in their development. In addition, leishmaniasis surveillance and control are also neglected. One of the main reasons for this neglect is that in developing countries, leishmaniasis is a disease of the poor. Risk for infection and clinical development are mediated by poverty, while leishmaniasis diagnosis and treatment are expensive and may lead to further impoverishment and reinforcement of the vicious cycle of disease and poverty (*31*).

In Europe, physicians are sometimes ill-informed on the diagnosis and treatment of leishmaniasis. In France, a telephone advice line was created in 2006 by the National Reference Centre of Leishmania to help physicians in their therapeutic diagnosis. A study in Germany, a non–disease-endemic country, showed that the median time between symptom onset and correct diagnosis was 85 and 61 days in case-patients of VL and CL, respectively (*32*). This value was lower in a leishmaniasis-endemic area, such as southern Italy (35 days, [*33*]). VL, which was initially a pediatric disease in Europe (hence the name of *L. infantum*), only began to gain attention when the co-infection of HIV/AIDS was documented. Between the late 1980s and early 2001, >1,900 cases were reported in southwestern Europe (*16*). Even though it was reported that both pathogens could be transmitted through sharing of needles among intravenous drug users (*34*), in many cases of co-infection, the parasite was already present at the time of HIV infection, which indicates that HIV infection would have an unmasking effect on the true endemicity of *Leishmania* infection. In other words, the wave of *Leishmania*/HIV co-infection showed that *L. infantum* could behave as an opportunistic parasite, with many asymptomatic carriers (*12*), and with the clinical syndromes being only the tip of the iceberg. Because of the highly active antiretroviral therapy, cases of co-infection generally decreased in the region, with the exception of Portugal (*35*).

Notification of VL varies according to the country. It does not belong to the list of 30 notifiable diseases in France. However, notification is compulsory in Greece, Italy, and Portugal, though only obligatory in 12 of 17 autonomous communities of Spain. Underreporting is common. In Portugal, for instance, 76 cases of autochthonous VL were officially reported at the country level from 2000 through 2005. During the same period, 127 cases (+67%) were observed in the Institute of Tropical Medicine of Lisboa (Table). In the case of autochthonous cutaneous leishmaniasis, consolidated data are lacking, but this clinical form is definitely underreported because of its benign nature and the fact that it usually does not require hospitalization. Nonetheless, leishmaniasis is not a disease placed under public health surveillance at the European level. It does not even belong to the package of rare diseases considered as a priority in the Public Health Programme 2003–2008. (Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases that are of such low preva-

lence [<5/10,000 persons] that special combined efforts are needed to address them so as to prevent significant illness or perinatal or early deaths or a considerable reduction in a person's quality of life or socioeconomic potential.) At the regional level, the only dedicated network of surveillance was the one launched by the World Health Organization and the Joint United Nations Programme on HIV/AIDS in 1993 for the surveillance of *Leishmania*/HIV co-infections, which essentially involved European countries as well as some developing countries.

The low-profile perception seen for human leishmaniasis differs dramatically from the veterinary world's perception. The high incidence of canine leishmaniasis in southern Europe makes *Leishmania* one of the main dog killers in the region, and private veterinarians are well aware of it. Dogs are treated individually to protect from sand fly bites, and those diagnosed as infected are considered extremely difficult to treat. Specific web sites are available for owners of infected dogs to discuss and compare treatment regimens and pose questions to veterinarians. Several pharmaceutical companies are investing in research and development of vaccines, drugs, and topical insecticides for specific cure and prevention of canine leishmaniasis. This high-profile perception, however, drops when dogs must be treated as the reservoir of human leishmaniasis. For instance, the issue of notification is treated differently in various leishmaniasis–endemic countries, but even where notification is compulsory (i.e., Italy and Spain), it is not a common practice. In Italy, the network Leishmap is currently monitoring the spread of canine leishmaniasis and vectors in northern Italy. Leishmap is a scientific network, supported by a private company (*36*). Furthermore, private interests are sometimes at odds with public health goals. Drugs for leishmaniasis are not regulated in the veterinary market, and medications intended for use in humans, such as Ambisome, are used in domestic pets, with the potential risk that they might be a source for the emergence and spreading of resistant strains.

