

A New Strategy for Fighting Vancomycin-Resistant Enterococci

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Introduction

Due to extensive use of antibiotics in clinical environments during the last two decades, gram-positive pathogens have been subjected to a great selective pressure. Antibiotic resistance has surged dramatically, making nosocomial pathogens even deadlier than before. Among the newcomers are nosocomial pathogens resistant to all antibiotics available. Vancomycin is considered the antibiotic of last resort against gram-positive pathogens. While staphylococci still remain relatively sensitive to vancomycin,¹ some enterococci have acquired the capability of neutralizing this drug's bactericidal activity.²

In recent years, researchers have tried to enhance the bactericidal activity of vancomycin by modifying the drug structure.³ However, due to the particular mechanism of resistance to this drug, some alternative strategies to which bacteria are less able to mount a defense are possible. Vancomycin kills bacteria by surrounding the normal peptidoglycan precursor terminus (D-Ala-D-Ala), thereby interfering with cell membrane formation, resulting in cell lysis. To resist vancomycin, enterococci synthesize an altered peptidoglycan precursor (D-Ala-D-Lac), resulting in a functionally identical peptidoglycan without any biological cost for the bacteria. However, the

change of an amide bond (D-Ala-D-Ala) to an ester bond (D-Ala-D-Lac) reduces the affinity of vancomycin to the precursor terminus by 1000-fold, neutralizing its bactericidal activity.⁴

The level of resistance to vancomycin is directly proportional to the percentage of altered precursor.⁵ Therefore, reducing the pool of altered precursors by cleaving the ester bond would displace the precursor pool to normal precursors. Hence, the bacteria should become sensitive to vancomycin.

Identifying an active compound

To identify active compounds that could enhance the bactericidal activity of vancomycin, we first screened non-biased combinatorial libraries of peptides in order to determine which were the minimal structural requirements necessary for selective and catalytic hydrolysis of the D-Ala-D-Lac ester bond. This information was then used in designing non-peptidic compounds that assemble the minimal requirements. Finally, the resulting compounds with the best *in vitro* hydrolytic activity were tested against resistant bacteria in combination with vancomycin.

A simple assay was designed to identify active molecules able to cleave the ester bond of the depsipeptide⁶ (Figure 1). Out of approximately 300,000 pep-

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Probiotics: Using Live Microbes to Decrease Antimicrobial Use

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Heavy use of antimicrobials is leading to serious problems with antimicrobial resistance and there is a compelling need to investigate alternative approaches to prevent and treat infections. One alternative approach is the use of "probiotics" – live microbes, such as yeast or bacteria, which are beneficial to their host. Evidence is accumulating that the use of appropriate probiotics may provide a viable alternative to, or adjunct to, antimicrobials for the prevention and treatment of certain infections. This commentary reviews the studies of probiotics in situations where an efficacious product would have a significant potential to reduce reliance on antimicrobials. Other uses of probiotics, such as to treat acute diarrheas, rotoviral diarrheas, irritable bowel syndrome and atopic dermatitis, are addressed in more comprehensive reviews.¹⁻⁴

In recent years, a number of probiotic products are being sold that have good *in vivo* survival and antagonistic properties against important pathogens. Randomized, controlled clinical trials of several probiotic products indicate promise for preventing some infections for which antimicrobial therapy would otherwise be indicated (Table 1).

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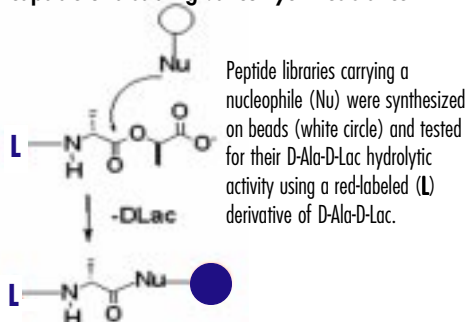
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Figure 1. Assay for the detection of molecules capable of disabling vancomycin resistance

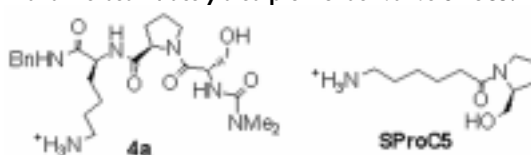


Peptide libraries carrying a nucleophile (Nu) were synthesized on beads (white circle) and tested for their D-Ala-D-Lac hydrolytic activity using a red-labeled (L) derivative of D-Ala-D-Lac.

tides screened in this assay, only a very particular subset exhibited activity. These had three features in common: 1) they all carried a nucleophile (always amino-terminal serine) and an electrophile (Lys, Cu^{2+} , backbone NH), 2) the conformational rigidity of these sequences suggested that these functionalities needed to be *a priori* favorably oriented, and 3) the exclusive presence of the dimethylurea group indicated that an enhanced nucleophilicity of the serine hydroxyl group was required for activity.

