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Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Antibiotic resistance in community-acquired pulmonary pathogens / F. Paradisi; G. Corti. - In: SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE. - ISSN 1069-3424. - STAMPA. - 21:(2000), pp. 33-43.

*Availability:*

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## Antibiotic Resistance in Community-Acquired Pulmonary Pathogens

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**ABSTRACT** Among infectious diseases, pneumonia is still the “captain of the men of death.” Etiologic diagnosis is often unreliable; consequently, clinicians must know epidemiology of community-acquired pneumonia for optimizing empiric antibiotic therapy. In recent years, all major pulmonary pathogens have become more and more resistant to conventional antibiotics. Penicillin-resistant and even multiresistant pneumococci have spread worldwide, but primarily in the United States, some European countries, South Africa, and the Far East. A similar trend is evidenced by ampicillin-resistant *Hemophilus influenzae*, whereas *Moraxella catarrhalis* almost invariably produces  $\beta$ -lactamases. The widening of methicillin-resistant *Staphylococcus aureus* from hospitals to the community may be the new reality of the 1990s. Increasing erythromycin resistance of *Streptococcus pyogenes* requires  $\beta$ -lactam therapy. The spread of both chromosomally and plasmid-mediated  $\beta$ -lactamases makes treatment of infections caused by gram-negative enterobacilli more difficult. Bacterial resistance creates a challenge for clinicians from the viewpoint of correct and successful management of patients with community-acquired pneumonia.

**Key Words:** Antibiotic resistance, community-acquired, lower respiratory tract infection

At the beginning of the 20th century, Sir William Osler termed pneumonia “captain of the men of death” because of its very high mortality and the absence of any etiologic therapy.<sup>1</sup> This situation has dramatically changed with the availability of antimicrobial agents; however, significant mortality is still associated with lower respiratory tract infection

(LRTI), whose overall death rates in the United States increased by 20% between 1980 and 1992.<sup>2</sup> In the United States, pneumonia is now the sixth leading cause of death and the most frequent cause of death from infection.<sup>3</sup> Mortality rate of community-acquired pneumonia (CAP) ranges from less than 1% if treated at home<sup>4</sup> to approximately 15% and

### Objectives

After reading this article, the reader will be able to discuss the presumptive etiology of community-acquired pneumonia and the antimicrobial susceptibility patterns of the microorganisms involved.

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The University of Michigan designates this educational activity for a maximum of 1.0 hours in category one credit toward the AMA Physicians Recognition Award.

### Disclosure

Statements have been obtained regarding the author's relationships with financial supporters of this activity. There is no apparent conflict of interest related to the context of participation of the author of this article.

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Tel.: +1(212) 584-4662. 1069-3424.p;2000,21,1,0033,0044,ftx,en;srm0015X

more than 35% when requiring hospitalization and intensive care unit (ICU) treatment, respectively. Again, CAP mortality changes on the basis of the etiologic agent(s): the relative percentage is very low with *Mycoplasma pneumoniae* and *Coxiella burnetii*; it varies from 5 to 15% with *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Streptococcus pneumoniae*, and *Legionella* species; and it can reach 30% and more with *Staphylococcus aureus* and most Enterobacteriaceae and 60% with *Pseudomonas aeruginosa*.<sup>5</sup>

Targeted therapy is the "gold standard" for the optimal management of each infection, and etiologic diagnosis is necessarily required. Although no advantages have been clearly demonstrated in identifying causative pathogens of CAP, a well-established rationale exists for determining an etiologic diagnosis of this infection:

- to permit the optimal selection of antimicrobial drugs because of the increasing emergence of bacterial resistance
- to limit the consequences of antibiotic misuse in terms of costs, resistance, and adverse drug reactions
- to identify epidemiologically important pathogens such as penicillin-nonsusceptible *S. pneumoniae* (PNSP)<sup>6</sup>

In the field of pneumonia, sputum Gram's stain and culture are the easiest diagnostic tools, but their value has been discussed for decades. A number of patients are unable to expectorate, and many false-negative results derive from either previous antibiotic treatment or the presence of organisms not readily cultured (viruses, mycoplasmas, chlamydias, legionellas, *C. burnetii*). On the other hand, there can be false-positive results due to upper airway contamination, primarily with *S. aureus* and gram-negative bacilli.<sup>7</sup> Other methods are generally of little diagnostic value: blood cultures are positive in approximately 10% of all cases; serologic tests are useful for epidemiological considerations alone because they turn positive late<sup>8</sup>; invasive techniques such as transtracheal aspiration, transthoracic needle aspiration, bronchoscopy with bronchoalveolar lavage or protected brush sampling, and open-lung biopsy are not appropriate for most patients with CAP.<sup>9</sup>

As a repercussion of the previous diagnostic difficulties, in as many as 50% of cases the causative pathogen is not found, so empiric antibiotic therapy is the rule not only as initial treatment but also frequently during the entire course of the infection.<sup>10</sup> Consequently, clinicians must know epidemiological features of CAP, including both prevalence rates of microorganisms and their antimicrobial susceptibility patterns.

## ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

In the preantibiotic era, *S. pneumoniae* accounted for more than 80% of cases of CAP,<sup>11</sup> and although its prevalence has been declining for decades, globally it is still the single most frequent pathogen.<sup>12</sup> *H. influenzae*, *S. aureus*, and gram-negative enterobacilli are each recovered from up to 10% of sputum cultures, whereas *M. catarrhalis* and *S. pyogenes* are less common agents. *Legionella* species, *M. pneumoniae*, and *C. pneumoniae*, agents of "atypical pneumonia," are isolated in up to 20% of all cases of CAP, but their frequency is believed to be increasing. Viruses account for up to 15% of cases, whereas the recovery of anaerobes, despite both increased awareness of their potential role and ameliorated diagnostic techniques, is limited to a minority of cases. A list of pathogens responsible for CAP is shown in Table 1.

Actually, wide variations occur in the etiology of CAP depending on different factors such as age and the presence of underlying conditions of the host. For example, in patients younger than 60 and without comorbidities, the so-called "big three" (*S. pneumoniae*, *M. pneumoniae*, and viruses) are prevalent, whereas *H. influenzae*, *C. pneumoniae*, and *Legionella* species play a secondary role. On the other hand, subjects over 60 with or without preexisting illnesses (including chronic obstructive pulmonary disease [COPD]) are prone to pneumonia caused by *S. pneumoniae*, *H. influenzae*, and gram-negative enterobacilli and only more rarely by *M. catarrhalis* and *S. aureus*.<sup>13</sup> Based on these factors as well as on the severity of the clinical picture and on whether or not admission to hospital was required, 7 years ago the American Thoracic Society and a Canadian consensus conference group published recommendations for the empiric antimicrobial treatment of CAP, dividing patients into several categories.<sup>14,15</sup> At the same time, the British Thoracic Society provided guidelines for empiric decision making based on

**Table 1. Prevalence Rate (%) of Microorganisms in the Etiology of Community-acquired Pneumonia**

Typical agents	
<i>Streptococcus pneumoniae</i>	20–60
<i>Hemophilus influenzae</i>	3–10
<i>Staphylococcus aureus</i>	3–5
Gram-negative bacilli	3–10
Miscellaneous ( <i>Moraxella catarrhalis</i> , <i>Streptococcus pyogenes</i> )	3–5
Atypical agents	10–20
<i>Legionellae</i>	1–5
<i>Mycoplasma pneumoniae</i>	1–8
<i>Chlamydia pneumoniae</i>	5–10
Viruses (influenza, parainfluenza, adenovirus)	2–15
Aspiration	1–10

(Modified from Bartlett and Mundy.<sup>8</sup>)

the severity of the pneumonia alone.<sup>16</sup> The goal of such recommendations would be to rationalize antibiotic consumption in this setting in order to limit the increase of both economic costs and bacterial resistance resulting from the unnecessary use of newer, broad-spectrum antimicrobial agents. In fact, outpatient antibiotic treatment of CAP varies very much between different countries: in northern Europe (Sweden, United Kingdom, and Holland) oral therapy with former molecules such as amoxicillin, erythromycin, or a tetracycline is by far prevalent, whereas in Italy more recent parenteral drugs (third-generation cephalosporins and carbapenems) are preferred by general practitioners.<sup>17</sup>

#### ANTIBIOTIC RESISTANCE AMONG PULMONARY PATHOGENS

Since the introduction of antimicrobial agents into clinical practice, it has become well-known that much of the antibiotic resistance found in bacterial pathogens was the obvious outcome of increased selective pressure, in turn linked to abuse or misuse of antibiotics. Not only is the selection of the most appropriate molecule for each infection crucial, but also whether antimicrobial treatment is necessary or not. Spanish researchers have recently published worrisome data on the frequency of resistant bacterial strains as agents of respiratory tract infections (RTIs) in their country. During the study period they noted a highly significant difference between the isolation rate of PNSP from infected patients not recently treated (50%) and those recently treated (90.5%) with antibiotics, and even the percentages of resistant strains of *H. influenzae* (43% and 23%, respectively) were significantly different.<sup>18</sup> If one considers that in the United States several million antimicrobial prescriptions for nonspecific RTIs (including the common cold) are made every year,<sup>19</sup> it is obvious that efforts must be made in order to improve awareness of this issue in clinicians, public health officials, and patients and to limit unnecessary antibiotic use in general and in RTIs in particular.<sup>20</sup>

The following sections of this paper will be entirely devoted to the issue of antibiotic resistance in single bacterial pathogens that cause CAP, primarily penicillin and multiresistance in *S. pneumoniae* as well as ampicillin resistance (due to the production of  $\beta$ -lactamases) in *H. influenzae* and *M. catarrhalis*, methicillin resistance in *S. aureus*, macrolide resistance in *S. pyogenes*, cephalosporin resistance linked to the production of chromosomally encoded Bush group 1  $\beta$ -lactamases and plasmid-mediated extended-spectrum  $\beta$ -lactamases (ESBLs) in members of the family Enterobacteriaceae, and multiresistance in *P. aeruginosa*.

