The vast majority of antimicrobial agents are prescribed empirically — therapy that is initiated without knowledge of the specific infecting pathogen, but generally based on several important variables. These include site and type of infection, presenting symptoms, patient history and local antimicrobial resistance patterns. Additional reasons for empiric prescription include relieving symptoms, preventing disease progression, and limited access to diagnostic services. Factors such as sensitivity versus resistance, intravenous versus oral administration, anatomical target sites, and costs have also become important parameters for selecting antimicrobial therapy and for the development of formularies.

We recently published a Formula to Help Select Rational Antimicrobial Therapy (FRAT) and applied it to community- and hospital-acquired urinary tract infections. The formula (Table 1) has also been used to assess method of physician remuneration and its impact on antibiotic prescription rates.
REMUNERATION continued from page 1

...prescription rates above the median of 1.51 per unique patient per year (OR=4.7, 95% CI 2.6-8.6, p<0.001) (Table 1). Physicians who prescribed to more unique patients were more likely to prescribe above the median rate (OR=2.2 per 100 extra patients, 95% CI 1.9-2.7, P<0.001) as were older physicians (OR=1.4 per decade, 95% CI 1.1-1.8, P=0.002). Those physicians who prescribed to a high proportion of elderly patients also were more likely to prescribe at higher rates (OR=2.0, 95% CI 1.3-3.3, p=0.002).

A comparison of prescribing rates by patient volume and mode of remuneration revealed that while rates for both groups of physicians increased with higher patient numbers, the association was far more prominent for fee-for-service physicians. A similar analysis using logistic regression adjustment for physician age, country of graduation, proportion of elderly patients, and St. John’s or rural practice confirmed the strong association between patient volume and fee-for-service physicians. A steep, step-wise relationship between number of patients prescribed to and the odds ratio of prescribing above the median was seen among fee-for-service physicians. No such relationship was observed for the salaried physicians.

Monetary factors play a significant role in the genesis of higher prescription rates, and have important implications for healthcare funding agencies everywhere.
In short, clear associations were found between antibiotic prescription rates and mode of physician remuneration. Fee-for-service physicians prescribed at a much higher rate than did salaried physicians. Though increasing patient volume was associated with higher prescription rates in the unadjusted analysis for salaried physicians, the association with volume of patients was much stronger for fee-for-service physicians.

These findings suggest that monetary factors play a significant role in the genesis of higher prescription rates, and have important implications for healthcare funding agencies everywhere. In the Canadian primary healthcare delivery system, in which remuneration per patient is low, fee-for-service general practitioners see very large numbers of patients with correspondingly short individual doctor-patient encounters. Prescription of antibiotics may be viewed by fee-for-service physicians as necessary to cope with daily patient numbers and to retain patients in their practices. In this time of rapidly evolving changes in all aspects of healthcare delivery, knowledge of and acceptance of non-medical influences on the prescribing practices of physicians should help guide fundamental decisions concerning primary care delivery and medical education that promote rational use of antibiotics.

### Table 1. Factors associated with high antibiotic prescription rates, as determined by logistic regression.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted regression</th>
<th>Adjusted regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (and 95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Method of remuneration (fee-for-service v. salary)</td>
<td>8.2 (5.1-13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of unique patients receiving prescriptions per year (per 100 patients)</td>
<td>2.2 (1.9-2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High proportion of elderly patients (&gt;median value of 23%)</td>
<td>1.4 (1.0-2.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Country of graduation (Canada v. elsewhere)</td>
<td>2.3 (1.6-3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Practice location (St. John’s v. elsewhere)</td>
<td>1.3 (0.9-2.0)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

OR = odds ratio.

