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別紙様式第2-1

No. 4

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	新医薬品等の区分	機構処理欄
				2006. 2. 21	該当なし	

一般的名称	新鮮凍結人血漿	研究報告の公表状況	Guevara RE, Tormey MP, Nguyen DM, Mascola L. Transfusion. 2006 Feb;46(2):305-9.	公表国
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社)			米国

研究報告の概要

○血小板製剤におけるリステリア菌:症例報告
背景:血小板製剤の細菌汚染低減のための取り組みから、製剤供給前の細菌検出を目的とした検査が実施されている。ヒトの病原体としては比較的まれであるが、リステリア菌は重篤な疾病を引き起こすことが多く、致死率は20%である。
症例報告:血小板供血歴の長い無症候性の58歳ヒスパニック系男性由来の血小板が、リステリア菌培養陽性となった。分離株のパルスフィールドゲル電気泳動(PFGE)パターンは、CDCのデータベースPulseNet中の他の分離株2株と一致した。公衆衛生調査からは、無症候性であったこの血小板供血者にこの2株が疫学的に関連しているという証拠は示されなかった。
結論:PFGE法によりリステリア症例のクラスターが検出されたが、臨床的意義は不明である。公衆衛生的に問題となる微生物は、衛生当局に報告される必要がある。血液製剤の安全性向上に向け、サーベイランス及び報告の改善が必要である。

報告企業の意見	今後の対応
58歳男性由来の血小板製剤から、リステリア菌が検出されたとの報告である。	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。 今後も情報の収集に努める。白血球除去の導入とともに細菌を不活化する方策についても検討を進める。

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」

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

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TRANSFUSION COMPLICATIONS

Listeria monocytogenes in platelets: a case report

Ramon E. Guevara, Michael P. Tormey, Dao M. Nguyen, and Laurene Mascola

BACKGROUND: Efforts to reduce bacterial contamination in platelets (PLTs) have led to implementation of tests for bacterial detection before product release. Although relatively rare as a human pathogen, *Listeria monocytogenes* often causes serious illness and has a case-fatality rate of 20 percent.
CASE REPORT: PLTs from an asymptomatic 58-year-old Hispanic male with a long history of PLT donation were culture-positive for the presence of *L. monocytogenes*. The pulsed-field gel electrophoresis (PFGE) pattern of the isolate matched two other *L. monocytogenes* isolates in the CDC National PulseNet database. Public health investigation found no evidence that the other two isolates were epidemiologically related to the PLT donor, who remained asymptomatic.
CONCLUSION: A cluster of listeriosis cases was detected by PFGE but the significance is unknown. Organisms of public health significance should be reported to health departments. Better surveillance and reporting are needed in the efforts to improve blood product safety.

With successes in reducing transfusion-transmitted viruses such as human immunodeficiency virus (HIV) and hepatitis viruses,[1-4] prevention of bacterial contamination has become the next goal for improving blood product safety. Bacterial contamination of cellular blood products occurs in approximately 33 per 100,000 cellular blood product units cultured,[5,6] with prevalence rates ranging from 8 to 80 per 100,000 whole blood–derived platelet (PLT) units, 0 to 230 per 100,000 apheresis PLT units, and 0 to 3 per 100,000 red blood cell (RBC) units.[7]

Septic transfusion events due to bacterial contamination are less frequent, however, occurring in 1 per 100,000 blood product recipients.[8] Estimates of transfusion-transmitted sepsis from different studies vary[8-10] but reflect prevalence of transfusion-associated sepsis at 16 per 100,000 PLT units[11] and 0.4 per 100,000 RBC units transfused.[6,7] Possible explanations for the difference in bacterial contamination and transfusion-transmitted sepsis rates include low bacterial counts insufficient to recipient symptoms, and the frequent use of antibiotics and other recipient treatment that may mask the effects of bacteremia, including onset of sepsis.[12-15] Also, one must recognize that observation bias exists, particularly in the United States, because reports of septic reactions likely reflect only the more severe life-threatening events;[6,7] only fatalities are required for reporting to the Food and Drug Administration, and at present there is no national surveillance for such reports. Moreover, underreporting occurs because clinical personnel tend to overlook the possibility of transfusion-associated septic events because many recipients are immunosuppressed or leukopenic and therefore are susceptible to bacteremia owing to underlying disease or other causes.[5,16] Thus, because of observation bias and underreporting, rates of transfusion-transmitted sepsis may be considerably higher.

Listeria monocytogenes is a gram-positive psychrophilic (cold-loving) bacillus that causes the disease listeriosis. Although widely distributed, *L. monocytogenes* is present in low numbers in most environmental habitats and is rarely a commensal organism among humans. Nevertheless, it can cause serious sporadic and epidemic food-borne disease usually among people with lowered immune systems, particularly the elderly, pregnant

ABBREVIATIONS: ARC = American Red Cross; LAC DHS = Los Angeles County Department of Health Services; PFGE = pulsed-field gel electrophoresis; PHL = (LAC) Public Health Laboratory.