#### STREPTOCOCCUS PNEUMONIAE

Many original papers and review articles have been published in the 1990s on epidemiological features, pathogenetic mechanisms, and therapeutic outcomes of resistant pneumococci as agents of a number of RTIs such as pneumonia, otitis media, and sinusitis. Indeed, this is a very important issue because *S. pneumoniae* is globally the most frequent agent of CAP and other RTIs, and the presence of a resistant pneumococcal strain can have fundamental repercussions on the therapeutic ground. The U.S. National Committee for Clinical Laboratory Standards has defined pneumococcal susceptibility to penicillin as a minimal inhibitory concentration (MIC) less than 0.125  $\mu\text{g}/\text{mL}$ , intermediate susceptibility as a MIC between 0.125 and 1  $\mu\text{g}/\text{mL}$ , and resistance as an MIC more than 1  $\mu\text{g}/\text{mL}$ .<sup>21</sup>

Penicillin resistance is due to stepwise alterations in pneumococcal molecular targets for  $\beta$ -lactams, in other words, the high-molecular-weight penicillin-binding proteins (PBPs) involved in the synthesis of the bacterial cell wall. Genetic and molecular studies have shown that mutations in PBP2b and even in PBP1a are important for the development of high-level penicillin resistance, whereas mutations in PBP2x and, to a much lesser extent, in PBP3 are essential for the development of resistance to cephalosporins.<sup>22,23</sup>

It is of crucial importance that changes in the sequences of genes encoding for PBPs occur, and the most common mechanism appears to be the incorporation into susceptible pneumococci (through recombinational events) of DNA molecules originating from more penicillin-resistant streptococci, such as *Streptococcus mitis*.<sup>24</sup> The resulting "mosaic" PBP genes can spread penicillin resistance horizontally among pneumococcal strains, and the geographic spread of resistant clones is another step. The most convincing finding of the latter phenomenon was the demonstration, by either DNA fingerprinting or pulsed-field gel electrophoresis, of the transmission of a multiresistant clone of type 6B *S. pneumoniae* from Spain to Iceland and of type 23F *S. pneumoniae* from Spain worldwide in the late 1980s.<sup>25,26</sup>

A further process is represented by the increase of MICs, mediated by either the introduction of point mutations into PBP genes<sup>27</sup> or the antibiotic selective pressure. In this latter connection, it must be noted that western European countries with lower  $\beta$ -lactam consumption (Germany and Italy) have very low rates of PNSP, and, on the contrary, France and Spain have higher rates of both  $\beta$ -lactam prescription and PNSP.<sup>28</sup>

Analyses by molecular techniques have shown large variations in the features of resistant pneumococci on the basis of their MIC of penicillin: isolates

with low-level penicillin resistance (MIC = 0.125–0.25 µg/mL) belong to multiple serotypes and are infrequently resistant to multiple antibiotics, strains with MIC of 1 to 2 µg/mL show a sharp reduction in both serotype distribution and variation of genetic background, and isolates with even higher MICs carry multiresistance traits (mostly to chloramphenicol, cotrimoxazole, erythromycin, and tetracycline) and belong to a few serotypes.<sup>29</sup> These latter are generally 6, 9, 14, 19, and 23, the so-called “pediatric” capsular types because they are most frequently isolated in children. Bacterial resistance seems to be much more prevalent among these serotypes, and the hypothesis that PNSP originates in children and then spreads to adults has been made, because outbreaks of resistant pneumococcal infections have been reported in child-care facilities and high consumption of antibiotics for therapy of upper RTIs is the rule in the pediatric age.<sup>30,31</sup>

Until 30 years ago, *S. pneumoniae* was invariably susceptible to penicillin and other β-lactams as well as to major antimicrobial agents.<sup>32</sup> The first clinical pneumococcal strain with reduced penicillin susceptibility (MIC = 0.6 µg/mL) was described in 1967 in Australia,<sup>33</sup> whereas 10 years later, in South Africa there was reported an outbreak of pneumococcal disease caused by multiresistant isolates with greatly increased MICs not only of penicillin but also of other drugs such as chloramphenicol, clindamycin, erythromycin, and tetracycline.<sup>34</sup>

Now, the epidemiological situation of penicillin resistance in pneumococci is worrisome worldwide. Results of the Alexander Project, a continuing multicenter study on the antimicrobial susceptibility of bacterial pathogens that cause community-acquired RTIs, showed that in the five most important countries of western Europe, the prevalence of *S. pneumoniae* isolates with penicillin-intermediate susceptibility (PISP) or resistance (PRSP) was 12.6% and 16.2%, respectively, with large country-to-country variations: the overall frequency of PRSP strains was higher in France (23%) and Spain (27.9%) and much lower (less than 1.5%) in Germany, Italy, and the United Kingdom. In the United States, PISP and PRSP were 11.3% and 7% of all pneumococcal isolates, respectively.<sup>35</sup> Another multinational study, carried out in children with acute otitis media, evidenced a similar prevalence (21%) for PNSP strains in the United States, whereas a much higher percentage (52%) was reported from Israel. In Eastern Europe, a 31% figure was observed, with large variations between the Czech Republic and Hungary (4 to 15%), and Slovakia, Bulgaria, and Romania (31 to 41%).<sup>36</sup>