References

Chile is Newest APUA Chapter

APUA welcomes Chile as the latest country to be added to its global network of chapters. Dr. Maria Eugenia Pinto, Faculty of Medicine, University of Chile, Santiago, will head its efforts. The main objective of APUA-Chile will be to encourage the development of a nationwide program devoted to promoting the proper use of antibiotics at all levels. The formation of this latest chapter coincides with Chile’s recent adoption of national regulations enforcing the prescription-only sale of antibiotics (see Vol. 18, No. 2 of the APUA Newsletter).
the utility of various antimicrobial agents in nosocomial pneumonia and in community-acquired respiratory tract infections. Data from the Alexander Project (1999) indicate that antimicrobial resistance among respiratory tract pathogens has increased. The incidence of penicillin-resistant S. pneumoniae (PRSP) and multiresistant S. pneumoniae, in particular, has seen a worrisome increase worldwide. For the purpose of applying the FRAT formula and demonstrating its utility, we elected to compare resistance data for respiratory pathogens causing community-acquired pneumonia (CAP).

Recently reviewed information relating to the etiological agents in CAP showed S. pneumoniae as the most frequent bacterial pathogen, accounting for 30-75% of cases, as compared to 4-5% for H. influenzae and 0-18% for Mycoplasma pneumoniae, Legionella pneumophilia, and Chlamydia pneumoniae. Additionally, S. pneumoniae accounted for approximately two-thirds of bacteremic patients with CAP.

Methods

Susceptibility data were taken from relevant publications and, as such data for atypical pathogens are rarely if ever generated in surveillance studies, we elected to use data as summarized in Blondeau 1999. The FRAT calculation for CAP, based on recently generated susceptibility data from Canada and the US, is shown in Table 2. Four classes of antimicrobial agents are represented. Differences in the susceptibility of clarithromycin, cefuroxime and amoxicillin in Canada and the US are noted and are clearly related to the differences in the rates of resistance between the two countries. Amoxicillin, cefuroxime and clarithromycin are 7.7% to 11.3% more susceptible in Canada than in the US.

While antimicrobial resistance has dramatically increased in S. pneumoniae to penicillins, cephalosporins, macrolides, tetracycline and trimethoprim/sulfamethoxazole, the same is not true of the fluoroquinolones, hence their inclusion in this calculation. These compounds retain high levels of activity against the respiratory pathogens, including those resistant to other agents.

The potential impact of the FRAT approach may be seen by comparing the striking differences between β-lactamase positive H. influenzae and penicillin-resistant S. pneumoniae in fluoroquinolones was assumed to be 100%. By comparison, susceptibility of the same atypical agents to amoxicillin and cefuroxime was assumed to be 0%. Therefore, differences seen in the FRAT comparisons are essentially based on differences in resistance rates for H. influenzae and S. pneumoniae.

Table 2. FRAT for CAP in the United States and Canada.

<table>
<thead>
<tr>
<th>United States*</th>
<th>Etiology</th>
<th>Moxifloxacin</th>
<th>Clarithromycin</th>
<th>Cefuroxime</th>
<th>Amoxicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suscep</td>
<td>Impact</td>
<td>Suscep</td>
<td>Impact</td>
<td>Suscep</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>65</td>
<td>99.8</td>
<td>64.9</td>
<td>77.1</td>
<td>50.1</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>12</td>
<td>100</td>
<td>10</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>7</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
<td>4</td>
<td>100</td>
<td>4</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>2</td>
<td>100</td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Total (%)</td>
<td>90</td>
<td>99.9</td>
<td>84.6</td>
<td>60.1</td>
<td>84.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Canada**</th>
<th>Etiology</th>
<th>Moxifloxacin</th>
<th>Clarithromycin</th>
<th>Cefuroxime</th>
<th>Amoxicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>65</td>
<td>100</td>
<td>65</td>
<td>92.4</td>
<td>60.1</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>12</td>
<td>100</td>
<td>12</td>
<td>95.6</td>
<td>11.5</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>7</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
<td>4</td>
<td>100</td>
<td>4</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>2</td>
<td>100</td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Total (%)</td>
<td>90</td>
<td>90</td>
<td>84.6</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>

