APUA Nepal Ushers In Antibiotic Guidelines
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To understand the challenges of rational antibiotic use in Nepal — a South Asian country with a population of 23 million — it helps to consider a few revealing statistics. The adult literacy rate is 36%. Only one physician is available to serve every 13,000 citizens. And the entire nation boasts only 400 qualified pharmacists.

In such a setting, rational antibiotic use is immensely difficult. By providing technical assistance and aid in developing treatment guidelines, APUA-Nepal has helped remedy the problem.

In 1978, Nepal instituted the Drug Act to: prohibit the misuse or abuse of drugs and allied pharmaceutical materials; control information about efficacy and application of drugs; and regulate and control the production, marketing, distribution, export-import, storage and utilization of drugs. The Act also requires that antibiotics be dispensed, sold, or distributed only in the presence of a pharmacist or a professional, and only with a prescription from a qualified medical doctor.

Clearly, more specific guidelines were needed. In 1999, Nepal’s Department of Drug Administration (DDA) recommended the creation of a national antibiotic policy. His Majesty’s Government Ministry of Health charged the DDA with preparing a policy draft. In June of that year, APUA-Nepal was founded with the objective of assisting the government in formulating new policies.

Resistant Respiratory Infections Threaten Developing Countries
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Widespread resistance to commonly used, affordable antibiotics has complicated the treatment of acute respiratory infections (ARI) — the leading cause of childhood deaths in most developing nations. In these resource-constrained countries, World Health Organization (WHO)-recommended algorithms for recognition and management of childhood pneumonia in the community and in health care facility settings have been essential in preventing ARI deaths. These algorithms emphasize early case recognition of severe ARI by community health workers or paramedics, based on the presence or absence of certain signs and symptoms; outpatient management with oral cotrimoxazole or amoxicillin for uncomplicated pneumonia; and hospital referral for children with more severe disease. Over the last two decades, WHO’s case-management approach has reduced ARI-related childhood mortality. Sadly, this success may soon be undermined by the emergence of significant levels of cotrimoxazole and amoxicillin resistance among common respiratory pathogens, suggesting a need for alternative and/or additional interventions.

Epidemiology of Antibiotic-Resistant Respiratory Pathogens

While antimicrobial resistance spawned by indiscriminate antibiotic use in developing countries has received much attention, less understood are the epidemiology of antibiotic resistance and factors contributing to regional differences. Prevalence rates of resistance among nasopharyngeal or bloodstream isolates of Streptococcus pneumoniae and Haemophilus influenzae from children in developing countries have recently been reviewed. The majority of S pneumoniae in South Asia are now cotrimoxazole-resistant — raising the question of whether WHO’s ARI program should shift from cotrimoxazole to more expensive amoxicillin for treatment of uncomplicated pneumonia. In Pakistan, cotrimoxazole therapy has increasingly failed; two studies have found cotrimoxazole to be ineffective in one-third of patients with pneumonia; and children under age year were especially susceptible to treatment failure.

Penicillin resistance among pneumococcal isolates in South Asia has also emerged and is gradually increasing, with 5-10% of isolates currently resistant. In India, ampicillin resistance among H. influenzae is a significant problem, with reported resistance rates of 40-60% in the prospective Invasive Bacterial Surveillance Studies. Meanwhile, India, Pakistan, and Bangladesh have seen widespread resistance of H. influenzae to cotrimoxazole.

Respiratory pathogens in African nations show regional variations in the prevalence of penicillin/ampicillin, cotrimoxazole and chloramphenicol resistance. South Africa and Malawi report...
DEVELOPING NATIONS FIGHT DRUG-RESISTANT INFECTIONS

Excerpts from Recent Studies

Colombia Zeros In On S. epidermidis

Self-Medication and Antibiotic-Resistant S. epidermidis Among Colombian Patients from Different Socioeconomic Strata.

Antonio Carlos Jaramillo, M.D. (APUA - Colombia Chapter Coordinator), Cesar Ponte, M.D., Alvaro Villanueva, M.D., Salim Mattar, Ph.D., Delfina Urbina, Q.F., Msd., Otto Susmann, M.D., Carlos Alvarez, M.D. (Members of the Colombian Society for Infectious Diseases)

A preliminary research project determined that 80% of S. epidermidis isolates in patients from Bogotá hospitals were resistant to oxacillin. The patients represented a range of socioeconomic strata. Self-medication, inadequate dosage, and incomplete treatments are considered the main risk factors.