In the United States, PISP stayed at levels of 5% all through the 1980s and then climbed up to 15% in the first half of the 1990s, when increasing per-

centages of highly PRSP strains appeared.<sup>37</sup> This latter trend has been observed in the American branch of the Alexander Project as well, because PRSP isolates were found in 5.6% of cases in 1992 and in 10.9% of cases in 1994.<sup>38</sup> A multicenter national surveillance study showed that PISP and PRSP were 14.1% and 9.5%, respectively, of all pneumococcal isolates from different body sites; the overall percentage of PNSP strains varied considerably from 2.1% in Philadelphia to 52.9% in Miami.<sup>39</sup> Another very large, but more recent, national study evidenced worryingly higher rates: 19.9% for PISP and 13.6% for PRSP isolates, with a cumulative figure of 33.5% ranging from 28.6% in the northeast to 40.4% in the southeast.<sup>40</sup>

A recent review on the epidemiology of antibiotic resistance among pathogens that cause RTIs has provided us with up-to-date and worldwide prevalence rates of PNSP isolates,<sup>41</sup> which can be observed in Table 2. In such a complex epidemiology, it is of crucial importance to keep in mind that some risk factors for PNSP acquisition (pediatric age, prevalence of “pediatric” serotypes, nosocomial acquisition, previous β-lactam therapy, and HIV infection) may explain even large discrepancies in the local prevalence rate.<sup>42</sup>

The highest overall resistance rate reported so far is very likely to come from South Korea: 37% and 33% of *S. pneumoniae* clinical isolates were PISP and PRSP, respectively, with a cumulative percentage of 70%.<sup>43</sup> It has been anticipated that by the year 2000 the prevalence of PNSP strains will reach 40 to 50% rates worldwide and that approximately half of these isolates will be high-level PRSP.<sup>37</sup>

Penicillin-resistant pneumococci are also resistant to aminopenicillins (MICs of amoxicillin with or without clavulanic acid being essentially equivalent to that of penicillin and one dilution lower than that of ampicillin) and oral cephalosporins; among the latter, cefpodoxime and cefuroxime yield the lowest MICs, which are 1 to 2 dilutions higher than

**Table 2. Worldwide Prevalence Rate of PNSP\***

Less than 10%	10–30%	More than 30%
Peru	Canada	United States
United Kingdom	Mexico	France
Scandinavian countries	Argentina	Spain
Benelux countries	Brazil	Slovakia
Germany	Portugal	Romania
Switzerland	Hungary	Bulgaria
Italy	Israel	Turkey
North African countries	Saudi Arabia	South Africa
New Zealand	Kenya	Thailand
	Nigeria	Japan
	Philippines	South Korea
	Australia	Taiwan

\*MIC greater than 0.125 µg/mL (Modified from Baquero et al.<sup>41</sup>)

that of amoxicillin.<sup>39</sup> However, the most alarming trait in *S. pneumoniae* is resistance to parenteral third-generation cephalosporins such as cefotaxime and ceftriaxone: for example, the frequency of resistance to either  $\beta$ -lactam agent increased from 2% in 1984 to 1988 to 9% in 1989 to 1993 in Spain,<sup>44</sup> where more recently 8.4% of PRSP strains and 4.2 to 5.6% of PISP isolates were not susceptible to both cephalosporins.<sup>45</sup> In the United States, PISP is very rarely resistant to third-generation cephalosporins, although ceftriaxone resistance increased from 0 in 1992 to 8.3% in 1994,<sup>38</sup> whereas 32 and 50% of PRSP strains are resistant to cefotaxime and ceftriaxone, respectively.<sup>39</sup> In South Korea, 67% of PISP and 98% of PRSP isolates are resistant to cefotaxime.<sup>43</sup> Furthermore, resistance to imipenem, the most active  $\beta$ -lactam agent against PRSP, is emerging as well.<sup>46</sup>

Unfortunately, pneumococcal resistance is not limited to penicillin and other  $\beta$ -lactams. Resistance to erythromycin and newer macrolides can be mediated by either specific drug-efflux pump or *ermAM* genes encoding for methylation of 23S ribosomal RNA. The latter mechanism confers high-level resistance to lincosamides and streptogramin B as well (MLS<sub>B</sub> resistance). An inducible acetyltransferase that inactivates chloramphenicol can be produced by pneumococci. The *tetM* gene confers resistance to tetracyclines protecting pneumococcal protein synthesis. Mutations producing reduced affinity of the target enzymes (dihydropteroate synthase and dihydrofolate reductase) in the folate biosynthesis are believed to be responsible for resistance to cotrimoxazole.<sup>47</sup> Primary targets for fluoroquinolone resistance are *parC* and *parE* genes encoding for the two subunits of topoisomerase IV, and the secondary target is the *gyrA* gene encoding for the A subunit of DNA gyrase.<sup>48</sup>