*d % occurrence of named bacterial pathogens. Totals do not equal 100; less common species not included. **% of pathogens susceptible to drugs in vitro. 7% impact factor = (% susceptibility x etiology)/100. 8Based on penicillin. 9Thornsberry et al, 1999; *Blondeau et al, 2000 (submitted).
Europe and Asia (Table 3). The susceptibility of H. influenzae to the atypical agents is assumed to remain unchanged to fluoroquinolones and macrolides. Susceptibility of clarithromycin ranges from a low of 49.5% in Hong Kong to a high of 95.4% in Austria. Susceptibility data summarized for ampicillin/amoxicillin are even more striking, varying from 79.6% in Austria to 37.9% in Hong Kong. As resistance rates vary considerably between countries, so should the effectiveness of antimicrobial agents. The FRAT formula helps to demonstrate this relationship. FRAT, like any tool, must be used appropriately for maximum effect. For example, this formula will always show the most potent, broadest-spectrum antimicrobial agent as having the highest overall level of activity. That does not always mean, however, that the specific agent showing the most effectiveness should be used, but rather identifies data that can help with management decisions. Where comparable data are available, ward-specific, hospital, state/provincial, national and international comparisons can be made with FRAT. It serves to identify specific problems or trends, and allows for comparisons that may provide insight into intervention to halt or reverse resistance. Potentially, we could learn a tremendous amount from countries that have either high or low specific resistance rates and compare that to data from our own countries to identify common issues. Regardless of what is learned, a measured, informed approach to antibiotic use should be the ultimate goal.

Table 3. FRAT impact and β-lactamase positive H. influenzae and penicillin-resistant S. pneumoniae in Europe and Asia.

<table>
<thead>
<tr>
<th>Country</th>
<th>Fluoroquinolone</th>
<th>Macrolide</th>
<th>Ampicillin/amoxicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>100%</td>
<td>82.8%</td>
<td>72.9%</td>
</tr>
<tr>
<td>Austria</td>
<td>96.7%</td>
<td>95.4%</td>
<td>79.6%</td>
</tr>
<tr>
<td>United Kingdom (London)</td>
<td>97.5%</td>
<td>88.9%</td>
<td>77.2%</td>
</tr>
<tr>
<td>France (Toulouse)</td>
<td>97.8%</td>
<td>69.4%</td>
<td>52.2%</td>
</tr>
<tr>
<td>Spain (Barcelona)</td>
<td>98.4%</td>
<td>84.9%</td>
<td>52.1%</td>
</tr>
<tr>
<td>Italy (Genoa)</td>
<td>96.0%</td>
<td>81.4%</td>
<td>79.0%</td>
</tr>
<tr>
<td>Mexico</td>
<td>97.2%</td>
<td>76.1%</td>
<td>NA</td>
</tr>
<tr>
<td>Brazil</td>
<td>97.7%</td>
<td>94.4%</td>
<td>69.8%</td>
</tr>
<tr>
<td>China (Hong Kong)</td>
<td>91.8%</td>
<td>49.5%</td>
<td>37.9%</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA = Data not available.

References

Continued Partner and Corporate Support Helps to Fund APUA Global Initiatives

Ask the Expert

Paul Farmer, M.D. Department of Social Medicine, Harvard Medical School, and the Division of Infectious Disease, Brigham and Women’s Hospital, Boston, Massachusetts

What is appropriate empiric therapy for active tuberculosis?