In Colombian patients, coagulase-negative Staphylococcus (CoNS) and S. epidermidis are common causes of infection. A recent study of 13 Bogotá hospitals found that, of 63,434 cultures positive for S. epidermidis, 80% were oxacillin-resistant. Most isolates came from patients with invasive devices, such as catheters, as well as from patients with impaired host defenses (cancer, chronic renal conditions, and AIDS).

In Colombia, antibiotics are dispensed freely in pharmacies and supermarkets. This trend toward self-medication raises the selection pressure for resistant bacterial strains. A recent study found that, annually, 55 tons of antibiotics were dispensed in Bogotá, and 137.5 tons in all of Colombia. Indeed, a single pharmacy in Montería, in the north of the country, dispensed 5.5 tons yearly without medical prescriptions.

References:
Philippines Issues Treatment Recommendations

Highlights of 2002 Antimicrobial Resistance Surveillance Program (ARSP) Data

Celia C. Carlos, M.D., (APUA-Philippines Chapter Coordinator), Chairperson, Department of Health Consultant in Pediatrics and Infectious Diseases and Head, Diarrhea Research Group, Medical Department, Research Institute for Tropical Medicine.

Selected recommendations:

- Empiric treatment for suspected typhoid fever should still consist of either chloramphenicol or cotrimoxazole or amoxicillin/ampicillin.
- Fluoroquinolones and third-generation cephalosporins are better treatment options for non-typhoidal Salmonella.
- Nalidixic acid should be considered the drug of choice for treatment of suspected shigellosis, whereas tetracycline remains effective for cholera.
- Infections secondary to Streptococcus pneumoniae and H emophilus influenzae can be covered with penicillin/chloramphenicol or amoxicillin/chloramphenicol, respectively. Although the resistance rate of S. pneumoniae to penicillin had significantly decreased (from 9% in 2001 to 6% in 2002), healthcare personnel must continue to monitor changing resistance trends among pneumococci, one of the most important etiologic agents of respiratory and CNS infections in all age groups.
- Hospitals should base their treatment recommendations for staphylococci and the Enterobacteriaceae on their institution’s prevailing resistance patterns. The continued rise in MRSA rates and cases of infection secondary to ESBL may indicate inadequate implementation of infection control procedures in some hospitals.
- Cefixime and ceftriaxone should remain empiric antibiotics of choice for gonococcal infections.
- The significant burden of tuberculosis and malaria on morbidity and mortality in the Philippines, and rising reports of drug resistance in these organisms, pose a need for antimicrobial resistance surveillance for tuberculosis and malaria.
- All stakeholders, including the Philippines government, should advocate immediate action to control the serious problem of antibiotic resistance. Interventions should include: strict implementation of laws regulating dispensing of antibiotics; intensive infection control measures in hospitals; and activities promoting rational antibiotic use. In this regard, hospital infection control committees (ICC) and therapeutics committees should be compelled to base therapy recommendations and antibiotic purchases on prevailing antibiotic resistance patterns within the hospital.

Guatemala Analyzes Pneumococcus Risks

Risk Factors for Antibiotic-Resistant Streptococcus pneumoniae Among Guatemalan Children from Different Socioeconomic Strata and Healthcare Delivery Systems

Edwin J. Asturias, M.D. (APUA-Guatemala Chapter Coordinator), Erica L. Dueger, D.V.M., Ph.D., Olga Torres, M.H.S., Carlos F. Grazioso, M.D., Jorge M. Figueroa, M.D.

In an initial APUA-funded study we determined the prevalence and risk factors for penicillin-resistant S. pneumoniae (PRSP) nasopharyngeal isolates from children in different socioeconomic strata attending healthcare and daycare facilities in Guatemala City. A total of 754 children between 5 and 60 months of age who had not received antibiotics in the previous 2 weeks and whose guardians signed a consent form, were enrolled in the study. The population included 199 (26.4%) children from a public hospital outpatient clinic, 191 (25.3%) from a public daycare center, 178 (23.6%) from four private daycare centers and 186 (24.7%) from two private pediatric clinics. Risk factor questionnaires and penicillin susceptibility of isolates (as determined by oxacillin disk only) were collected over an 11-month period.

