collected unit; this phenomenon has previously been noted in association with Gram-negative organisms.[3]

Detection of bacterial contamination in pooled WB-derived PLTs remains a challenge. Because of the short storage time for WB-derived PLTs (i.e., 5 days), the blood center in our investigation performs sampling within 2 hours after separation of the components. This technique does not allow for an additional 24-hour holding period to improve the sensitivity of the test. Both the shorter holding period and the smaller sampling size (i.e., 1.6 to 2.4 mL in each tubing segment) are likely to decrease the sensitivity of the method when compared to comparable apheresis testing procedures. The sensitivity of the method described, however, is likely to be superior to pH and glucose measurements commonly used for WB-derived PLTs QC. At the blood center reporting this case, the overall incidence of true-positive bacterial contamination (i.e., confirmed by replicate growth on the units from which the tubing segment was obtained) using the method described is 1 in 21,000 WB-derived PLT units[18] (which can be estimated as 1 in 3500 WB-derived PLT pools if we assume that 1 segment in each pool of 6 was contaminated), whereas the incidence of true-positive bacterial detection on apheresis PLT units at this same institution is 1 in 2700.

Although alternative devices for prepooling and sampling for culture have been approved by the FDA,[31] these alternatives, as currently configured, require the use of proprietary blood collection bags, leukoreduction filter, and bacterial growth detection systems that are not compatible with the bacterial detection systems used at all blood establishments, including the blood establishment where the PLTs in this report were prepared.

The BacT/ALERT culture method was approved by the FDA in 2002 for QC of bacterial contamination of single-donor PLT (SDP) units only. Because use of the BacT/ALERT method for individual WB-derived PLT units is not practical due to the small volume of each unit, a study was conducted in 2005 to validate the use of this method for the detection of bacterial contamination in WB-derived PLTs in a pooled format.[32] This study demonstrated that the BacT/ALERT method is capable of detecting very low concentrations of bacteria in a single WB-derived PLT unit when the contaminated unit is pooled with 5 other sterile units for culturing. In this validation study, both aerobic and anaerobic bottles were used. Although the use of one aerobic bottle and one anaerobic bottle is strongly recommended by the manufacturers of BacT/ALERT, the majority of the blood centers only use one aerobic bottle[33] as reported in our investigation. A recent study done by Brecher and Hay[34] using *Staphylococcus lugdunensis* suggested that the use of both aerobic and anaerobic bottles may significantly increase sensitivity of screening, particularly when the inoculum is low. It is unclear, however, whether this increase in sensitivity is due to the use of anaerobic media or simply reflects an increase in total volume inoculated.

Non–culture-based screening methods have been suggested for detection of bacterial contamination in WB-derived PLT units;[8] however, these methods are typically less sensitive than culture. FDA recently approved a rapid test to be used to supplement current screening strategies for detection of bacterial contamination in PLTs.[35] This supplemental test is to be used near the time of transfusion and can detect bacterial contamination that was not detected by culture. The performance of this new test in WB-derived PLTs is unknown, however, since studies were conducted using leukoreduced apheresis PLTs.

Our report and others[2,6,7,36] indicate that current screening methods to prevent transfusion of bacterially contaminated PLTs can be improved. Further studies to evaluate the sensitivity of culture and non–culture-based screening methods for detection of bacterial contamination in WB-derived PLTs are needed. Efforts to improve recognition of bacterial contamination of PLTs also need to continue. If transfusion-related bacteremia is suspected, the residual blood product unit should be saved by the hospital and the blood center immediately informed. Timely information will allow blood centers to rapidly trace and quarantine potentially contaminated cocomponents made from the same donation. Finally, the BacT/ALERT package insert's recommendations should be followed, particularly concerning the use of one aerobic and one anaerobic culture bottle with sufficient volume. β-Hemolytic streptococci are facultative anaerobes and may be better recovered under anaerobic conditions.[37]

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No. 11

医薬品 研究報告 調査報告書

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販売名(企業名)	クロスエイトM250(日本赤十字社) クロスエイトM500(日本赤十字社) クロスエイトM1000(日本赤十字社)			英国

研究報告の概要

○血友病患者の剖検時にvCJD異常プリオンタンパク質が発見された

vCJDとは関係のない疾患により死亡した血友病患者(年齢70歳以上)の剖検時に、患者の脾臓からvCJDの異常プリオンタンパク質感染の証拠が見つかった。この患者は、生前vCJD及び神経学的症状は示していなかった。

英国健康保護局は、英国血友病センター医師会と共同し、現在詳細調査中であるこの予備情報が出血性疾患患者すべてに確実に伝わるよう尽力しているが、この新たな知見により血友病患者の看護や治療の方法が変わることはない。

伝播経路の調査は継続中であり最終的な見解はまだ得られていない。

当該患者は、vCJDに関する血液安全性改善措置が導入された1999年以前に、英国内で供血された凝固因子製剤による治療を受けたことが判明しており、その中に供血の6ヶ月後にvCJDの症状を発現した供血者由来血漿から製造された第VIII因子製剤1バッチが含まれていた。