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women, neonates, patients under immunosuppressive therapy, and patients with cancer, renal disease, HIV or AIDS, or any other immunocompromising disease or condition. Common signs and symptoms of listeriosis include fever, muscle aches, nausea, diarrhea, headache, stiff neck, confusion, loss of balance, convulsions, premature birth, and stillbirth. Unlike reports for more common food-borne diseases like salmonellosis and campylobacteriosis, reports of listeriosis usually describe serious illness, like sepsis or meningitis, causing hospitalization and sometimes death. *L. monocytogenes* causes approximately 2500 illnesses, 2300 hospitalizations, and 500 deaths in the United States per year and has a case-fatality rate of 20 percent.[17] Risk foods include raw milk, raw-milk products like soft cheese, raw fruits and vegetables, raw or undercooked meats and seafood, and ready-to-eat foods like bagged salads, hot dogs, and deli meats. Because the incubation period of *L. monocytogenes* ranges from 3 to 70 days with a median of 3 weeks, identifying the source of infection is often very difficult.

We report a case of PLT contamination detected before product release. Since late February 2004, the American Red Cross (ARC) of Southern California has tested all PLTs for bacteria. *L. monocytogenes* has not been previously reported as a PLT contaminant. The investigation of this case demonstrates how an organism of public health importance has potential health implications for the donor and recipients and why collaborating with the health department is important.

CASE REPORT

In October 2004, the ARC of Southern California reported a repeat-positive bacterial culture result from an apheresis PLT product that was subsequently split into 2 units. The contaminating organism was identified as *L. monocytogenes*. The contaminated PLTs were destroyed and not released for transfusion. The donor made four apheresis PLT donations in the subsequent month at a hospital-based blood bank and these all tested negative for bacterial contamination.

MATERIALS AND METHODS

To test for bacterial contamination, the ARC of Southern California used an automated system (BacT/ALERT 3D, bioMérieux, Durham, NC) with each aerobic bottle (BacT/ALERT BPA) inoculated with 4.0 mL of PLT product. Sampling devices included a sampling kit (SampLok, Innovation Technology Licensing, Canberra, Australia) and a sterile tubing welder (Terumo, Tokyo, Japan). Sampling was carried out 24 hours after donation in a laminar flow hood. A contracted microbiology reference laboratory performed Gram stain and species identification. For the described donor case, the mother bag and two daughter bags were sampled with BacT/ALERT BPA aerobic bottles. In addition, with the Terumo sterile tubing welder and plastic transfer packs, 50 to 100 mL from each daughter bag was taken for microbiologic testing.

To test for bacterial contamination in the later apheresis PLT donations by the described case, the hospital blood bank used the classic bioMérieux BacT/ALERT automated system. Each BacT/ALERT BPA aerobic bottle was inoculated with 4.0 mL of PLT product and sampling devices included a Terumo sterile connecting device with a Charter Medical (Winston-Salem, NC) plasma-fluid transfer set. Sampling was performed 24 to 36 hours after donation and was not in a laminar flow hood.

The Los Angeles County Department of Health Services (LAC DHS) performs surveillance on listeriosis by requiring all diagnostic laboratories and health-care providers licensed in LAC to report cases and submit *L. monocytogenes* isolates to the LAC Public Health Laboratory (PHL). The PHL confirms identification of *L. monocytogenes* and uses *AscI* and *ApaI* enzymes to analyze isolates by pulsed-field gel electrophoresis (PFGE).[18] The PHL submits results to the Centers for Disease Control and Prevention (CDC) for comparison to a US national database called PulseNet.[19] When an isolate from LAC has a similar if not indistinguishable PFGE pattern with any other isolate in the national database and the collection dates of the isolates occur within 120 days of each other, CDC informs LAC DHS. Since 1985, LAC DHS has investigated, collected, and analyzed listeriosis case data for disease trends and outbreak detection.

Case investigation normally consists of collaborations with hospital infection control practitioners, medical records offices, and LAC DHS public health nurses to collect data on clinical presentation and predisposing factors. Ultimately the listeriosis surveillance epidemiologist at LAC DHS interviews cases or available case relatives for medical, food, and travel history.

The occurrence of at least two listeriosis cases with the same source of infection confirms an outbreak. Since 1999, LAC DHS has used PFGE to assist in the identification of outbreaks,[20] particularly when PFGE patterns are rare and occur suddenly in more numbers. When investigating situations that may become outbreaks, LAC DHS investigators develop hypothesis-generating questionnaires to gather more details of possible sources of infection. The hypothesis-generating questionnaire for the investigation described in this report consisted of questions on history of blood transfusion, dental work, excavation around the home, travel, and food history specifics such as purchase location, dates, frequency of consumption, and food product brands and names. To improve case detection, LAC DHS alerted all infection control practitioners in LAC of the PLT findings and requested immediate reports of listeriosis cases not yet reported.

RESULTS

In October 2004, the ARC of Southern California called LAC DHS to ask if blood banks were required to report blood products testing positive for the presence of *L. monocytogenes* even if the donor was asymptomatic and had no history of illness. LAC DHS verified that such instances needed to be reported and learned from ARC that two PLT bags from a single apheresis donation by a 58-year-old Hispanic male with no signs or history of illness tested positive for the presence of *L. monocytogenes* (Case 1). Bacterial contamination was detected at 21.4 hours of incubation. The two daughter bags from the plateletpheresis collection were quarantined, and although each tested negative for the presence of bacteria after 5 days of incubation of the BacT/ALERT BPA aerobic bottles, one of the 50 to 100 mL samples from the daughter bags grew *L. monocytogenes*. This was the first time the ARC of Southern California had identified *L. monocytogenes* in a blood product.