The term “multidrug-resistant tuberculosis” (MDR-TB) is used to refer to disease due to strains of Mycobacterium tuberculosis resistant to isoniazid and rifampin, the two most powerful antituberculous drugs. Although drug-resistant TB is a growing problem in much of the world, most cases of TB are still caused by pan-susceptible strains of M. tuberculosis.\(^2\) This is true in the US, even in settings such as New York City, that have known recent outbreaks of MDR-TB. It’s for this reason that current recommendations from the Centers for Disease Control (CDC) and the American Thoracic Society suggest that empiric treatment with ethambutol or streptomycin.2 Standardized drugs: isoniazid, rifampin, pyrazinamide, and fluoroquinolones. Another strategy is to begin treatment with a drug to which the infecting isolate is resistant should be discontinued; treatment should be reinforced by drugs to which there is documented susceptibility. As long as a strain is susceptible to both isoniazid and rifampin, therapy can be as short as six months, although some argue that therapy should be continued for 9-12 months in certain instances (e.g., HIV co-infections, Pott’s disease or other TB of the skeletal).\(^3\)

If a strain is shown to be resistant to both isoniazid and rifampin, most feel that patients should be referred to specialists, since the second-line drugs, with the exception of the fluoroquinolones, are now little used. Many have adverse effects or drug-drug interactions requiring careful management.\(^4\) Furthermore, a pulmonary TB patient who has received empiric short-course chemotherapy and then subsequently shown to have MDR-TB should be considered infectious, since he or she will not have received 2-3 weeks of combination therapy with mycobactericidal drugs. Aggressive contact tracing is mandated by most public-health authorities.

There are instances in which empiric therapy including second-line drugs should be contemplated. If the newly diagnosed patient is the close contact of a patient with documented pulmonary MDR-TB, then basing empiric therapy on the contact’s DST results would be considered standard of care as long as good (smear-positive) specimens of sputum or tissue are obtained prior to the initiation of therapy.\(^5\) Empiric therapy that includes second-line drugs may also be needed in the context of well-defined outbreaks of MDR-TB.\(^6\) Such strategies were briefly recommended in New York among patients with histories of residence in shelters or prisons. Many would favor the inclusion of isoniazid and rifampin pending confirmation of MDR-TB. This is because of the relative potency and relatively few side effects of these two drugs, and also because contact histories are not reliably predictable of DST results. Only the laboratory can confirm such suspicions.

Other controversies in antituberculous drug choice include the use of ethambutol in the pediatric age group. Retrolubural neuritis, an important adverse effect of this drug, is rare at the recommended dosage of 15 mg/kg/day (although ethambutol is likely only mycobacteriostatic at this dose). Many favor visual and color acuity screening prior to use of ethambutol, and since young children cannot always report visual acuity, the drug has been long avoided, replaced in most countries by streptomycin. Overall, children have voiced strenuous objections to intramuscular injections, and in some settings, including the US, streptomycin is difficult to obtain. A recent review of this topic concludes that ethambutol at this dose is not contraindicated for children with TB.\(^7\) Again, a DST that reveals the disease is due to a pan-susceptible strain would make a fourth agent unnecessary. A two-month “initiation” treatment phase consisting of three drugs, two of which are isoniazid and rifampin, followed by a four-month continuation phase consisting only of these two drugs is still potent therapy for uncomplicated tuberculosis.

References

APUA Newsletter, 2000, Vol.18 No. 3

APUA News

Alliance Spearheads Global Advisory on Antibiotic Resistance Data

On September 16th, during Global Resistance Day, Dr. Stuart B. Levy, President of APUA, announced a cooperative effort to address the problem of antibiotic resistance. This announcement came as part of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Toronto, Canada, September 16-19, 2000. Three multinational enterprises — Bristol-Myers Squibb, SmithKline Beecham, and an infectious disease service company called MRL — have joined forces with APUA to spearhead a global partnership on antibiotic resistance. As members of this project steering committee, they will lead a coalition called the Global Advisory on Antibiotic Resistance Data (GAARD) and will collaborate with other public health authorities, such as the World Health Organization, to promote optimal antibiotic use and to slow or reverse resistance.