Macrolides are important alternatives to  $\beta$ -lactams in the antibiotic therapy of RTIs. Pneumococci yield cross-resistance to macrolides; however, not all macrolide-resistant strains are resistant to clindamycin,<sup>49</sup> therefore confirming the importance of efflux mechanisms for the emergence of resistance. Current levels of macrolide resistance in *S. pneumoniae* vary widely from country to country and on the basis of the MICs of penicillin. Data from the Alexander Project show a steady increase of erythromycin resistance between 1992 and 1994, primarily among PRSP isolates (from 19.3 to 52.1%).<sup>35</sup> In the United States and Italy, resistance percentages to erythromycin, azithromycin, and clarithromycin were 4% and 11% among penicillin-susceptible *S. pneumoniae* (PSSP), 19 to 20% and 48% among PISP, and 49% and 65% among PRSP, respectively.<sup>39,50</sup> Erythromycin resistance affected 73% of PRSP strains in South Korea<sup>43</sup> and reached lower levels in

western Europe (approximately 30%), where the highest rates are observed in countries with the highest macrolide consumption.<sup>28</sup> In Spain, 43.4% of PISP and 57.7% of PRSP strains have been recently found to be resistant to erythromycin.<sup>45</sup>

Pneumococcal resistance to other non- $\beta$ -lactam agents depends on the resistance patterns to penicillin, as evidenced by the results of the Alexander Project; the highest resistance prevalence is yielded by PRSP strains to cotrimoxazole, in other words, more than 97%.<sup>35</sup> Among United States PSSP, PISP, and PRSP isolates, 1, 7, and 32%, respectively, were resistant to chloramphenicol, 0.3, 17, and 43% to tetracycline, and 6, 40, and 80% to cotrimoxazole.<sup>39</sup> In South Korea, higher rates of chloramphenicol resistance have been reported (13, 50, and 82%, respectively).<sup>43</sup> In western Europe, 25 to 50% of pneumococcal strains in Spain and less than 10% in Sweden, Switzerland, and Italy are resistant to cotrimoxazole, whereas more than 25% of isolates are resistant to tetracycline in Spain, France, and Italy.<sup>51</sup>

Finally, the activity of fluoroquinolones is unrelated to penicillin resistance patterns: ciprofloxacin resistance varies from 15% of PSSP, to 10% of PISP, and to 20% of PRSP isolates in South Korea.<sup>43</sup> Lower MICs (0.25 to 2.0  $\mu\text{g}/\text{mL}$ ) than that of former fluoroquinolones (ciprofloxacin and ofloxacin) have been found with newer molecules with increased activity against gram-positive cocci, including PNSP (trovafloxacin, tosufloxacin, grepafloxacin, sparfloxacin, and levofloxacin).<sup>52</sup>

What is the best choice in the antibiotic therapy of RTIs, considering the emergent problems caused by penicillin-resistant pneumococci? This is a very complex and multifaceted issue. Spanish researchers found no significant effect of resistance to penicillin or cephalosporin on mortality of patients with pneumococcal pneumonia, although most study isolates were only intermediately resistant; mortality rates were influenced by other risk factors such as advanced age; severe underlying conditions; presence of shock or multilobar involvement, or both; leukopenia; and nosocomial acquisition. Furthermore, the response to antibiotic therapy with penicillin G, ampicillin, cefotaxime, or ceftriaxone was not significantly affected by  $\beta$ -lactam resistance, so the authors concluded that high-dose intravenous penicillin G might be effective in pneumococcal pneumonia due to strains with MICs ranging from 0.125 and 2  $\mu\text{g}/\text{mL}$ .<sup>44</sup> On the contrary, patients with PRSP infection should be considered at risk of therapeutic failure with conventional  $\beta$ -lactam therapy; therefore one should consider the use of imipenem or, rather, vancomycin, to which resistance has been not yet detected among pneumococci.<sup>53</sup>

Empiric therapy of RTIs, mainly in the ambulatory setting, raises different problems and solutions. In countries with high prevalence of PNSP, and primarily PRSP, conventional oral therapy with  $\beta$ -lactam and  $\beta$ -lactamase inhibitor combinations,  $\beta$ -lactamase-stable cephalosporins, macrolides, or doxycycline can fail. On the basis of both in vitro activity against pulmonary pathogens including PNSP and clinical efficacy in LRTIs,<sup>54</sup> more recent guidelines have been provided suggesting the alternative use of newer fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin).<sup>6</sup> For initial treatment of severe CAP requiring hospitalization, the combination of vancomycin with a third-generation cephalosporin has been advocated if high-level PRSP is suspected.<sup>55</sup> However, glycopeptide agents must be used prudently because they are the last-chance antibiotic therapy against other multiresistant microorganisms such as enterococci and methicillin-resistant *S. aureus* (MRSA). The rapid emergence of vancomycin-resistant enterococci (VRE) in the United States has induced the Centers for Disease Control and Prevention (CDC) to publish recommendations for prudent use of vancomycin in order to limit both the spread of VRE and the risk of transfer of vancomycin resistance to MRSA and, possibly, to multiresistant pneumococci.<sup>56</sup>

An alternative to glycopeptides for therapy of infection caused by high-level PRSP can be represented by quinupristin plus dalbapristin, a new injectable streptogramin combination that is uniformly active in vitro against pneumococcal strains regardless of their penicillin and erythromycin susceptibility.<sup>57</sup>

Prevention of PNSP infection requires a multifaceted strategy, including (1) improved efficacy of surveillance programs by the universal adoption of interpretive standards for detection of diminished susceptibility and by the collection and spreading of comprehensive and up-to-date prevalence data; (2) reduction of inappropriate antibiotic consumption; and (3) increased pneumococcal vaccination coverage.<sup>58,59</sup>