One of the active peptides, BnNH-Lys-D-Pro-L-Ser-dimethylurea (peptide 4a, Figure 2) was used as a model to study the mechanism of action of these compounds. Although peptide 4a had a modest *in vitro* activity, it was highly selective. Precursor molecules for the synthesis of peptide 4a (BnNH-D-Pro-L-Ser-dimethylurea 6 or BnNH-L-Lys-dimethylurea 8) or peptide 4a with the hydroxyl group blocked (peptide 7), alone or combined had no activity, indicating that a fully assembled structure was needed for activity. Furthermore, the enantiomer of peptide 4a was less active, suggesting that chiral complementarity to the D-Ala-D-Lac moiety was needed for an optimal hydrolysis of the altered termini.

Figure 2. Chemical structure of the model peptide 4a and the best N-acetylated prolinol derivative SProC5.



Using this structural information we searched for non-peptidic compounds that could mimic peptide 4a activity. We synthesized a family of related acylated-prolinol derivatives that varied in the length of the acylating moiety. All these were tested *in vitro* for the hydrolysis of the D-Ala-D-Lac ester bond. SProC5 (Figure 2), a derivative harboring the ϵ -amino-caproic acid as the acylating chain, was the most active compound. This molecule, although structurally much simpler, showed two-fold increased activity compared to the peptide 4a.

Effectiveness against bacteria

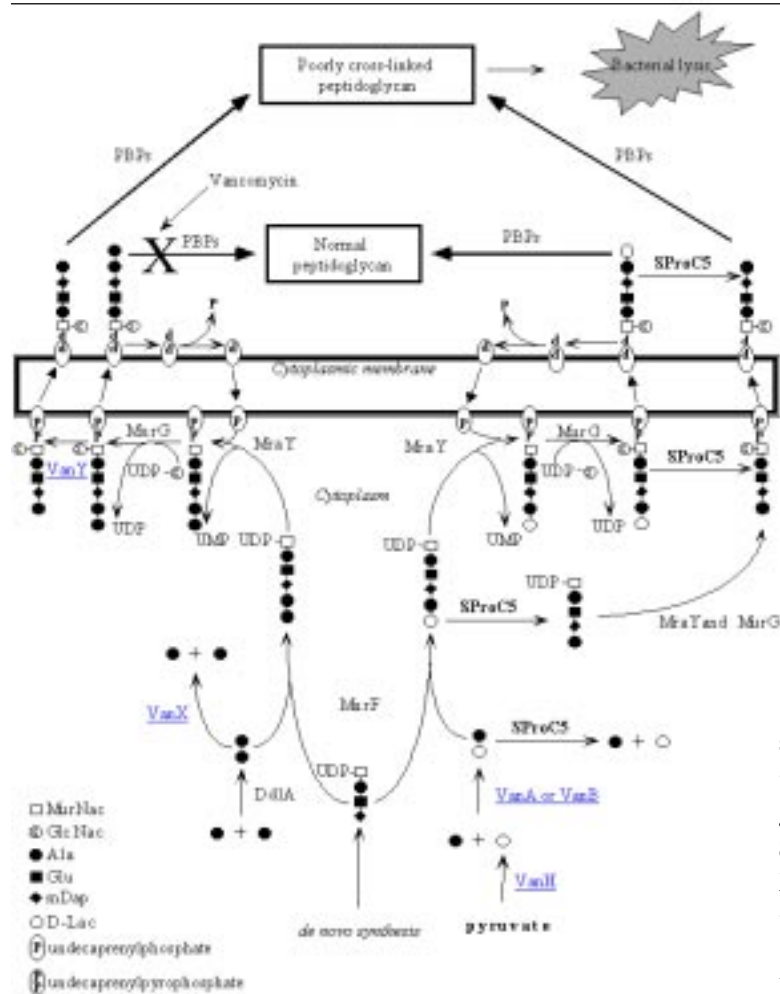
The next step was to test these compounds against bacteria. We used *Enterococcus faecium* strain 228⁷ as the reference organism. This bacterial strain is *vanA* positive with a minimal inhibitory concentration (MIC) of 1000 $\mu\text{g/ml}$ of vancomycin. SProC5 (50 mM) was tested combined with a range of concentrations of vancomycin. Bacteria could not grow at 62.5 $\mu\text{g/ml}$ of vancomycin in the presence of SProC5, a 16-fold decrease in the MIC (Table 1). Inhibition of growth was further confirmed to be due to bacterial death as the bacterial load (CFU/ml) that survived the treatment had been reduced by 3-fold when compared to vancomycin (250 $\mu\text{g/ml}$) or SProC5 (50 mM) alone.