In mid-November 2004, CDC informed LAC DHS that two subsequent cases, one in LAC (Case 2) and one in Colorado (Case 3), shared the same PFGE pattern defined by the *Asc*I and *Apa*I enzymes. Including these three incidents, the pattern appeared only eight times (0.19%) in the national database of 4167 isolates analyzed by both enzymes. LAC had two other isolates with this pattern, one occurring in 2003 (Case 4) and one in 1999. Despite a health alert to all infection control practitioners in LAC, no further listeriosis cases with this PFGE pattern were reported.

Case investigation focused on the two 2004 LAC cases but extended to Case 3 and Case 4 (Table 1). The PLT donor (Case 1) had no risk factors for listeriosis and ate only a few risk foods (cottage cheese, Gouda cheese, mozzarella cheese). He had no symptoms of illness before or during his *Listeria*-positive PLT donation. Since 2001, he donated PLTs only and had made 12 donations since the ARC started testing PLTs for bacteria. Because previous donations were culture-negative and he was asymptomatic, the donor was allowed to continue donation. He was not recultured, but he subsequently made four separate apheresis PLT donations at a hospital blood bank during October and November and these were all negative for the presence of bacterial contamination. In Case 2, a 58-year-old Hispanic woman developed symptoms and died around the same time as the PLT donation of Case 1. She died the day after hospital discharge with the cause of death listed as breast cancer. Although her surviving relatives recalled her getting a blood transfusion for anemia 2 months before her illness onset, hospital and hospice records documented only the anemia and not the transfusion. This case had multiple risk factors including breast cancer with metastases to liver, bone, lung, and brain; recent chemotherapy and steroid medication; and recent antacid use. The patient of Case 2 also ate several risk foods, such as Mexican-style fresh cheese, soft cheese, deli meats, and raw seafood. The only common food to Cases 1 and 2 was mozzarella cheese. The distance between the case residences, different brands of mozzarella, and lack of further cases with history of mozzarella consumption made the cheese an unlikely common source. Including information from Case 3, a 74-year-old woman with listeriosis in October 2004, and Case 4, a 59-year-old man from LAC with listeriosis and metastatic adenocarcinoma in August 2003, no useful epidemiologic connections could be made among these four cases other than the PFGE pattern.

TABLE 1. Listeriosis cases with indistinguishable PFGE pattern—United States, 2003 to 2004

Case	Age (years)	Sex	Location	Specimen collection date
1	58	Male	LAC, CA	September 27, 2004
2	58	Female	LAC, CA	October 1, 2004
3	74	Female	Colorado	October 19, 2004
4	59	Male	LAC, CA	August 14, 2003

DISCUSSION

The most unusual characteristic of this listeriosis investigation was that the PLT donor was asymptomatic with no history of recent illness. Listeriosis cases with bacteremia normally have fever or at least some other symptom. In a review of 1036 listeriosis cases in LAC, only one other nonpregnant adult case had bacteremia and was asymptomatic. The best explanation the authors have regarding the PLT donor is transient bacteremia. Bacterial contamination of blood products has been ascribed to transient bacteremia in the past.[6,7,21] Because CDC found two other cases with the same rare PFGE pattern around the same time frame, the reference laboratory of the ARC of Southern California grew cultures from two of five samples taken at different times, and the PHL confirmed *L. monocytogenes*, environmental contamination, false-positive laboratory results, and skin contamination were thought to be less likely explanations. Furthermore, the lack of predisposing medical conditions in Case 1 probably contributed to his lack of symptoms as the other cases had risk factors for listeriosis.

Listeriosis caused by transfusion has not yet been reported, at least in the literature. In 1998, a case report from Trinidad described a premature infant returning to the hospital with septicemia and meningitis due to *L. monocytogenes* approximately 4 days after receiving a whole-blood transfusion.[22] Transfusion-transmitted listeriosis, however, was not definite because the mother was not

ruled out as the source of infection and the whole blood used for transfusion was not cultured. Over 3 years of active surveillance of 60 to 70 percent of blood banks in the United States, the Assessment of the Frequency of Blood Component Bacterial Contamination Associated with Transfusion Reaction Study (BaCon) found no *L. monocytogenes* bacteremia cases; however, the BaCon study defined bacteremia cases as blood product recipients with signs or symptoms occurring within 4 hours of transfusion and required culture confirmation in both the blood component and the patient, reducing sensitivity for reported cases.[8]

The LAC case of the contaminated PLTs was detected because the ARC of Southern California began testing apheresis PLTs for bacterial contamination in February 2004. This was in anticipation of the standard the AABB adopted on March 1, 2004, for blood banks and transfusion services to have methods to detect and limit bacterial contamination in all PLT components.[23] Whole blood–derived PLTs, RBCs, and plasma are not typically cultured to detect bacterial contamination. Other proposed methods to reduce bacterial contamination in blood products include improving donor screening, better skin disinfection, pathogen inactivation by chemical or photochemical methods, and testing RBC units during the second week of storage.[5-7,24-27] The overall benefits, costs, and risks need to be carefully considered before implementing any method to improve blood safety.

