# 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)<br>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。

| 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。<br>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**

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

ORIGINAL ARTICLE 10.1111/j.1469-0691.2005.01260.x

# 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.

## 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.

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### 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, cotrimoxazole, 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[a] | | | |
| 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[a] | 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[a] | | | |
| 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[a] | 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[a] | 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.
[a]$p \leq 0.05$.

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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# 医薬品 研究報告 調査報告書

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**研究報告の概要**

○スウェーデンにおける梅毒の再興:2004年サーベイランスの結果
1999年以来、スウェーデンにおける梅毒の症例数は、主として男性と性交渉を持つ男性(MSM)の間で増加している。
2004年は前年比7%増の192例で、1980年代半ば以来最高の水準である。報告されたうちの大半(60%、101/169)は男性間性交渉、38%は男女間性交渉による感染である。約半数(n=97)がストックホルム郡から報告された。
ストックホルム郡では、患者の出生地が判明した症例(n=72)のうちスウェーデン生まれは60%だったのに対し、郡外(n=64)ではわずか24例(38%)だった。郡内の症例の大半(82%)は男性間性交渉で感染し、80%(n=53/66)は国内、46例はストックホルム市内で感染、3例は感染経路不明である。郡外の症例のうち2例は海外で血液製剤によって感染し、17例は感染経路は報告されていない。
ストックホルム郡が依然としてMSM間の梅毒感染拡大の中心地となっている一方、男女間の感染は郡外の報告の方が多かった。後者は海外での感染が多く、スウェーデン生まれは少数だった(n=9、26%)。
梅毒感染MSMのおよそ30%がHIVに重複感染していたが、これはロンドンの53%と比べて低率である。ストックホルム郡のMSM感染例と男女間感染例の割合は、感染初期ではロンドンの割合と類似していた。郡外の男女間感染で感染後期に診断されたものは、海外で感染し入国後に診断されたと考えられる。
この調査では、ヨーロッパの他の国と類似した疫学的傾向の知見を反映している。予防プログラム、早期診断、追跡調査、治療のすべてが感染拡大を防ぐために重要である。

| 報告企業の意見 | 今後の対応 |
|---|---|
| スウェーデンにおける梅毒の症例数が、主として男性と性交渉を持つ男性(MSM)の間で増加しているとの報告である。 | 今後も引き続き、新興・再興感染症の発生状況等に関する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

## Re-emergence of syphilis in Sweden: results from a surveillance study for 2004

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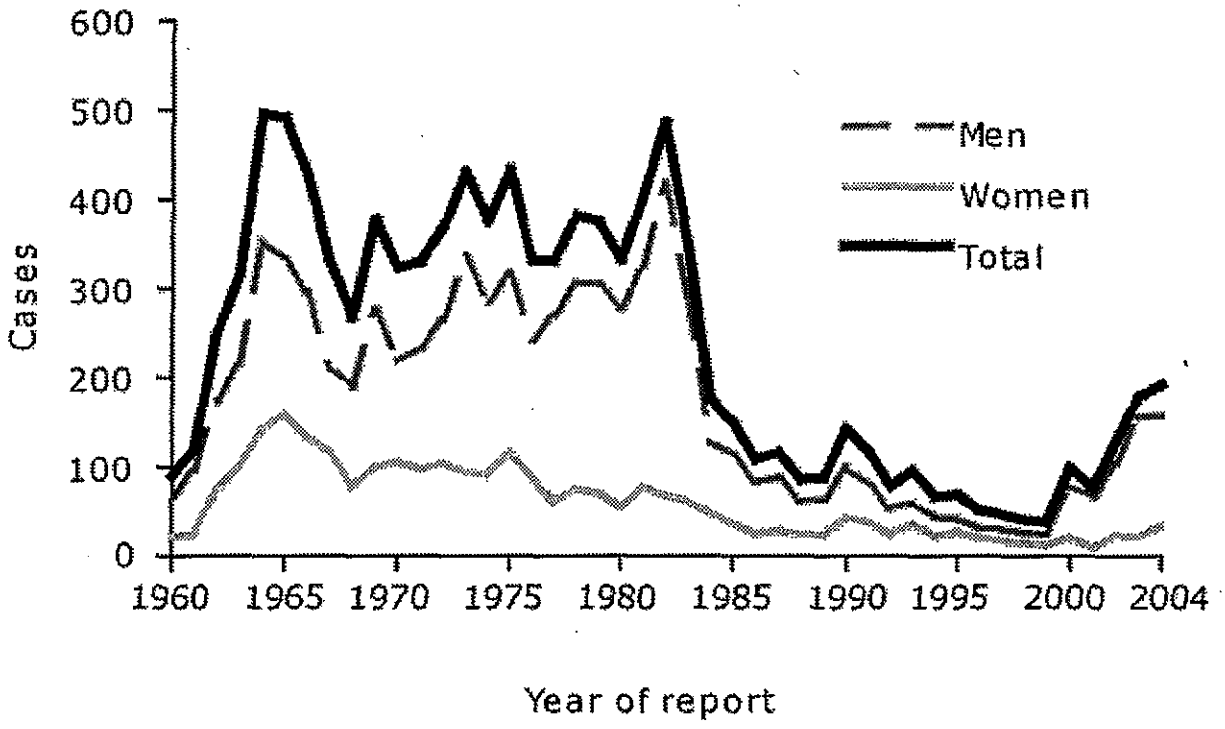
Since 1999, the annual number of syphilis cases has risen in Sweden due mainly to an outbreak among men having sex with men (MSM) [1].

