and donations with low anti-HBc and anti-HBs titers are rejected [9]. Nevertheless, anti-HBc testing cannot be implemented in high-endemic countries without compromising blood availability (e.g. Sub-Saharan Africa, Southeast Asia).