Countering the Neglect

Since 2001, several research consortia gathered scientists from Euro-Mediterranean countries (www.leishrisk.net). These consortia and other research groups generated knowledge, tools, and education packages and led to a solid European research network dedicated to the study of leishmaniasis. Bridging research with surveillance and control is an issue of dialogue and advocacy. On one hand, health professionals need to be in close contact with scientists to help translate basic research into relevant and applicable tools. For instance, sequencing the whole genome of *Leishmania* represented a technologic challenge, but the next challenge is to exploit this sequencing for the benefit of the patient (www.leishrisk.net). On the other hand, scientists

must market their results to influence health policy. Changes in health policy are being made; during manuscript revision, we were informed of the selection of leishmaniasis among the priority zoonoses addressed by the Episouth network (www.leishrisk.net).

Deciding health policy is a complex social, economic, and political interrelationship that is much broader than leishmaniasis alone (or even infectious diseases generally). However, if Europe justifiably wants to invest more in surveillance of vector-borne diseases, the time has come to recognize its real impact on both animal and human health and include leishmaniasis as one of these diseases.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日 2008. 5. 26	新医薬品等の区分 該当なし	機構処理欄
一般的名称	人血清アルブミン		研究報告の公表状況	Patel KK, Andrzejewski C Jr, Webley WC. American Society for Microbiology 108th General Meeting; 2008 Jun 1-5; Boston.	公表国	
販売名（企業名）	赤十字アルブミン20（日本赤十字社） 赤十字アルブミン25（日本赤十字社）				米国	

研究報告の概要	○市販アルブミン製剤におけるクラミジアの存在 目的：人血清アルブミン（HSA）は、多数の健康なボランティアドナーから採血された全血由来のプールから製造され、一般的には病院で、特に治療的プラズマフェレーシスを行う患者の補液療法に用いられている。我々の研究室他における以前の調査から、C. pneumoniae（Cp）組織体が、これらの健常ドナー及び採血された血液細胞製剤から分離された。これらの知見に基づき、無細胞性の血液製剤であるHSAについてクラミジアが存在するか分析することにした。 方法：様々なHSA製剤のボトルをApheresis Medicine Service at Baystate Medical Centerから入手した。これらの素材は品質管理目的に使用された廃棄製剤や期限切れロット、アフェレーシス療法を中断した際の補液の残りである。クラミジアの検出は標準PCR、ウエスタンブロット、組織培養、免疫蛍光染色を用いて行った。 結果：メーカー4社が製造しているHSA製剤20種類を検討した。クラミジア特異的DNAがPCRで20本全て（100%）から検出された。種特異的プライマーを使用したところ、17検体（90%）がCP DNA陽性となったが、Chlamydia trachomatis（Ct）DNAが陽性となったものはなかった。クラミジア特異的ポリクローナル抗体を用いたウエスタンブロットで、PCRのデータが裏付けられた。培養では、クラミジア生菌が11（55%）のHSA製剤で認められた。 結論：PCR及びウエスタンブロットを用いて、20本のHSA製剤全てにおいて、クラミジアの存在が確認された。予期せぬ事だったが、これら無細胞性HSA製剤において、in vitro培養を行ったところ、11検体でクラミジア生菌が生育した。	使用上の注意記載状況・ その他参考事項等 赤十字アルブミン20 赤十字アルブミン25 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
PCR及びウエスタンブロットを用いて、20本の市販人血清アルブミン製剤全てにおいて、クラミジアの存在が確認され、in vitro培養を行ったところ、11検体でクラミジア生菌が生育したとの報告である。	これまで、本製剤によるC. pneumoniae感染の報告はない。クラミジアは熱感受性で56℃30分で不活化されるとの報告もあるが、日本赤十字社が製造販売している赤十字アルブミンははるかに厳しい、60℃10時間の液状加熱で不活化を行なっている。また最終製剤についてPCR法で試験したところC. pneumoniaeは検出されなかったことから、本製剤の安全性は確保されていると考えるが、今後も情報収集に努める。

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Abstract Title: *Chlamydia* Presence in Commercial Albumin Preparations

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Keywords: Chlamydia,Human Albumin,transfusion