S. pneumoniae was isolated from 483 (64.1%) children; 107 (22.2%) of these isolates were non-susceptible to penicillin. Nasopharyngeal (NP) colonization was 19% lower in children from the highest income group compared to children in either of the other income groups (P < 0.002). Among NP carriers, prevalence of PRSP increased significantly between each successively higher income group, with a 79% increase in non-susceptible isolates in the highest income group relative to the lowest (P < 0.0001). While penicillin usage during the last 3 months was 22% lower in the highest income group compared to the two lower income groups (P < 0.027), the use of macrolides and cephalosporins was at least 58% and 63% higher, respectively, in the two higher income groups relative to the lowest income group (P < 0.015).

History of rhinitis, large numbers of household members relative to number of household bedrooms, and attendance at public daycare were significant in predicting odds of NP colonization. Of particular note, children who attended public daycare had 3.6-fold increase in odds of NP colonization than children who did not attend daycare. Among those colonized, use of cephalosporins in the previous 3 months and higher monthly income were associated with a 2.5- and 9.7-fold increase, respectively, in the odds of PRSP. In addition, attendance at private or public daycare was associated with a 3.9- and 6.4-fold increase, respectively, in the odds of PRSP in colonized children.

From the Center for Disease Studies and Control (CECEN), Johns Hopkins School of Public Health (EJA, ELD), INCAP (OT); San Juan de Dios General Hospital and Centro Clinico Pediatrico de Guatemala (CFG); and the Centro Clinico Pediatrico de Guatemala (JMF).
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and rules governing antibiotic use. The National Antibiotics Policy was drafted by APUA-Nepal, with the counsel of physicians, veterinarians, and pharmacists. The policy highlights the problem of antibiotic misuse and the need for specific interventions.

National Drug Policy

Nepal’s National Drug Policy (NDP), implemented in 1995, was amended in 2001 by adding “prudent use of antibiotics” as one of its major goals. The prudent use strategies included:

1. Careful management of antibiotics in food products, animal feeds and agricultural substances.
2. Supervision and monitoring of antibiotic use, and reduction of misuse.
3. Classification of antibiotics according to therapeutic effectiveness by medical doctors, veterinary doctors and other health care personnel.
4. Establishment of a National Antibiotic Control Committee, composed of experts in human and animal health, agriculture, professional organizations, and consumer groups.
5. Establishment of a National Antibiotic Therapeutic Advisory Committee (NATAC) to advise on the prudent use of antibiotics.

Antibiotic Use and Misuse

Antibiotics are the most widely used drugs in Nepal, representing 15% of the total drug market in 1999-2000. Most antibiotics are used empirically, without the benefit of specimen culturing. And many patients use antibiotics improperly, raising the risk of resistance.

In Nepal, investigators have carried out several studies of antibiotic use. Among their findings:

- A study of outpatients in three tertiary care hospitals found that 40% received antibiotics.
- A study conducted in 20 health posts in the Kathmandu Valley found that antibiotics were prescribed in 43% of patient visits. A separate study of individual private prescribers and nursing home prescribers found that in 80% of prescriber/patient encounters, patients received one or more antibacterials.
- A study evaluating the impact of a wall poster on antibiotic use (developed by Pharmaceutical Horizon of Nepal, or PHON) found that patients more easily recalled a simple message conveyed in a simple design than a lengthy and complex message.

Training

In January 2002, APUA-Nepal organized a training workshop for house officers and new medical graduates on rational use of antimicrobials. The workshop significantly raised awareness of factors contributing to the emergence of drug resistance. Similarly, APUA-International funded a study of interventions aimed at improving antibiotic use in the community, through educating schoolteachers and women’s groups. The study evaluated teachers’ and housewives’ awareness of proper antibiotic use before the training, two months later, and six months later. Families of schoolchildren were also evaluated. The study found that all three groups improved their understanding of antibiotic use and misuse.
Conclusion

In spite of these successful interventions, rational antibiotic use is still a distant goal in Nepal. The problem is all the more worrisome because, as a relatively poor nation, Nepal can ill afford to spend money on drugs that are not clinically justified. On a positive note, it is heartening that such simple measures as wall posters can significantly boost consumer awareness about proper antibiotic use.

Building on its successes to date, APUA-Nepal will play an effective role in the future by: monitoring resistance trends, educating medical interns about the rational use of antibiotics; increasing awareness of the problem among dispensers and the general public; advocating for policies that require antibiotics to be dispensed only with a prescription from a registered medical practitioner; and advocating for curricula in medical, pharmacy and nursing schools that underscore rational antibiotic use. (For most recent APUA-Nepal guidelines activity, see p.7)

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significant resistance of 30-40%, while Kenya and Ghana report penicillin resistance in only 5-10% of pneumococci. Similar variations are seen in H. influenzae, where reported resistance rates to ampicillin and cotrimoxazole are 1-6% in Central African Republic, 20-30% in Cameroon, Senegal, and Kenya, and 40-50% in Malawi. Fluoroquinolones, recently introduced in many developing countries, have spawned rapid resistance among enteric pathogens. Unfortunately, resistance among respiratory organisms will likely soon follow.