This investigation revealed that in conducting surveillance for listeriosis, blood-related issues need more scrutiny. Although iron overload has been established as a risk factor for listeriosis,[28,29] measurement of this suffers from diagnostic bias because testing really only happens for patients with repeated transfusions for severe or chronic anemias such as thalassemia major, myelodysplasia (including sideroblastic anemia), moderate aplastic anemia, and Diamond-Blackfan anemia.[30] Given published evidence of iron increasing the growth and lethality of *L. monocytogenes*,[31-33] researchers should measure recent history of anemia, blood transfusions, and iron supplements as risk factors for listeriosis.

The critical event for this case report was the ARC reporting to the health department. Reporting by blood banks and health-care facilities is necessary to determine the risks and boundaries of possible outbreaks, particularly if contaminated products are released for transfusion. Although the contaminated products were not released in this case, the donation history of the PLT donor became important to determine whether he previously donated RBC units that might have caused other cases. Health departments in areas with little or no experience with listeriosis might not have required notification of this case. Because PLTs and other blood components found to be positive for the presence of reportable organisms require notification of public health authorities, health departments at all levels of government should ensure that reporting requirements are clear for various reporting sources, especially blood banks, and in other settings in which there are new guidelines or standards. A recent CDC survey of clinicians demonstrated low awareness of the new AABB standard for bacterial testing of PLTs and of transfusion-transmitted infectious disease risks by bacteria-contaminated PLTs.[34] This finding, plus the inclusion of several statements to save culture isolates and notify appropriate state and local health departments in the AABB February 2005 guidelines for recognizing and managing transfusion reactions,[35] reflect the fact that better surveillance and reporting are needed in the efforts to improve blood product safety.

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医薬品 研究報告 調査報告書

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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)			スペイン

研究報告の概要

○肺炎連鎖球菌の院内感染
スペインの2つの大きな医大付属病院の成人患者における肺炎連鎖球菌菌血症の後ろ向き研究から、1020件中108件(10.6%)が院内肺炎球菌血流感染(NPBI)であることが明らかになった。血流感染とは、血液培養が陽性となり、敗血症の症状のあるものを指す。十分なデータがあり解析に利用できた症例は77件あった。入院から血液培養陽性となるまでの期間は、3～135日(中央値17日、四分位範囲8～27日)であった。基礎疾患のうち主なものは、悪性腫瘍(31%)、慢性閉塞性肺疾患(28.6%)、心不全(16.9%)、慢性腎不全(15.6%)、肝硬変(13%)、HIV感染(13%)であった。感染時の主な症状は、肺炎(70.1%)、髄膜炎(5.2%)、原発性腹膜炎(5.2%)であった。全体で、患者の31.2%が重度の敗血症、11.7%が敗血症ショック、3.9%が多臓器不全を発症した。原因菌の血清型のうち、78%は23価多糖体ワクチンに含まれていた。35名(45.5%)の患者が死亡し、そのうち21名(27.3%)がNPBIに関連すると考えられた。多変量解析を行ったところ、年齢による調整後、独立して予測される死亡因子は次の通りであった。最終的に基礎疾患による死亡(OR 8.9、95%CI 0.8-94.3、p<0.001)、急速な基礎疾患による死亡(OR 15.0、95%CI 2.8-81.3、p<0.001)、心不全(OR 8.11、95%CI 1.1-60.8、p<0.03)、不十分な経験療法(OR 10.6、95%CI 1.2-97、p<0.003)、重度の敗血症スコア(OR 9.5、95%CI 1.9-47.0、p<0.001)、敗血症ショックまたは多臓器不全(OR 63.7、95%CI 4.9-820.7、p<0.001)である。十分な経験療法は独立した予防因子(OR 0.05、95%CI 0.04-0.58、p<0.005)であったが、2種類以上の抗菌薬の使用は予防因子とならなかった。

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

報告企業の意見	今後の対応
スペインの2つの大きな医大付属病院の成人患者における肺炎連鎖球菌菌血症の後ろ向き研究から、1020件中108件(10.6%)が院内感染であることが明らかになったとの報告である。輸血後細菌感染の調査には、院内感染など輸血以外の伝播ルートについて考慮する必要がある。	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。 今後も情報の収集に努める。白血球除去の導入とともに細菌を不活化する方策についても検討を進める。

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Nosocomial bloodstream infections caused by *Streptococcus pneumoniae*