Purpose: Human serum albumin (HSA) prepared from large pools of whole blood collected from normal volunteer donors, is commonly used in hospitals for fluid replacement therapy, especially in patients undergoing therapeutic plasmapheresis. From previous investigations by our lab as well as others, *C. pneumoniae* (Cp) organisms have been isolated from these normal blood donors and cellular blood products collected from them. Based on these previous findings we elected to assess HSA, an acellular derivative of donor blood, for the presence of *Chlamydia*. **Methods**: Bottles of various preparations of HSA were obtained from the Apheresis Medicine Service at Baystate Medical Center, Springfield MA. These materials were obtained from discarded stocks used for quality control purposes, outdated lots and from residual replacement fluids from truncated apheresis procedures. Detection of *Chlamydia* was accomplished through standard PCR, Western blotting, tissue culture, and immunofluorescence techniques. **Results**: Twenty different HSA preparations from four different manufacturers were examined. *Chlamydia*-specific DNA was detected by PCR in all 20 [100%] HSA preparations examined. Using genus-specific primers, 17 samples [90%] were positive for *Cp* DNA, while zero samples were positive for *Chlamydia trachomatis* (*Ct*) DNA. Western blotting analysis uing *Chlamydia*-specific polyclonal antibody supported the PCR data. Culture analysis demonstrated that viable *Chlamydia* was present in 11 [55%] of these commercial HSA preparations. **Conclusions**: The presence of *Chlamydia* was evidenced by both PCR and western blotting techniques in all 20 HSA preparations examined. Unexpectedly, in these acellular HSA preparations, in vitro culture analysis revealed that 11 [55%] of the samples tested harbored viable *Chlamydia*.

医薬品 研究報告 調査報告書

識別番号・報告回数				報告日	第一報入手日 2008. 8. 18	新医薬品等の区分 該当なし	機構処理欄
一般的名称	新鮮凍結人血漿		研究報告の公表状況		Polizzotto MN, Neo H, Spelman D, Shortt J, Cole-Sinclair MF, Borosak M, Wong P, Wood EM. Transfusion. 2008 Jul;48(7):1520-1.	公表国 オーストラリア	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)						

研究報告の概要	○赤血球輸血に関連した*Streptococcus pneumoniae*菌血症 我々の知る限り初めての赤血球(RBC)輸血による*Streptococcus pneumoniae*感染の1例を報告する。受血者は骨髄異形成症候群と汎血球減少症を発症した79歳男性である。輸血前の診察では平熱だったが、血小板輸血に続いて赤血球1単位を輸血した40分後に39.6℃の発熱、悪寒、背部痛、血圧低下、低酸素血症を発症した。輸血を中止し、抗菌薬による治療を行ったところ回復した。 受血者及びRBCバッグの残存血液検体の培養により*S. pneumoniae*血清型4が生育した。付属セグメントとRBCバッグ本体に色調の違いはなかった。また、RBCの前に輸血した血小板製剤の残りは得られなかった。輸血されたRBC製剤は採血後10日間保存された物で、採血、製造工程での異常はなかった。供血者は53歳の男性で、脾臓摘出術、喫煙、呼吸器感染症など*S. pneumoniae*感染のリスク要因はなく、これまで30年以上供血を続けてきた。血液、鼻腔、咽喉検体の培養は、尿の肺炎球菌抗原検査と共に陰性だった。 *S. pneumoniae*が冷蔵保存されたRBC製剤中で生存、増殖するというデータはこれまでなかったが、今回、RBC製剤1単位に1×10^8の*S. pneumoniae*を接種し、4℃で10日間保存後に採取した検体を培養したところ、持続的な増殖が認められた。ただ、21日後の検体では増殖は認められなかった。 感染の原因は供血者の一時的な菌血症と考えられるが、先に輸血された血小板製剤の汚染の可能性も否定できない。本症例は、通常考えられない細菌によるRBCの汚染も疑う必要があることとヘモビジランスの重要性を物語る。輸血後の敗血症の迅速な診断と抗生物質療法、原因の追及と、随伴製剤の回収が重要である。	使用上の注意記載状況・その他参考事項等 新鮮凍結血漿「日赤」 新鮮凍結血漿-LR「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