Factors Contributing to Resistance

The primary driving force behind rising resistance is antibiotic use and misuse, which leads to selection pressure favoring the emergence and spread of drug-resistant microbes. In developing countries, a wide array of socioeconomic and behavioral factors contribute to this increased use and misuse. Infectious diseases are far more common in these countries because of warmer climate, unsafe drinking water, unsanitary conditions, and crowding. Appropriate microbiologic facilities are rarely available or affordable, leading to empirical antibiotic use for a wide range of illnesses, which may or may not be caused by bacteria. Antibiotics are freely available over-the-counter (OTC), and many sufferers self-medicate to save the time and money needed to consult a healthcare provider. Antibiotic misuse by unskilled practitioners is also rampant. Poor drug quality, due to improper antibiotic manufacture or storage and use of expired drugs, further contributes to resistance because poor drug quality leads to sub-inhibitory levels of antibiotics, favoring selection of resistant microbes.

Can We Stem the Tide?

In developing countries, the huge burden of infectious diseases and serious lack of healthcare resources have hobbled most strategies against antibiotic resistance. The answer is investment in the healthcare infrastructure: clean water, adequate sewage disposal and sanitation, reduced air pollution and crowding, and universal immunization against common respiratory and enteric pathogens. Though many essential vaccines are available (H. influenzae type b, pneumococcus conjugate vaccine, typhoid vaccine, oral cholera vaccine, intranasal influenza vaccine), poor nations cannot afford them.

In the short-term, the best approaches rely on educating healthcare providers and the public about the dangers of antibiotic misuse; developing antibiotic use guidelines for practitioners in diverse settings; restricting the choice of available antibiotics; and mounting surveillance systems that provide feedback to practitioners on local patterns of antibiotic resistance. More immediately, WHO guidelines for rational antibiotic use in developing countries should be adapted for local use.

References:

Antibiotics Policy and Practice in Animal Food Production

The Facts about Antibiotics in Animals and the Impact on Resistance (FAAIR) II Project is nearly complete. FAAIR II has fostered discussion among a diverse group of expert stakeholders, with the goal of forging consensus about how best to gather data on antimicrobial usage in food animals in the United States. Committee meetings were held on November 21, 2002, and May 19, 2003. A comprehensive report, detailing the methods and major results of the project, is slated for publication in early 2004.

Ecology Program staff members Stephen DeVincent, DVM, MA and Christina Viola have begun work on two additional projects. The first provides technical and manuscript preparation assistance to Richard Fister, Ph.D., Assistant Professor, Tufts University School of Veterinary Medicine, who is conducting a demonstration project on antimicrobial resistance in swine herds. The US Centers for Disease Control and Prevention is funding the project. The second project, funded by the Agricultural Research Service of the U.S. Department of Agriculture, will determine the prevalence of select bacteria in waterways and domestic pets in the northeastern U.S., comparing the results with those obtained from the southeastern part of the country.

The FAAIR II Panel includes representatives from food animal producer groups (e.g. National Aquaculture Association, National Pork Board); academic institutions; veterinary professional organizations (e.g. American Veterinary Medical Association); public interest advocacy groups (e.g. Institute for Agriculture and Trade Policy, Union of Concerned Scientists); government agencies (e.g. Centers for Disease Control and Prevention, FDA Center for Veterinary Medicine, USD Department of Agriculture); and pharmaceutical industry groups (e.g. Animal Health Institute, Pfizer Animal Health, Elanco Animal Health).

McDonald’s Corporation and the Danish Veterinary Institute Awarded for Efforts to Preserve Power of Antibiotics

APUA honored McDonald’s Corporation and scientists at the Danish Veterinary Institute at its 2003 Annual Leadership Award Reception, held at the 43rd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago. Each year, APUA recognizes outstanding global contributions and commitment to preserve the power of antibiotics. This year’s recipients were honored for leadership in reducing the overuse of antibiotics in food animals for the protection of human health.

The awards honoring Dr. Frank M. Aarestrup and Dr. Henrik C. Wegener of the Danish Veterinary Institute. Accepting the award on behalf of McDonald’s Corporation was Bob Langert, Senior Director, Social Responsibility.