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ABSTRACT

A retrospective study of *Streptococcus pneumoniae* bacteraemia among adult patients in two large teaching hospitals in Spain identified 108 (10.6%) of 1020 episodes as nosocomial pneumococcal bloodstream infections (NPBIs). Seventy-seven clinical records with sufficient data were available for analysis. The interval between admission and a positive blood culture was 3–135 days (median 17 days; interquartile range 8–27). The main underlying and predisposing conditions for NPBI were malignancy (31%), chronic obstructive pulmonary disease (28.6%), heart failure (16.9%), chronic renal failure (15.6%), liver cirrhosis (13%) and infection with human immunodeficiency virus (13%). Overall, 31.2% of patients developed severe sepsis, 11.7% septic shock, and 3.9% multi-organ failure. The main portals of entry were pneumonia (70.1%), meningitis (5.2%) and primary peritonitis (5.2%). Of the responsible serogroups, 78% were included in the 23-valent polysaccharide vaccine. Thirty-five (45.5%) patients died, with death considered to be related to the NPBI in 21 (27.3%) cases. Following multivariate analysis, factors that independently predicted death after adjusting for age were: ultimately fatal underlying disease (OR, 8.9; 95% CI, 0.8–94.3; $p < 0.001$); rapidly fatal underlying disease (OR, 15.0; 95% CI, 2.8–81.3; $p < 0.001$); heart failure (OR, 8.11; 95% CI, 1.1–60.8; $p < 0.03$); inadequate empirical therapy (OR, 10.6; 95% CI, 1.2–97; $p < 0.003$); a severe sepsis score (OR, 9.5; 95% CI, 1.9–47.0; $p < 0.001$); and septic shock or multi-organ failure (OR, 63.7; 95% CI, 4.9–820.7; $p < 0.001$). Adequate empirical therapy was an independent protective factor (OR, 0.05; 95% CI, 0.04–0.58; $p < 0.005$), but the use of more than one antimicrobial agent was not.

Keywords Bacteraemia, bloodstream infection, nosocomial infection, pneumococci, risk factors, *Streptococcus pneumoniae*

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INTRODUCTION

Nosocomial pneumococcal bloodstream infections (NPBIs) are reported infrequently in the literature, despite the fact that they represent 8.9–41% of all pneumococcal bloodstream infections [1–8]. This study describes the incidence, clinical manifestations, treatment and outcome of NPBI in two large teaching hospitals in Spain.

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PATIENTS AND METHODS

Study design and settings

The study was a retrospective cohort study carried out in two large teaching hospitals located in the city of Madrid, Spain. The study was performed during the 8-year period from January 1995 to December 2002, and included all adult patients (aged >16 years) with one or more blood cultures from which *Streptococcus pneumoniae* was isolated, and who were considered to have acquired the infection in the hospital (see below). Charts were reviewed according to a pre-established protocol.

Microbiological identification and susceptibility testing

S. pneumoniae was identified using standard and well-recognised procedures. Capsular serotyping of isolates was performed at the Centro Nacional de Microbiología (Instituto de Salud Carlos III, Majadahonda, Madrid). Antimicrobial susceptibility tests were performed using a microdilution technique (Sensititre; Trek Diagnostic Systems, East Grinstead, UK) and interpreted according to NCCLS recommendations [9].

Definitions and classifications

Nosocomial infections were defined according to CDC recommendations [10]. NPBIs were defined as infections that were demonstrated ≥72 h after admission, excluding those patients who were suspected of having pneumococcal disease present or in incubation at admission [11]. The underlying condition of each patient before pneumococcal disease was rated according to the McCabe and Jackson criteria [12], and categorised according to the Charlson co-morbidity index [13]. The severity of the clinical condition of each patient with NPBI was assessed by the APACHE II score for those admitted to the intensive care unit (ICU) [14]. The maximum severity of septic illness until the moment of discharge or death of each patient was assessed according to Bone's score [15]. The following potential predisposing conditions for nosocomial bloodstream infections were recorded: tracheal intubation, upper or lower gastrointestinal endoscopy, bronchoscopy, nasogastric tube insertion, central catheter line, indwelling bladder catheter, surgery (in the previous 7 days), use of antimicrobial agents (within 30 days before the episode) or corticosteroids (at least 10 mg of prednisone or equivalent for at least 7 days in the 2-week period before the episode), hospitalisation within the preceding 3 months, liver cirrhosis, diabetes mellitus, total parenteral nutrition (before the episode), low serum albumin (< 3 g/dL), solid or haematological malignancy, heart failure, alcoholism (> 50 g of alcohol ingestion/day), splenectomy (at any time in the past), infection with human immunodeficiency virus, chronic obstructive pulmonary disease, and chronic renal failure (creatine > 1.5 mg/dL). The clinical origin of NPBI was defined on the basis of clinical data or as a consequence of the isolation of *S. pneumoniae* from a focus of infection.

Treatment parameters

Treatment parameters recorded were: number of active antimicrobial agents received simultaneously for a minimum of 2 days, length of days on active antimicrobial therapy (receiving at least one active drug), and treatment with penicillins, cephalosporins (third and fourth generation), macrolides, co-trimoxazole, fluoroquinolones and other drugs (carbapenems, other cephalosporins, aminoglycosides and glycopeptides). Antimicrobial therapy during the first 24 h of treatment was considered to be adequate when the patient received at least one active antimicrobial agent during this period.

Outcome

Patients were finally classified as deceased or as having been discharged. Death was classified as related to the NPBI when persistence of a clinical picture of sepsis at death could be attributed to pneumococcal infection, or when death occurred during the first week after blood cultures were taken.

Statistical analysis

Quantitative variables were calculated as a mean and standard deviation (SD). Median and interquartile range were calculated when appropriate. Categorical data were analysed using the chi-square test or Fisher's exact test, as appropriate, with statistical significance set at $p \leq 0.05$. All p values were two-tailed. A logistic regression model was used to examine the effects of multiple risk-factors on mortality. Variables included in the model were those found to reach a significance level of $p < 0.1$ in the univariate analysis, together with the age of the patients, since age is known to be a variable that has an important impact on mortality.