報告企業の意見	今後の対応
赤血球輸血による*Streptococcus pneumoniae*敗血症の初の報告例である。本症例では、患者とバッグ内の残存血液から細菌が検出され、再現実験も行われているが、通常4℃の低温下では増殖しないとされている菌であり、因果関係を断定するにはなお十分な検証が必要と考える。	日本赤十字社では、輸血情報リーフレット等により、細菌感染やウイルス感染について医療機関へ情報提供し注意を喚起している。また、「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)における「本ガイドライン対象以外の病原体の取扱い イ. 細菌」に準じ細菌感染が疑われる場合の対応を医療機関に周知している。今後も細菌やウイルスの検出や不活化の方法について情報の収集に努める。

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LETTERS TO THE EDITOR

Streptococcus pneumoniae septicemia associated with red blood cell transfusion

Bacterial contamination of blood components, including red blood cells (RBCs), remains an important risk of transfusion. Bacteria responsible for clinically significant contamination of RBCs include both skin commensals and organisms that are able to proliferate even in refrigerated storage conditions.[1] We describe a case of transfusion-transmitted *Streptococcus pneumoniae* infection caused by contaminated RBCs. This highly pathogenic, but fragile, noncommensal organism has not to our knowledge been reported previously as a cause of transfusion-transmitted bacterial infection.[2]

The recipient was a 79-year-old man with myelodysplastic syndrome and pancytopenia. He had neither history of splenectomy nor evidence of functional hyposplenism. He was afebrile with a normal physical examination before blood transfusion. He received a transfusion of pooled platelets (PLTs) without complication which was followed by transfusion of a unit of RBCs suspended in additive solution and citrate-phosphate-dextrose additive (Adsol, Baxter Healthcare, Deerfield, IL). After approximately 40 minutes, the recipient developed a fever of 39.6°C, rigors, back pain, hypotension, and hypoxia. The transfusion was discontinued and he was treated with intravenous piperacillin-tazobactam, vancomycin, and gentamicin.

Blood samples from the recipient at the time of the fever, together with the residual contents of the container of the RBCs, were available for further testing, but the container of the previously transfused unit of PLTs was not retrievable. The residual contents of the unit of RBCs were not discolored compared with the attached segments. A Gram stain was negative. Cultures were performed separately on the blood samples from the recipient and the residual contents of the unit of RBCs (BacT/ALERT, bioMérieux, Durham, NC). These cultures flagged positive within 12 hours, and subcultures demonstrated Gram-positive α-hemolytic diplococci that were optochin-sensitive and bile-soluble, characteristic of *S. pneumoniae*. Automated identification and susceptibility testing (Vitek 2, bioMérieux) confirmed these findings and demonstrated β-lactam sensitivity. The organisms from both the unit and the recipient were serotype 4.

The recipient made a gradual clinical recovery. Subsequent blood cultures were negative. He became afebrile within 24 hours. He completed a 5-day course of piperacillin-tazobactam (vancomycin and gentamicin were withdrawn after availability of sensitivities) and was discharged with a 10-day course of oral amoxicillin. He remained well at last review.

We assessed possible sources of this unusual contamination of RBCs. The implicated unit of RBCs had been collected 10 days before transfusion. The phlebotomy and processing had been uncomplicated, with no apparent breach of aseptic technique or evidence of respiratory droplet contamination. Plasma from the same blood collection was discarded for an unrelated reason; no PLTs had been made. Components associated with the previously transfused unit of PLTs were also cultured and showed no growth.

The donor was a 53-year-old man, with no history of splenectomy, tobacco use, or respiratory tract infection. He had not been immunized against *S. pneumoniae*. He had donated on numerous occasions more than 30 years before the implicated donation without complication. He had no symptoms suggesting infection at the time of blood collection, but he did report a dental infection 3 months previously. This infection had been treated by tooth extraction and oral antibiotics. There was no evidence of a persistent infection. There had been no other procedures in the intervening period. Physical examination was normal. Cultures of blood and of swabs from the donor's antecubital fossae, nose, and throat were negative, as was urinary testing for pneumococcal antigen.

S. pneumoniae has been reported as a rare contaminant of PLTs,[3] but unlike commensal streptococci (which have infrequently been implicated in cases of contamination of RBCs[4]), there has been no evidence that this organism survives and proliferates outside a host in refrigerated storage of RBCs.[2] Its ability to survive under these conditions was further explored (though without direct evidence of proliferation in RBCs). A unit of RBCs was inoculated with 1×10^3 organisms of *S. pneumoniae* from the original cultures. The inoculated unit of RBCs was maintained at 4°C for 10 days, after which samples were cultured and identified as above. These again demonstrated sustained growth of *S. pneumoniae*. Further cultures performed on separate samples taken after 21 days of incubation at 4°C showed no growth.