Among other initiatives, GAARD will develop a comprehensive information source on resistance and surveillance by creating a databank of summary data, and will publicize the issue through various media. It will also facilitate efforts to improve laboratory methods and data management in developing countries, and will help countries establish and maintain their own surveillance systems, linking them to larger networks. A Project Advisory Board (PAB) will also be created, comprised of 20-30 other surveillance professionals, such as those who attended the 1998 APUA surveillance meetings, including representatives from the US Department of Defense, US Food and Drug Administration, Pan American Health Organization, and various academic and national/local public health institutions/surveillance networks. The PAB will provide advice to the Project Steering Committee and lend additional expertise to project design and implementation, offering suggestions on timely research topics or leading training sessions to initiate or improve surveillance systems that would eventually link to the project data bank.

For more information on GAARD, or to find out how to join the advisory group’s efforts, contact Dr. Barbara Souder at barbara.souder@tufts.edu or call 617-636-0966.

APUA CHAPTER MEETING at ICAAC

APUA chapter representatives from nearly a dozen countries gathered at the 40th ICAAC conference, held in Toronto, Canada, September 16-19, 2000, to share their experiences and express their concerns. Leaders from Argentina, Australia, Brazil, Chile, Costa Rica, the Dominican Republic, Ecuador, Greece, Turkey, Uruguay, and Venezuela participated. The meeting also allowed recognition of Chile as APUA’s newest chapter. Drs. Stuart B. Levy, APUA President, Thomas F. O’Brien, Vice President, Kathleen T. Young, Executive Director, Dr. Anibal Sosa, Director, Latin America Regional Initiative, and Nancy Pollock, Chapter Development Coordinator, also participated.

Various topics were discussed, among them the availability of antibiotics without prescription, which was cited as a major contributing factor to the development of antimicrobial resistance. In areas where prescribing regulations were already in place but compliance was poor, stricter enforcement was recommended. In Australia, where per capita antibiotic consumption is high, the increased availability of antibiotics due to subsidized prices seems to counteract benefits achieved through the prescription-only sale of antibiotics. The importance of multiple interventions targeted toward different audiences was stressed by the group, and the involvement of the media was encouraged.

Chapter leaders from Chile and Uruguay reported recent regulations mandating the sale of antibiotics by prescription only. It was suggested the lessons learned from this process be documented in order to aid other countries working toward this goal. APUA chapters were also encouraged to write up the results of research projects and model interventions for publication in the APUA Newsletter.

APUA-Belarus Holds Conference on Problems of Antibiotic Use

APUA-Belarus, with support from APUA’s Small Grants Program, recently sponsored the conference, "Problems of Rational Application of Antibiotics," on October 12-13, 2000, in Vitebsk, cosponsored by the Belarus Ministry of Health, the Infectious Disease Society of the Republic of Belarus, and Vitebsk State Medical University. Participants included (photo, from L-R) were: Prof. Valeri M. Semenov, APUA-Belarus, Prof. Leonid P. Titov, Director, Institute of Epidemiology and Microbiology, Minsk, Belarus, Dr. Tatyana Dmitrachenko, APUA-Belarus, and Prof. Leonid S. Stratchounski, APUA-Belarus, and, Dr. Giuseppe Cornaglia, APUA-Italy, and Prof. Roman Kozlov, APUA-Russia, also spoke.
Alliance for the Prudent Use of Antibiotics
75 Kneeland Street
Boston, MA 02111-1901 USA

If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

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APUA . . . preserving the power of antibiotics throughout the world.

The Alliance for the Prudent Use of Antibiotics is a non-profit organization dedicated exclusively to curbing antibiotic resistance and improving the use of antibiotics throughout the world. Founded in 1981 as a global grassroots organization, APUA’s mission is to improve public health through education and research concerning antibiotic use and resistance. With members in over 100 countries and numerous foreign chapters, APUA provides a unique network to support country-based activities and facilitate international communication and planning.

APUA’s resources include an international scientific advisory board with members of national academies of medicine and science, and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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