RESULTS

The population served by the two institutions between 1995 and 2002 remained stable, at close to 1 175 000 inhabitants. Between January 1995 and December 2002, there were 1092 episodes of pneumococcal bloodstream infections in patients of all ages, of which 1020 (93.4%) occurred in the adult population. Overall, the estimated incidence of pneumococcal bloodstream infections in adults was 10.7 episodes/100 000 inhabitants/year. Of the 1020 episodes of pneumococcal bloodstream infections in adults, 108 (10.6%) were considered to be nosocomial. Clinical charts with adequate information were available for 77 of these 108 patients.

Of the 77 patients analysed, 55 were male and 22 were female, with a mean age of 64.34 years (SD, 16.89 years). The interval between admission and the day of positive blood cultures for *S. pneumoniae* ranged from 3 to 135 days (median, 17 days; interquartile range, 8–27 days). Patients with NPBI were located mainly in medical units (76.6%), followed by surgical departments (13%) and ICUs (10.4%). There was no evidence of nosocomial outbreaks or in-hospital transmission. The main underlying and predisposing conditions of the patients with NPBI are summarised in Table 1.

The severity of the underlying condition was: rapidly fatal, 8 (10.4%); ultimately fatal, 34 (44.2%); and non-fatal, 35 (45.5%). Co-morbidity was variable and ranged from 0 to 11 (median 2; interquartile range 2–7), according to Charlson's index. The mean APACHE II score of the 17 patients who were admitted to the ICU ranged from 6 to 25 (mean, 13.18; SD, 6.19). The percentages of patients who developed different degrees of sepsis were: sepsis only, 53.2%; severe sepsis, 31.2%; septic shock, 11.7%; and multi-organ failure, 3.9%.

Table 1. Main underlying conditions and predisposing factors for 77 patients with nosocomial pneumococcal bloodstream infections in two hospitals in Spain (1995–2002)

	% of patients
Underlying condition	
Malignancy	31
Chronic obstructive pulmonary disease	28.6
Heart failure	16.9
Chronic renal failure	15.6
Liver cirrhosis	13
HIV infection	13
Diabetes mellitus	11.7
Alcoholism	10.4
Splenectomy	0
Predisposing factor	
Low serum albumin	54.5
Antimicrobial agents	45.5
Corticosteroids	44.2
Bladder catheter	32.5
Prior hospitalisation	23.4
Central catheter	23.4
Nasogastric tube	18.2
Tracheal intubation	18.2
Prior surgery	10.4
Gastroenteric endoscopy	9.1
Bronchoscopy	9.1
Parenteral nutrition	7.8

HIV, human immunodeficiency virus.

Table 2. Serotypes of 72 *Streptococcus pneumoniae* isolates from patients with nosocomial pneumococcal bloodstream infections in two hospitals in Spain (1995–2002)

Serotypes	*n*	%
14	12	16.7
23F	8	11.1
19	5	6.9
4	4	5.6
10	4	5.6
15F	4	5.6
8	3	4.2
23	3	4.2
34	3	4.2
3	2	2.8
6A	2	2.8
9N	2	2.8
9V	2	2.8
15	2	2.8
19F	2	2.8
23A	2	2.8
6	1	1.4
6B	1	1.4
11	1	1.4
15A	1	1.4
15B	1	1.4
18C	1	1.4
22	1	1.4
25	1	1.4
42	1	1.4
Non-typeable	3	4.2

Portals of entry of NPBI were pneumonia (70.1%), meningitis (5.2%), primary peritonitis (5.2%), catheter infection (3.9%), upper respiratory tract infection (2.6%) and bone and joint infection (1.3%). NPBI presented as primary bacteraemia in 11.7% of the episodes. The episode was monomicrobial in 66 (85.7%) patients, and part of a polymicrobial bacteraemia in 11 (14.3%) patients. In polymicrobial cases, the accompanying microorganisms were *Staphylococcus aureus* (seven patients), *Corynebacterium* spp. (two patients), *Bacteroides fragilis*, *Pseudomonas aeruginosa*, *Salmonella enteritidis* and *Haemophilus influenzae* (one patient each).

In total, 57 (74.0%) patients had chest X-ray abnormalities. More than one lobe of the lung parenchyma was involved in 25 (32.5%) patients. There were cavitations in three patients, and a lung abscess in one case. Overall, 23 (29.9%) patients had pleural effusions of different sizes.

Serotyping results were available for the isolates from 72 patients (Table 2). The most common serotypes were 14 (16.7%), 23F (11.1%) and 19 (6.9%). Overall, 78.0% of the serogroups obtained in this series are included in the 23-valent polysaccharide vaccine.

Antimicrobial susceptibilities were available for all the bloodstream isolates; the frequencies of penicillin-susceptible, -intermediate and -resistant isolates were 54.5%, 18.2% and 27.3%, respectively. With respect to other drugs, the frequency of resistant isolates was as follows: cefotaxime, 9.2%; erythromycin, 24.7%; tetracycline, 35.1%; chloramphenicol, 23.7%; clindamycin, 22.1%; and trimethoprim–sulphamethoxazole, 38.7%.