A 7% increase on the previous year was observed in 2004, with 192 cases - the highest number of annual notifications since the mid-1980s (Figure 1). The majority of infections were reported to have been acquired through sex between men (60%, 101 /169), with 38% of infections acquired heterosexually. Nearly a half (n=97) of all notifications were reported in Stockholm County (which includes city of Stockholm).

**Figure 1.** Number of syphilis cases reported by year, Sweden 1960-2004




To gain a better understanding of the epidemiology of reported cases, syphilis statutory notifications in Sweden in 2004 were reviewed. Notifying physicians were sent a short form requesting confirmation of the original notification details and collecting further information on patient's country of birth, HIV status, syphilis stage at diagnosis, how the partner probably acquired syphilis, place of infection, and any contact tracing undertaken.

For Stockholm County, 91 forms were returned for the 97 cases notified in 2004. Where the patient's country of birth was known (n=72), 60% were born in Sweden. The majority (82%) of cases in Stockholm County were acquired through sex between men, with 80% of patients (n=53/66 reported as having acquired infection in Sweden and 46 cases in the city of Stockholm. For three cases, no infection route was reported. Outside of Stockholm County, epidemiological information was provided for 81 of 89 notifications. Where country of birth was known (n=64), only 24 (38%) were born in Sweden. Two cases were infected through blood products abroad, and infection route was not reported for 17 cases.

The median age of diagnosis was higher among MSM than heterosexuals.

**Table.** Epidemiology of statutory notified syphilis cases, Sweden 2004

| Infection route | | Stockholm County (N=91) Cases (n) | Information available (N) | % | Outside Stockholm County (N=81) Cases (n) | Information available (N) | % |
|---|---|---|---|---|---|---|---|
| ***Sex between men*** | | 72 | 88 | 82 | 21 | 64 | 33 |
| Infection acquired in Sweden | | 53 | 66 | 80 | 10 | 21 | 48 |
| Infection acquired in Stockholm | | 46 | 46 | 100 | 0 | 7 | -- |
| Partner infected in Sweden | | 7 | 9 | * | 3 | 5 | * |
| Positive HIV status | | 21 | 67 | 31 | 4 | 20 | 20 |
| Syphilis stage | Primary | 26 | 66 | 39 | 8 | 16 | 50 |
| | Secondary | 16 | 66 | 24 | 5 | 16 | 31 |
| | Early latent (<2yrs) | 19 | 66 | 29 | 3 | 16 | 19 |
| | Late latent (>2yrs) | 3 | 66 | 5 | 0 | 16 | -- |
| | Tertiary | 2 | 66 | 3 | 0 | 16 | -- |
| Median age at diagnosis (Range) | | 40 years (22-76) | | | 44 years (25-68) | | |
| ***Sex between men and women*** | | 16 | 88 | 18 | 41 | 64 | 64 |
| Infection acquired in Sweden | | 10 | 16 | 63 | 6 | 39 | 15 |
| Infection acquired in Stockholm | | 8 | 8 | * | 0 | 6 | -- |
| Partner infected in Sweden | | 4 | 5 | * | 3 | 9 | * |
| Positive HIV status | | 0 | 12 | -- | 1 | 33 | 3 |
| Syphilis stage | Primary | 7 | 16 | 44 | 6 | 23 | 26 |
| | Secondary | 5 | 16 | 31 | 4 | 23 | 17 |
| | Early latent (<2yrs) | 2 | 16 | 13 | 5 | 23 | 22 |
| | Late latent (>2yrs) | 2 | 16 | 13 | 7 | 23 | 30 |
| | Tertiary | 0 | 16 | -- | 1 | 23 | 4 |
| Median age at diagnosis (Range) | | 33 years (18-61) | | | 34 years (19-58) | | |

* No percentages given due to small numbers

**Contact tracing**

For Stockholm County, of the 49 cases with infection acquired in Sweden, 4.35 partners/case were recalled and 57% contacted and tested (for 44 cases). Outside Stockholm, of 12 cases infected in Sweden, 2.25 partners/case were recalled. Of the total 27 partners, 16 were contacted and 5 identified as syphilis positive.

**Discussion**

*In 2004, Stockholm County remained the focus of the syphilis epidemic among MSM, whereas among*

heterosexuals, more cases were reported outside Stockholm County. This latter group mostly acquired their infections abroad with a minority being Swedish born (n=9, 26%). Overall, little information was known about the partner's country of infection.

Concurrent HIV-infection in syphilis-infected MSM has been reported in many European countries [1-6]. Approximately 30% of MSM with syphilis in 2004 also had HIV infection; which is less than the 53% prevalence among infected MSM in London [8]. Percentages of MSM and heterosexuals in Stockholm County identified at the primary stage of infection are however similar to rates reported for London [7]. The later stage syphilis diagnoses in heterosexuals outside of Stockholm County probably reflect infections acquired abroad being diagnosed on arrival to Sweden.

In Sweden, contact tracing is undertaken for all syphilis cases identified. It is also mandatory in Sweden to be tested for a sexually transmitted infection if identified through contact tracing as having been at risk of exposure to some STIs (as listed in Communicable Disease Act 2004) [8]. Results here indicate that for infections acquired in Sweden, over half the sexual partners recalled through partner follow-up were successfully contacted and tested. Those not contacted included partners recalled who are anonymous or living abroad and could not be reached.

In Sweden it is recommended that all pregnant women be offered syphilis and HIV testing [9]. No congenital syphilis cases were reported in 2004. Only one congenital case has been reported in Sweden since 1997.

This review of syphilis cases from 2004 in Sweden echoes similar findings to epidemiological trends identified within other European countries. Prevention programmes, prompt diagnosis, contract tracing and successful treatment, all remain vital to prevent increases in incidence.

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