The crucial importance of the judicious use of antimicrobials is very clear if one considers that several million antibiotic prescriptions for viral RTIs, including the common cold and acute bronchitis, are made every year in the United States.<sup>60</sup> In the specific field of pneumococcal disease, the effectiveness of limiting antimicrobial use draws strong evidence from a preliminary Icelandic study associating the declining prevalence of PNSP strains with reduced antibacterial consumption over a 3-year period.<sup>61</sup>

The currently available 23-valent polysaccharide vaccine covers most serotypes causing invasive pneumococcal diseases, including the so-called "pe-

diatric" ones, among which bacterial resistance seems to be much more prevalent, and is approximately 60% effective.<sup>32</sup> Once again, U.S. health authorities have recently published recommendations for pneumococcal vaccination in subjects at increased risk of severe pneumococcal infection including: adults age 65 years or older and persons age more than 2 years with chronic pulmonary or cardiovascular disease or living in special environments or settings or with an underlying condition causing immunodeficiency.<sup>62</sup> Previously, the U.S. Department of Health and Human Services had called for immunizing at least 60% of persons at risk for pneumococcal disease by the year 2000,<sup>63</sup> but those coverage levels are still far from being reached despite a steady increase. In 1993, 28.7% of persons age 65 years or older received pneumococcal vaccine,<sup>64</sup> whereas in 1995 the vaccination rate rose up to 35.6%.<sup>65</sup>

Because the polysaccharide vaccine is not effective for prevention of pneumococcal infection in children under 2 years, conjugated vaccines containing a limited number of serotypes are under study for effective immunization of this age group.<sup>66</sup>

#### HEMOPHILUS INFLUENZAE

*H. influenzae* was uniformly susceptible to ampicillin until the early 1970s, when the first  $\beta$ -lactamase-producing (BLP) strains appeared. Today, production of plasmid-mediated  $\beta$ -lactamases, primarily TEM-1 although other enzymes such as ROB-1 and VAT-1 can be also involved, is by far the most common mechanism by which nontypeable *H. influenzae* acquires resistance to aminopenicillins and partly to former oral cephalosporins, remaining almost invariably susceptible to  $\beta$ -lactam and  $\beta$ -lactamase inhibitor combinations and third-generation cephalosporins. However, because of the currently high frequency of BLP isolates (see later), there is the possibility for point mutations producing ESBLs that are resistant to  $\beta$ -lactamase inhibitors or are active against broad-spectrum cephalosporins, as in the case of Enterobacteriaceae.<sup>40</sup> The proportion of amoxicillin-resistant non-BLP *H. influenzae* ranges from 3 to 10% of all strains<sup>31,67</sup>; this type of resistance is believed to be due to the alteration of PBPs, and such strains are also less susceptible to amoxicillin and clavulanic acid (amoxiclav) and broad-spectrum cephalosporins.<sup>46</sup>

Results of the Alexander Project showed that the mean prevalence of BLP *H. influenzae* isolates was 14.3% in western Europe, varying from 5% in Germany to 28.6% in Spain, and 28.2% in the United States,<sup>35</sup> where more recent large multicenter studies found higher rates of 33 to 36%.<sup>40,67,68</sup>

Another multinational study, which was carried out in children with acute otitis media, showed that the frequency of BLP strains was as high as 47% in the United States, whereas much lower percentages, 13 and 26%, were reported from eastern Europe and Israel, respectively.<sup>36</sup> It has been anticipated that because of the calculated linear increase in prevalence rates of 2 to 3% annually, approximately 50% of clinical isolates of *H. influenzae* are likely to produce  $\beta$ -lactamases by the year 2000.<sup>37</sup>

Resistance to non- $\beta$ -lactam agents develops through genetic and molecular mechanisms similar to those involved in pneumococcal strains.<sup>47,48</sup> Macrolide susceptibility of *H. influenzae* depends on the intrinsic activity of the individual molecules, being close to 100% for azithromycin and lower only for clarithromycin, whereas, on the contrary, erythromycin resistance is a common finding.<sup>35,37</sup> Resistance to chloramphenicol, cotrimoxazole, and tetracyclines is not frequent. Susceptibility of *H. influenzae* to chloramphenicol ranges from 98 to 100% in western Europe (except for Spain, where 90% figures have been generally reported) and reaches 100% in the United States. Resistance to cotrimoxazole is limited to within 10 to 15% (but in Spain, again, it can exceed 50%), and most isolates are susceptible to tetracyclines.<sup>35,67</sup> Current rates of ciprofloxacin resistance are less than 1%,<sup>35,41</sup> although increasing numbers of resistant strains have been emerging in subjects undergoing prolonged fluoroquinolone courses such as patients with cystic fibrosis.<sup>69</sup>

#### MORAXELLA CATARRHALIS

*M. catarrhalis* was uniformly susceptible to ampicillin and amoxicillin before the early 1970s, when the first BLP isolates appeared.  $\beta$ -lactamases of *M. catarrhalis* are typically chromosomal, constitutively produced, and belong to the BRO class (BRO-1 and, to a much lesser extent, BRO-2).<sup>51</sup> By the late 1980s, more than 80% of clinical strains were BLP, and this trend was confirmed by the Alexander Project, which reported rates of 81.2% in western Europe (from 77.3% in Italy to 91.4% in Germany) and of 86.1% in the United States.<sup>35</sup> In the latter, the prevalence of BLP isolates has recently exceeded 90%.<sup>40</sup>