Treatment and outcome

The numbers of patients who received different antimicrobial agents were: third- or fourth-generation cephalosporins, 41 (53.2%); penicillins, 31 (40.2%); fluoroquinolones, 11 (14.3%); macrolides, 6 (7.8%); trimethoprim–sulphamethoxazole, 1 (1.3%); and other antimicrobial agents, 41 (52.2%). Two or more effective drugs were administered simultaneously to 20 (26%) patients for at least 48 h. The mean duration of treatment was 11.75 days (SD 6.99; range 0–31 days). Empirical therapy was considered adequate for 65 (84.4%) patients.

Overall, 35 (45.5%) patients died with NPBI; death was considered to be related directly to the NPBI in 21 (27.3%) patients, and was considered to be unrelated in the remaining 14 (18.2%). Patients who received more than one active drug had a mortality rate of 35% (7/20), compared with 49% (28/57) for those who received a single active drug (p 0.27). Factors that correlated with mortality ($p < 0.10$) in a univariate analysis were:

Table 3. Comparison of patients who died and survived (univariate analysis)

	Survived (n = 42)	Died (n = 35)	p
Age (years)	61.5 ± 17.3	67.7 ± 15.9	0.1
Male	31 (73.8%)	24 (68.6%)	0.6
Hospital 1	10 (23.8%)	12 (34.3%)	0.3
Hospital 2	32 (76.2%)	23 (65.7%)	0.3
Medical service	34 (81.0%)	25 (71.4%)	0.2
Surgical service	6 (14.3%)	4 (11.4%)	0.2
Intensive care unit	2 (4.8%)	6 (17.1%)	0.2
Classification of underlying disease*			
McCabe I	3 (7.1%)	5 (14.3%)	0.006
McCabe II	13 (31.0%)	21 (60.0%)	0.006
McCabe III	26 (61.9%)	9 (25.7%)	0.006
Underlying diseases			
Liver cirrhosis	5 (11.9%)	5 (14.3%)	0.7
Diabetes	4 (9.5%)	5 (14.3%)	0.5
Malignancy	13 (31.0%)	11 (31.4%)	0.9
Heart failure*	3 (7.1%)	10 (28.6%)	0.016
Alcoholism	5 (11.9%)	3 (8.6%)	0.6
HIV infection	7 (16.7%)	3 (8.6%)	0.3
Chronic obstructive pulmonary disease	12 (28.6%)	10 (28.6%)	1.0
Chronic renal failure	5 (11.9%)	7 (20.0%)	0.3
Sepsis score*			
Sepsis	31 (73.8%)	10 (28.6%)	< 0.001
Severe sepsis	10 (23.8%)	14 (40.0%)	< 0.001
Septic shock	1 (2.4%)	8 (22.9%)	< 0.001
Multi-organ failure	0 (0%)	3 (8.6%)	< 0.001
Predisposing conditions			
Mechanical ventilation	8 (19.0%)	6 (17.1%)	0.8
Gastrointestinal endoscopy	4 (9.5%)	3 (8.6%)	0.8
Bronchoscopy	4 (9.5%)	3 (8.6%)	0.8
Nasogastric tube	6 (14.3%)	8 (22.9%)	0.3
Prior antibiotic therapy	20 (47.6%)	15 (42.9%)	0.6
Prior hospital admission	10 (23.8%)	8 (22.9%)	0.9
Corticosteroid therapy	18 (42.9%)	16 (45.7%)	0.8
Prior surgery	4 (9.5%)	4 (11.4%)	0.7
Parenteral nutrition	3 (7.1%)	3 (8.6%)	0.8
Low serum albumin	22 (52.4%)	20 (57.1%)	0.6
Central catheter line	11 (26.2%)	7 (20.0%)	0.5
Indwelling bladder catheter	12 (28.6%)	13 (37.1%)	0.4
Origin of pneumococcal infection			
Pneumonia	27 (64.3%)	27 (77.1%)	0.3
Upper respiratory tract	2 (4.8%)	0 (0%)	0.3
Central catheter	3 (7.1%)	0 (0%)	0.3
Primary peritonitis	2 (4.8%)	2 (5.7%)	0.3
Bone and joint infection	0 (0%)	1 (2.9%)	0.3
Meningitis	2 (4.8%)	2 (5.7%)	0.3
Primary infection	6 (14.3%)	3 (8.6%)	0.3
Chest X-ray abnormalities			
Pleural effusions	11 (26.2%)	12 (34.3%)	0.4
Cavitations	1 (2.4%)	2 (5.7%)	0.4
Lung abscess	1 (2.4%)	0 (0%)	0.3
Abnormalities present	30 (71.4%)	28 (80.0%)	0.6
More than one lobe involved	12 (28.6%)	13 (37.1%)	0.4
Polymicrobial bacteraemia*	9 (21.4%)	2 (5.7%)	0.008
Antimicrobial susceptibility			
Penicillin-susceptible	23 (54.8%)	19 (54.3%)	0.9
Cefotaxime-susceptible	38 (90.5%)	32 (91.4%)	0.8
Erythromycin-susceptible	31 (73.8%)	27 (77.1%)	0.7
Therapy			
Adequate therapy*	40 (95.2%)	25 (71.4%)	0.004
More than two effective drugs	13 (31.0%)	7 (20.0%)	0.2

HIV, human immunodeficiency virus.
*$p \leq 0.05$.

a rapidly or ultimately fatal disease on the McCabe scale (p 0.006); a severe sepsis score ($p < 0.001$); inadequate empirical antimicrobial therapy during the first 24 h (p 0.009); heart failure (p 0.016); and polymicrobial bacteraemia (p 0.008) (Table 3).

