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From the Fifth International Conference on the
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Is *Streptococcus pneumoniae* a Nosocomially Acquired Pathogen?

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ABSTRACT

Streptococcus pneumoniae is most prominently a major cause of community-acquired infections of the respiratory tract, central nervous system, and bloodstream, but there is an increasing interest in its role in the epidemiology of hospital-acquired infections. Penicillin-resistant pneumococcal strains appeared 3 decades ago and now are present worldwide, often displaying multiple resistance due to antibiotic selective pressure. Horizontal spread can cause either sporadic cases or hospital outbreaks, primarily in younger children and elderly patients. Pneumococcal transmission from one patient to another can be documented by polymerase chain reaction or pulsed-field gel electrophoresis typing. Nosocomial acquisition of infection, along with pediatric age, previous hospitalization, and previous β -lactam therapy, are the main risk factors significantly associated with penicillin-resistant pneumococcal infections. Nosocomial

acquisition also is associated with higher mortality from pneumococcal disease. The importance of penicillin resistance as a risk factor significantly associated with higher mortality from pneumococcal infection is found in some studies, but not in others. Mortality from pneumococcal pneumonia is approximately the same for human immunodeficiency virus (HIV)-infected patients without acquired immunodeficiency syndrome (AIDS) as for HIV-negative subjects, but it is significantly higher in AIDS patients. Penicillin-resistant strains are involved in the vast majority of hospital outbreaks, whether presenting as clinically manifest infection or a simple colonization. Pneumococcal vaccination is recommended universally in order to lower the incidence of invasive infection, although a number of problems can limit its effectiveness (*Infect Control Hosp Epidemiol* 1998;19:578-580).

Streptococcus pneumoniae is a major and well-known cause of community-acquired infections. It is the most prevalent agent of acute sinusitis, acute otitis media, pneumonia, and bacterial meningitis, accounting for 30% to 42% of each syndrome,^{1,4} and is the second cause of bacteremia and of acute exacerbations of chronic obstructive pulmonary disease, accounting for approximately 22%.^{5,6}

S. pneumoniae was recognized as a common cause of hospital-acquired infection before the introduction of penicillin into clinical practice,^{7,8} but now it seems to be much less frequent, being responsible for 4% of nosocomial acute sinusitis, 5% of bacterial meningitis, 2% of bacteremias, and a low percentage of pneumonias.^{4,5,9,10} Nevertheless, *S. pneumoniae* is being recognized increasingly as a nosocomial pathogen in some subgroups of patients. For instance, in the elderly, up to 20% of hospital-acquired pneumonias are caused by *S. pneumoniae*,¹¹ and, in subjects admitted to oncology wards, outbreaks of pneumococcal pneumonia have been described.¹² Furthermore, nosocomial pneumococcal bacteremia afflicts patients with ultimately fatal diseases, such as malignant neoplasias, at rates higher than seen in the outpatient setting.^{13,14}

Presently, most pneumococcal isolates remain susceptible to penicillin with minimum inhibitory concentra-

tions (MICs) lower than 0.1 mg/L.¹⁵ However, the clue of reduced sensitivity to penicillin (0.1-1 mg/L) has been well recognized for the last 3 decades.¹⁶ Strains with high-level penicillin resistance (MIC >1 mg/L) appeared in 1977 in South Africa, along with multiple antibiotic resistance (the latter being defined by resistance to three or more classes of antibiotics),¹⁷ and spread worldwide.^{18,19} Multiresistant pneumococcus is an important challenge to both microbiologists and clinicians on therapeutic grounds, where vancomycin or, alternatively, imipenem must be considered the drug of choice.²⁰

The infecting strain of *S. pneumoniae* may originate from the patient's upper respiratory tract bacterial flora, whether acquired before or after admission to the hospital, from subjects with pneumococcal disease, or from asymptomatic carriers.²¹ This latter case may be much more frequent than believed, if one considers that approximately 30% of children admitted at a South African hospital were nasopharyngeal carriers of pneumococci.¹⁷

Either sporadic cases or epidemics may derive from horizontal spread of *S. pneumoniae* in the hospital. Serological typing and antibiotic susceptibility profiles are not sufficiently discriminatory, so DNA fingerprinting by polymerase chain reaction (PCR)²² and pulsed-field gel