This previously unreported cause of contamination of RBCs and transfusion-transmitted *S. pneumoniae* infection had significant adverse clinical consequences and has implications for clinicians and blood services. This case illustrates the importance of a high index of clinical suspicion for RBC contamination, even where the organism is atypical, and the role of robust hemovigilance systems. Prompt recognition of the source of sepsis enabled timely institution of antibiotic therapy and liaison with the blood service to review the donor's health status, collection, and production processes and to enable immediate recall of associated blood components. The source of contamination could not be established definitively. We postulate that it may have originated from a transient bacteremia. While

unlikely, the possibility of retrograde contamination from the previously transfused PLTs cannot be excluded.[5] This episode was not preventable, given the absence of symptoms that might have led to donor deferral and the lack of visual evidence of contamination.

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Unusually strong, but transient, nonspecific human immunodeficiency virus types 1 and 2 antibody reactivity

In low-risk populations, such as nonremunerated voluntary blood donors, a high proportion of reactive screening immunoassay (IA) and indeterminate immunoblot results represent nonspecific reactivity due to cross-reacting antibodies. To reduce the number of donors with nonspecific indeterminate immunoblot results the Australian Red Cross Blood Service uses a dual IA strategy for human immunodeficiency virus types 1 and 2 antibody (anti-HIV-1 and -2), hepatitis C virus antibody (anti-HCV), and human T-lymphotropic virus types I and II (anti-HTLV-I and -II) screening whereby blood donors' samples that test reactive on a primary screening IA are retested on a secondary IA and further tested by immunoblot only if reactive on both IAs.[1] All donations are screened also by nucleic acid testing for HIV-1 and HCV RNA using a dedicated tube. We report the case of a donor with apparent transient nonspecific reactivity on primary and secondary anti-HIV-1 and -2 IAs and HIV Western blot.

Between July 2002 and August 2006, blood samples from six donations by a female donor all tested nonreactive by the anti-HIV-1 and -2 primary screening IA (PRISM HIV O Plus chemiluminescent immunoassay [ChLIA], Abbott Diagnostic Laboratories, Delkenheim, Germany). A sample from the donor's seventh donation in November 2006, however, tested strongly reactive by the ChLIA with a mean sample-to-cutoff (S/CO) ratio of 6.15. The sample was further tested in duplicate on the secondary IA (Genscreen Plus HIV Ag-Ab EIA, Bio-Rad, Marnes La Coquette, France) with a mean S/CO ratio of 24.2. The Western blot (HIV blot 2.2, MP Biomedicals, Irvine, CA) result showed 1+ reactivity to p24 and gp160 antigen bands and therefore was interpreted as indeterminate according to the criteria of the National Serology Reference Laboratory, Australia. The donor was recalled 3 weeks later, and a blood sample was retested by the same IAs and found to be nonreactive by both (PRISM S/CO, 0.69; Genscreen S/CO, 0.05) with no band reactivity on the Western blot. All seven donations (tested in pools of 16) and the recall sample (tested individually) were nonreactive by the HIV-1 and HCV assay for HIV-1 and HCV RNA (Procleix, Chiron Blood Testing, Emeryville CA). At a recall interview, the 48-year-old donor did not report any risk factors for HIV infection, but indicated a history of rheumatoid arthritis and a current pruritus.

Although the donor's blood sample gave unusually high S/CO ratios on both the PRISM and Genscreen IAs and an indeterminate Western blot result, follow-up testing indicated that these results were due to nonspecific reactivity. None of the donations had detectable HIV-1 RNA and the serologic reactivity was transient, becoming undetectable within 3 weeks. In addition, the transient serologic reactivity was associated with a clinical condition involving an underlying immune response, consistent with previous studies reporting an association between nonspecific reactivity with evidence of a concomitant immune response.[2-4] We believe that it is unlikely that the sample that showed reactivity on two IAs and the Western blot was contaminated because there were no anti-HIV–positive donor samples in the laboratory at the time. As well, instrument carryover from a positive control is unlikely because testing is fully automated and a new disposable tip is used to sample from each tube.

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