血友病患者または血漿分画製剤の治療を受けた患者にvCJD異常プリオンタンパク質が見つかったのはこれが初めてである。

血友病患者は、すでに「公衆衛生上vCJDリスクを有する状態」に分類されることが医師から知らされているが、リスクの状態が変更されるものではない。

この新たな知見は、これまで理論上のリスクであったものが、血漿分画製剤を投与された特定の個人に対する現実のリスクとなる可能性を示すものと考えられるが、当該リスクはまだ非常に低いであろうと考えられる。

1999年以降、凝固因子製剤製造に英国内の血漿は使用されておらず、必要な患者には遺伝子組換製剤が使用されている。

報告企業の意見	今後の対応
英国でvCJDとは関係のない疾患により死亡した血友病患者の剖検時に、初めてvCJDの異常プリオンタンパク質感染の証拠が見つかり、当局はすべての出血性疾患患者への情報提供と伝播経路の調査を実施しているとの報告である。	プリオン病の原因とされる異常プリオンが分画製剤製造工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、血漿分画製剤を介して伝播するという証拠は無かった。しかし、原因が特定されていないものの、本報告で初めて、第Ⅷ因子製剤を介してvCJDに感染する可能性が示唆された。引き続きプリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。 なお、日本赤十字社は、CJD、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)、CJDの既往歴(本人、血縁者)、hGH製剤投与の有無を確認し、該当するドナーを無期限に献血延期としている。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

海外症例報告:
2009年03月05日付3-08000044

vCJD abnormal prion protein found in a patient with haemophilia at post mortem

17 February 2009

Evidence of infection with the agent (abnormal prion protein) that causes variant Creutzfeldt-Jakob Disease (vCJD) has been found at post mortem in the spleen of a person with haemophilia.

The patient, who was over 70 years old, died of a condition unrelated to vCJD and had shown no symptoms of vCJD or any other neurological condition prior to his death. The vCJD abnormal prion protein was only identified during post mortem research tests.

The Health Protection Agency is working with the UK Haemophilia Centre Doctors Organisation to ensure all patients with bleeding disorders are made aware of this preliminary information which is being further investigated. This new finding will not change the way patients with haemophilia are cared for or treated.

A final view as to how vCJD abnormal prion protein was transmitted to this haemophilia patient has yet to be reached because investigations are continuing to determine the most likely route of transmission. It is known that the patient had been treated with several batches of UK sourced clotting factors before 1999, which is when measures to improve the safety of blood in relation to vCJD were introduced. The patient's treatment had included one batch of Factor VIII that was manufactured using plasma from a donor who went on to develop symptoms of vCJD six months after donating the plasma in 1996.

This is the first time that vCJD abnormal prion protein has been found in a patient with haemophilia, or any patient treated with plasma products. This new finding, however, does not change the public health vCJD 'at risk' status of patients with bleeding disorders.

Haemophilia patients have previously been informed by their doctors of their possible increased risk of exposure to vCJD via clotting factors. In 2004 all patients with bleeding disorders who had been treated with UK-sourced pooled plasma products between 1980 and 2001 were told that, owing to potential vCJD infectivity from these products they were to be classified as at-risk of vCJD for public health purposes.

Professor Mike Catchpole, Director of the Health Protection Agency's Centre for Infections, said:

"This new finding may indicate that what was until now a theoretical risk may be an actual risk to certain individuals who have received blood plasma products, although the risk could still be quite low. We recognise that this finding will be of concern for persons with haemophilia who will be awaiting the completion of the ongoing investigations and their interpretation.

The priority is to ensure that patients are informed of this development and have access to the latest information and specialist advice from their own haemophilia centre doctor as soon as possible.

"This finding does not change our understanding of the risk from vCJD for other people in any specific way. But it does reinforce the importance of the precautionary measures that have been taken over the years.

"Since the risk of vCJD transmission through blood was first considered, a number of precautionary measures have been introduced to minimise the risk from the UK blood supply. UK plasma has not been used for the manufacture of clotting factors since 1999 and synthetic clotting factors are provided for all patients for whom they are suitable."

Ends

Notes for editors

1) The post-mortem tests were carried out as part of a research study jointly coordinated by the UK Haemophilia Centre Doctors Organisation and the National CJD Surveillance Unit. The study was commissioned in 2001 and is ongoing.

2) The likelihood of a person who is infected with the vCJD abnormal prion protein going on to develop symptoms of the disease is uncertain and may depend on individual susceptibility. It is possible that infected individuals may never develop symptoms.

3) Haemophilia is a genetic blood condition in which an essential clotting factor is either partly or completely missing. This causes a person with haemophilia to bleed for longer than normal. Treatment for haemophilia is usually by replacing the missing clotting