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electrophoresis typing²³ are now mandatory. In a pediatric intensive-care unit, a 5-month-old girl developed a severe pneumococcal pneumonia after staying in a bed adjacent to an 11-month-old boy with meningitis due to multiply antibiotic-resistant *S pneumoniae* serotype 23F. DNA fingerprinting by PCR revealed that both children were infected by the same strain.²² A very unusual route for transmission was suggested by Mehtar and coworkers, who reported the isolation of *S pneumoniae* type 6 in two neonates resuscitated consecutively with the same piece of equipment 48 hours apart.²⁴ In a 4-year-old boy with nosocomial epiglottitis caused by multiply antibiotic-resistant *S pneumoniae* serotype 15B, neither hospital acquisition of the infecting strain nor origin from the patient's upper respiratory tract could be ascertained.²⁵

Nosocomial epidemics of pneumococcal infection can occur as well, primarily in elderly patients. In 1992, an outbreak of penicillin-resistant *S pneumoniae* type 9 infection was described in an acute medical ward of a British hospital; four elderly subjects had pneumonia and three had septicemia, one of whom died.²⁶ The year after, in another British hospital for the elderly, 10 penicillin-resistant *S pneumoniae* type 9 infections were observed, 8 of which were hospital-acquired. This outbreak probably was favored by the fact that the index case remained unrecognized for more than 2 weeks and was treated with antibiotics without knowing the *in vitro* susceptibility profile. The outbreak probably would not have occurred if the index-case strain had been fully sensitive to the initial antibiotic treatment or if the patient had been isolated.²⁷

Hospital outbreaks of antibiotic-resistant *S pneumoniae* colonization have been described as well, most prevalently in the extreme ages. In younger children, exposed to relatively frequent hospitalization and concomitant administration of antimicrobials, it is important to restrict unnecessary antibiotic use to avoid the emergence of resistant strains.²⁸ In the elderly, the presence of underlying conditions (eg, chronic obstructive pulmonary disease, malignant neoplasias), frequent hospitalization, or stay in a nursing home facility maximize the risk for colonization by antibiotic-resistant *S pneumoniae*.²⁹

Nosocomial acquisition of infection is one of the many risk factors significantly associated in univariate and logistic regression analyses with penicillin-resistant pneumococcal infections, along with pediatric age, previous hospitalization, and previous β -lactam therapy.³⁰⁻³² In younger children, multiple risk factors can be present, eg, relatively frequent hospitalization and concomitant exposure to antibiotics.³¹ In the case of erythromycin-resistant *S pneumoniae*, only an age <5 years and nosocomial acquisition have been found to be independent risk factors.³³

Nosocomial acquisition of infection, along with advanced age and the presence of severe underlying conditions or complications (eg, shock, multilobar involvement, leukopenia), are risk factors significantly associated with higher mortality from pneumococcal disease.³⁴⁻³⁶ Surprisingly, recent studies have not found penicillin resistance to be related significantly to clinical course or mortality,

ty,^{34,35} in contrast with a former study in which the overall mortality rate was significantly higher in patients with penicillin-resistant pneumococcal bacteremic pneumonia (54% vs 25%; $P=.03$) than in subjects with penicillin-sensitive strains.³⁰

Although pneumococcal bacteremia is much more frequent in human immunodeficiency virus (HIV)-infected patients (9.4 cases/1,000 population per year) than in sickle-cell anemia (0.86/1,000), splenectomized (0.92-2.1/1,000), or healthy (7.5-16.4/100,000) subjects,³⁷ HIV-infected patients have the same³⁸ or even a significantly lower³⁴ mortality from pneumococcal pneumonia than HIV-negative subjects do. However, in patients with advanced HIV disease (acquired immunodeficiency syndrome), mortality is the highest observed in any subgroup of subjects with pneumococcal infection.³⁹

Lastly, the administration of pneumococcal vaccines is recommended universally in order to lower the incidence of pneumococcal invasive infection, although a number of problems can limit its effectiveness. First, the geographic distribution of serotypes varies greatly: types 6, 14, and 19 are present worldwide; type 18 is prevalent in developed countries; types 1 and 5 are common in developing countries; and types 3, 9, and 23 are important causes of otitis media. Consequently, the formulation of a complete vaccine suitable for use in all areas is difficult. For instance, a classic formulation containing types 6B, 14, 19F, 23F, 9V, 4, and 18C would include 65% of all pneumococcal isolates in Spain, more than 85% in Finland and the United States, 59% in Gambia, and less than 35% in Rwanda, Egypt, and Papua-New Guinea.⁴⁰ Secondly, an impaired response to pneumococcal vaccines can be observed on a genetic basis, in infants of less than 2 years, and in patients with congenital immunological disorders (a- or hypogammaglobulinemia), chronic renal disease, or HIV infection.⁴¹

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