BLP clinical strains of *M. catarrhalis* are expected to be resistant to penicillin, ampicillin, and amoxicillin, whereas they remain highly susceptible to the other oral antimicrobial agents available for treatment of domiciliary RTIs: amoxiclav, cephalosporins, macrolides, tetracyclines, and cotrimoxazole.<sup>35</sup> Indeed, resistance is almost invariably unknown with amoxiclav and cephalosporins and

remains below 3% with tetracycline, below 5% with macrolides, and below 7% with cotrimoxazole,<sup>51</sup> and there is no evidence that these patterns will change in the near future.<sup>37</sup>

Despite the minor role of *H. influenzae* and *M. catarrhalis* in the etiology of CAP, the severity of this entity can explain why  $\beta$ -lactamase-stable antimicrobial agents are preferred as first-line therapy of LRTI,<sup>6,14,15</sup> differently from recommendations on amoxicillin use for initial therapy of nonlife-threatening and often self-limiting infections such as acute otitis media.<sup>70</sup>

#### STAPHYLOCOCCUS AUREUS

Currently, most *S. aureus* strains isolated from community-acquired LRTIs are BLP (approximately 80% in Europe and 90% in the United States) and therefore resistant to penicillin and ampicillin, whereas the distribution of methicillin resistance is highly variable depending on geographic location (mean value, 10%).<sup>71</sup> Methicillin resistance is prevalent in the hospital setting; in western Europe, it ranges from less than 1% in Scandinavian countries and the United Kingdom to more than 30% in Mediterranean countries.<sup>72</sup> Resistance to methicillin is chromosomally mediated by the *mecA* gene, which encodes for  $\beta$ -lactam target, in other words, PBP2a; unfortunately, MRSA is resistant to all  $\beta$ -lactams and to many other antimicrobial agents such as aminoglycosides, cotrimoxazole, lincosamides, macrolides, and tetracyclines<sup>53,71</sup> and is becoming more and more resistant to ciprofloxacin (80 to 90% of all strains).<sup>73,74</sup> *S. aureus*, including MRSA isolates, has been recognized as a nosocomial pathogen for three decades, and it is now the leading cause of hospital-acquired infections such as surgical site infection and pneumonia as well as the second most frequent cause of nosocomial blood stream infection, primarily in the ICU.<sup>75</sup> However, current trends in shortening hospital stays, performing outpatient surgery, and providing home parenteral therapies as well as the use of broad-spectrum antibiotics for community-acquired infections and contact with MRSA-colonized subjects all increase the risk of the spread of hospital-acquired MRSA to the community.<sup>76</sup> Domiciliary infections caused by MRSA, including pneumonia, have been most often seen in high-risk patients such as intravenous drug abusers.<sup>77</sup>

Apart from selected therapeutic use of cotrimoxazole, fluoroquinolones, or other compounds on the basis of in vitro susceptibility tests, glycopeptides remain the cornerstone for treatment of serious infections caused by MRSA. However, strains with reduced vancomycin susceptibility have been



recently isolated in Japan,<sup>78</sup> the United States,<sup>79</sup> and France,<sup>80</sup> so raising the fear of a potential transfer of high-level vancomycin resistance from other microorganisms, such as VRE, to MRSA isolates and its consequent spread among the latter.

As in the case of multiresistant pneumococci, quinupristin plus dalbapristin will serve as an important alternative to glycopeptides for therapy of severe infections caused by MRSA because of its high *in vitro* activity.<sup>57</sup>

### STREPTOCOCCUS PYOGENES

Although *S. pyogenes* is uniformly susceptible to penicillins and cephalosporins, increasing resistance to erythromycin is becoming an important challenge. Traditionally, erythromycin resistance in *S. pyogenes* has been considered as mediated by the *ermAM* gene encoding for a methylase; this enzyme alters the 23S ribosomal RNA and prevents binding not only of erythromycin and other macrolides but also of lincosamides and streptogramin B (MLS<sub>B</sub> phenotype) with their ribosomal target, whereas streptogramin A agents and combinations of streptogramins A and B such as quinupristin plus dalbapristin remain active.<sup>47</sup> However, evidence for macrolide efflux systems encoded by the *mefA* gene and conferring resistance to 14- and 15-membered macrolides alone (M phenotype) has also been found recently.<sup>81</sup> Erythromycin-resistant *S. pyogenes* has a low frequency in most areas of the world including the United States,<sup>82</sup> whereas it is of important concern in selected countries such as Taiwan (56.4%)<sup>83</sup> and Italy (26.8%),<sup>84</sup> where the most recent data show prevalence rates of 30 to 40% with peaks of as high as 81% in the northern regions.<sup>85,86</sup>

The issue of erythromycin resistance in *S. pyogenes* is one of the most striking examples of correlated changes in policy on the use of antibiotics and in the frequency of bacterial resistance to them. A close association between the initial increase of both macrolide consumption and prevalence of streptococcal resistance to erythromycin and between the subsequent reduction of both macrolide prescriptions and resistance has been found worldwide in the last 25 years, primarily in Japan and Finland.<sup>87</sup> Obviously, all the previous data call for (1) the preference of  $\beta$ -lactams for initial treatment of some RTIs and (2) once again, the recommendation for judicious use of antibiotics.