The following APUA Corporate Members were thanked at the reception:

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David Bell, CDC; Pat McDermott, FDA; Stuart Levy, APUA; Karin Travers, APUA; and Rich Besser, CDC attended APUA’s Awards Reception at ICAAC 2003
News from the APUA International Chapter Program

APUA Launches Philippines Chapter
APUA-Philippines will hold an inaugural program at the Philippine Society for Microbiology and Infectious Diseases (PSMID) on December 3 and 4, 2003. APUA International Program Director Anibal Sosa, M.D., will attend and present. Lecture topics will include “Global Problem of Antimicrobial Resistance”; “The Impact of APUA in the Promotion of Rational Antibiotic Use”; and “Antibiotic Policies in Developing Countries.”

APUA Welcomes APUA-Nicaragua
The Nicaragua chapter will be jointly led by Sheyla Silva B., M.D., and Mercedes Cáceres, M.D., Ph.D., Children’s Hospital “La Mascota,” Managua, Nicaragua.

APUA at the Nicaraguan Association of Infectology
Anibal Sosa participated in the third annual congress of the Nicaraguan Association of Infectology, held July 3-5 in Managua. Dr. Sosa gave presentations on community-acquired pneumonia, pneumococci with reduced susceptibility to penicillins, and antimicrobial resistance in Latin America.

Grassroots Global Research to Improve Antimicrobial Policy and Practice (GRIP)
The GRIP program provides technical assistance and small research grants to research teams in developing countries for work on antimicrobial resistance.

APUA-Nepal Completes National Antibiotic Guidelines
With support from a small grant from GRIP in Fall 2003, APUA-Nepal has produced National Antibiotic Treatment Guidelines. The guidelines provide a framework for the development of local antibiotic guidelines applicable to all health facilities in Nepal. The guidelines take into account the susceptibility of current local isolates, drug costs, and local preferences. Over 18 months, APUA-Nepal convened stakeholders from the disciplines of general medicine, surgery, obstetrics/gynecology, pediatrics, otolaryngology, and ophthalmology to contribute to and review the guidelines. Upon completion, the guidelines were submitted for approval and action to the Drug Advisory Committee in the Department of Drug Administration at the Nepal Ministry of Health.

APUA-Brazil Finishes Year-long Education Initiative
APUA-Brazil trained more than 100 healthcare workers in antimicrobial resistance testing. The chapter held five conferences and two short courses covering such topics as clinical case discussions, and correct use and interpretation of various susceptibility tests based on NCCLS guidelines.

APUA-Uruguay Conducts Cost Analysis of MRSA and MSSA
APUA-Uruguay used a GRIP grant to study the costs of methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA) infections in University Hospital in Montevideo. The study found that nosocomial MSSA and MRSA infections led to high hospital expenditures. Few statistically significant differences were found between the costs of the two types of infections.

APUA-Russia Conducts Cost Analysis of Automated Process for Culturing
APUA-Russia conducted a study to determine whether an automated system, miniVITAL, was more cost-effective than routine microbiological procedures for culturing blood from ICU sepsis patients. Using data from three Smolensk hospitals and established criteria, the study concluded that the automated system is more cost-effective.

For more information about these projects and the GRIP program, consult http://www.tufts.edu/med/apua/Chapters/SmallGrants.html.

GAARD Network Meets at ICAAC
The Global Advisory on Antibiotic Resistance Data (GAARD) project was established by APUA in 1998 to seek solutions to the increasing problem of antibiotic resistance by promoting the coordination of existing surveillance systems. The GAARD Network held a meeting on September 16, 2003 at the ICAAC conference in Chicago. Participants represented surveillance systems of Glaxo-SmithKline (Alexander N network), Bristol-Meyers Squibb (SENTRY), AstraZeneca (MYSTIC), the WHO Collaborating Centre, and the Centers for Disease Control and Prevention. Other guests included Aventis (Protek) and the European Antimicrobial Resistance Surveillance System (EARSS). Dr. Herman Goossens, Project Leader for the European Surveillance of Antimicrobial Consumption (ESAC) and EARSS representative for Belgium, delivered a thought-provoking talk comparing government-supported surveillance of antimicrobial consumption and resistance in Europe to similar surveillance in the U.S., which is largely conducted by the pharmaceutical industry. Dr. Goossens is a member of the APUA Scientific Advisory Board.

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