Following multivariate analysis, factors that independently predicted death after adjusting by age were: ultimately fatal underlying disease (OR, 8.9; 95% CI, 0.8–94.3; $p < 0.001$); rapidly fatal underlying disease (OR, 15.0; 95% CI, 2.8–81.3; $p < 0.001$); heart failure (OR, 8.11; 95% CI, 1.1–60.8; p 0.03); inadequate empirical therapy (OR, 10.6; 95% CI, 1.2–97; $p < 0.003$); and a severe sepsis score (severe sepsis: OR, 9.5; 95% CI, 1.9–47.0; $p < 0.001$; septic shock or multi-organ failure: OR, 63.7; 95% CI, 4.9–820.7; $p < 0.001$). Adequate empirical therapy was found to be an independent protective factor (OR, 0.05; 95% CI, 0.04–0.58; $p < 0.005$). The predictive ability of the variables included in the model was 80% sensitivity to predict death and 93% specificity to predict survival.

DISCUSSION

This study shows that a significant proportion of bactaeremic pneumococcal infections appear in the hospital setting. NPBI usually appears in patients with severe underlying diseases and is associated with a high mortality. Pneumococcal infections in children and adults are mainly community-acquired; however, *S. pneumoniae* was already recognised as a common cause of nosocomial infection before the introduction of penicillin into clinical practice [16,17]. In the antibiotic era, nosocomial pneumococcal infections have been reported to account for 4% of cases of acute sinusitis, 5% of cases of bacterial meningitis and 2% of bacteraemias [18–22]. In a prospective study of all infections caused by *S. pneumonia* in one of the institutions in Madrid during a 22-month period, pneumococcal infection was nosocomial in 25% of cases [23]. Some subgroups of patients, such as the elderly, those with malignancy, and those with ultimately fatal diseases, have a much higher rate of nosocomial pneumococcal infection [24–27]. The incidence of pneumococcal bloodstream infections in Madrid increased significantly between 1986 and 2000, in both adults (from 8.2 to 16 episodes/100 000 population) and children (from 3.6 to 14.8 episodes/100 000 population) [28]. Similar increases have been demonstrated in other geographical areas [29–33].

The proportion of pneumococcal bloodstream infections occurring in hospitalised patients is estimated to represent 10–41% of all cases [4,8,34]. It can be argued that many of the so-called NPBIs are actually community-acquired, but manifest

following hospital admission with a delay slightly over the breakpoint of 48 h. The present study only included episodes that manifested ≥72 h following hospitalisation of patients with no evidence of infection on admission. The study confirmed that NPBI tends to occur after a relatively prolonged period of hospitalisation (mean period of 22.56 days), a result that is quite similar to the mean of 17 days reported by Canet *et al.* [8] from another hospital in Spain. There was no evidence, either epidemiological or based on the identification of serotypes, for any major or minor outbreak that might result in nosocomial transmission from patient to patient in the institutions studied.

NPBI occurred mainly in patients with severe underlying conditions, including neoplasia, chronic obstructive pulmonary disease, heart failure, renal failure and cirrhosis [4,26,35]. Almost half of the patients in the present series developed severe forms of sepsis, including septic shock or multiorgan failure, and a high proportion required ICU admission [4]. The series found that lung infections were the portal of entry in only 70% of cases, and that the absence of pneumonia does not rule out the possible presence of *S. pneumoniae* in the blood cultures of hospitalised patients. NPBI may also occur as a complication of a wide variety of focal infections, including peritonitis, meningitis, and catheter, upper respiratory tract and bone and joint infections. In addition, NPBI can appear as 'primary' bactaeremia in a significant proportion of patients [8].

NPBI is associated with a higher mortality rate (40–74%) [3,8,36] than community-acquired infection (14–27%) [37,38]. The above-mentioned conditions explain the high mortality in the series, which was independently predictable on the basis of the severity of sepsis, presence of heart failure and administration of inadequate antimicrobial therapy. The most obvious area for potential intervention is inadequate antimicrobial therapy. The question of treatment with single vs. double antimicrobial agents for severe pneumococcal infections has been discussed previously [39–42]. The present study found that there was a trend towards a better prognosis for those patients who received two active antimicrobial agents, but this did not reach statistical significance, probably because of the limited number of patients.

The worldwide escalation of antimicrobial resistance in *S. pneumoniae* has prompted the introduction of vaccination [4], and >70% of the isolates responsible for nosocomial infections in the present study would have been covered by the 23-valent polysaccharide vaccine. Unfortunately, pneumococcal vaccination was not a common practice in Spain during the period of the study. It is clear that *S. pneumoniae* infections should be added to the list of severe nosocomial diseases. NPBI has a severe prognosis that justifies novel therapeutic and prevention strategies.

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