### GRAM-NEGATIVE ENTEROBACILLI

Both the Enterobacteriaceae, primarily *Klebsiella pneumoniae* and *Escherichia coli* and secondarily

*Enterobacter* spp. and *Proteus* spp., and the nonfermenters, such as *P. aeruginosa*, have always been associated with nosocomial LRTIs, but their role as important agents of CAP has been increasing, mainly in elderly subjects and in patients with underlying conditions.

Members of the Enterobacteriaceae family, except for *Enterobacter* spp., were uniformly susceptible to third-generation cephalosporins before the mid 1980s, when first chromosomally encoded inducible *ampC*  $\beta$ -lactamases (primarily cephalosporinases) appeared, more frequently among *Enterobacter* spp. as well as in *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp., and *Serratia* spp.,<sup>88</sup> and then plasmid-mediated ESBLs were detected, mainly in *Klebsiella* spp.<sup>89</sup> Bush group 1 cephalosporinases confer resistance to third-generation cephalosporins, aztreonam, and  $\beta$ -lactam and  $\beta$ -lactamase inhibitor combinations, so that 30 to 40% of *Enterobacter cloacae* isolates are resistant to cefotaxime and ceftazidime.<sup>90</sup> Most strains are still susceptible to carbapenems and fourth-generation cephalosporins (cefepime and ceftipime),<sup>91</sup> and it has been observed that the concomitant use of an aminoglycoside can decrease the risk of isolation of resistant group I  $\beta$ -lactamase-producing microorganisms.<sup>92</sup>

From a clinical viewpoint, ESBLs are the most interesting of the plasmid-mediated enzymes. They are members of the TEM and SHV families, with the TEM-1 enzyme accounting for about 80%, SHV-1 for little more than 5%, and TEM-2 for less than 4% of all plasmid-encoded  $\beta$ -lactamases.<sup>93</sup> Their prevalence among *Klebsiella* spp. and *E. coli* is increasing, primarily in teaching hospitals and ICUs; in some European countries, 50 to 60% of *Klebsiella* isolates from ICU patients produce ESBLs, which confer resistance to oxymino- $\beta$ -lactams such as third-generation cephalosporins (ceftazidime, cefotaxime, and ceftriaxone) and aztreonam,<sup>94</sup> whereas up to 10% of *E. coli* and *K. pneumoniae* strains isolated in the United States are ESBL positive.<sup>90</sup> Carbapenems are the drugs of choice for infections caused by ESBL-producing Enterobacteriaceae, and  $\beta$ -lactam and  $\beta$ -lactamase inhibitor combinations, especially those including clavulanic acid or tazobactam, are effective at high doses, whereas many ESBL-positive isolates are resistant to aminoglycosides and fluoroquinolones.<sup>30</sup> Fourth-generation cephalosporins are also active.

*P. aeruginosa* is an important cause of domiciliary LRTIs in specific subgroups of patients such as those with COPD and, above all, cystic fibrosis. This nonfermentative aerobic gram-negative microorganism is of great concern because of its resistance to multiple antimicrobial agents.  $\beta$ -lactam resistance is generally mediated by  $\beta$ -lactamases, whether they are chromosomally- or plasmid encoded, although

barrier or efflux mechanisms have been also advocated, primarily in strains with cross resistance to both  $\beta$ -lactams and aminoglycosides. Resistance to antipseudomonal penicillins and ceftazidime is rare among outpatients, ranging from 5.5 and 8.5%, but the lowest rates, less than 2.5%, are observed with carbapenems.<sup>95</sup> However, it is noteworthy that resistance to imipenem, mediated by either the loss of a specific outer membrane protein or the production of a plasmid-encoded imipenemase, can spread as the consequence of the increasing use of carbapenems.<sup>96</sup> Resistance to aminoglycosides is due either to the production of inactivating enzymes or to reduced membrane permeability. Whereas amikacin- and gentamicin-resistant strains are rarely found in western Europe<sup>95</sup> and in the United States,<sup>90</sup> their incidence can reach 24 and 40%, respectively, in certain Latin-American countries.<sup>97</sup>

A major concern is now the increasing resistance to fluoroquinolones, the only oral agents that were uniformly active in vitro against *P. aeruginosa* prior to their introduction into clinical practice in the mid 1980s. Mechanisms of resistance include mutations either in the structural genes governing the target, in other words, the DNA gyrase, or in the regulatory genes responsible for bacterial permeability or efflux capacity. In these latter cases, increased MICs of some unrelated antibiotics such as  $\beta$ -lactams are observed as well.<sup>98</sup> Recent studies have shown that ciprofloxacin resistance of *P. aeruginosa* varies from 7% in Europe<sup>95,99</sup> to 17% in the United States,<sup>100</sup> but it can reach levels as high as 35 to 46% in some countries of the Far East such as Philippines, Japan, and Thailand.<sup>101</sup> Our data on the prevalence of ciprofloxacin resistance in nosocomial isolates from the lower respiratory tract gave a 6.8% figure.<sup>102</sup>

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