SProC5 synergistic activity with vancomycin was compared to a related

Table 1: Effectiveness of test compounds at lowering MIC for vancomycin

Compound tested with vancomycin	Compound concentra	MIC for vancomycin ($\mu\text{g/ml}$)	
		Strain EF228	Strain JH2-2
0	0 mM	1000	1.5
SProC2	5 mM	1000	1.5
	10 mM	1000	1.5
	50 mM	250	1.5
	100 mM	not determined	1.5
SProC5	5 mM	1000	1.5
	10 mM	500	1.5
	50 mM	62.5	1.5
	100 mM	62.5	1.5
RProC5	100 mM	1000	1.5
C5	100 mM	1000	1.5

APUA Project Partners include: American College of Physicians - American Society of Internal Medicine, Cambridge Schools Massachusetts, Centers for Disease Control and Prevention, Coalition for Affordable Quality Healthcare, Focus Technologies, Inc., The Grodzins Fund, International Society for Infectious Diseases, The Joyce Foundation, Management Sciences for Health, Massachusetts Department of Public Health, Massachusetts Medical Society, The Nathan Cummings Foundation, National Institute for Allergies and Infectious Diseases, Pan American Health Organization, Pan American Society for Infectious Diseases, U.S. Agency for International Development, University of Illinois, World Bank, World Health Organization, and other foundations. APUA projects are supported by private donations, government grants, and individual memberships. APUA gratefully acknowledges unrestricted corporate contributions from: Benefactors: AB Biodisk, Bayer Pharmaceuticals Inc., Bristol-Myers Squibb Co., Clorox Co., GlaxoSmithKline, Lilly Research Laboratories, Ortho-McNeil Pharmaceutical Inc. and the RW Johnson Pharmaceutical Research Institute of Johnson & Johnson, Pharmacia Corporation, Procter & Gamble Pharmaceuticals Inc., Roche Pharmaceuticals. Partners: Schering-Plough, 3M Health Care. Associates: Abbott Laboratories, Paratek Pharmaceuticals, Inc. Affiliates: Alcon Research, Ltd., Burstein Technologies, Inc., Cubist Pharmaceuticals, Inc., DSM Anti-Infectives B.V., Essential Therapeutics Inc., Wyeth-Ayerst Research. Pro Bono: Legal services by Holland & Knight, LLP.



molecule SProC2, characterized by a more modest *in vitro* D-Ala-D-Lac hydrolytic activity. SProC5 synergy with vancomycin was dose-dependent and maximal for 50-100 mM. SProC2 had a very modest synergistic activity with vancomycin at the maximal concentration tested (50 mM), reducing the MIC to the antibiotic only by 4-fold (Table 1). These results are consistent with their *in vitro* hydrolytic activity, again suggesting that synergy is due to the reduction of the pool of altered precursors. The activity of SProC5 was then compared to its enantiomer RProC5 and its five-carbon subunit (an ϵ -amino-caproic acid derivative). None of the control molecules exhibited synergistic effect when combined with vancomycin, even at 100 mM.

Finally, the compounds were tested against the *Enterococcus faecalis* strain JH2-2,⁸ a vancomycin-sensitive strain that relies only on normal precursors terminating with D-Ala-D-Ala to build its peptidoglycan layer. None of the molecules showed any synergistic activity with vancomycin, indicating that SProC5 is effective only in resistant strains. Taking all the data together, the mode of action of SProC5 in combination with vancomycin appears to rely on its ability to selectively and specifically cleave the depsipeptide bond of the altered precursor (Table 1). Figure 3 illustrates the different stages where SProC5 might hydrolyze the D-Ala-D-Lac bond and the consequent interference with the ability of the pathogen to weave a normal cell wall. This leaves the bacteria weakened and susceptible to death due to osmotic pressure.

Figure 3. Peptidoglycan metabolic pathway of vancomycin-resistant enterococci

Proteins involved in the alternative metabolic pathway for the synthesis of altered precursors are underlined. Ubiquitous eubacterial proteins involved in the synthesis of the normal precursors and assembly of the peptidoglycan layer are indicated for each biosynthetic step. SProC5 (in bold) could hydrolyze the D-Ala-D-Lac bond at different steps of the alternative metabolic pathway. The most efficient way would be to cleave D-Ala-D-Lac directly in the cytoplasm before it is ligated by MurF protein to the UDP-MurNac-tripeptide. This would lead to enrichment in D-Ala-D-Ala terminating precursors, allowing vancomycin to be more efficient in blocking peptidoglycan synthesis.

SProC5 could also cleave UDP-MurNac-tripeptide-D-Ala-D-Lac in the cytoplasm or when anchored to the lipid carrier undeprenylphosphate. In that case, SProC5 activity would lead in the incorporation of GlcNac-MurNac-tetrapeptides into the peptidoglycan. These precursors do not bind vancomycin but cannot sustain peptidoglycan synthesis. The tetrapeptide precursors can be used as donor precursors during cross-linking of the peptidoglycan. However, only pentapeptide precursors can be used as acceptors. The presence of the carboxylic terminal D-Ala or D-Lac is essential for a precursor to function as an acceptor since the energy bond between D-Ala-D-Ala and D-Ala-D-Lac is used by penicillin-binding proteins (PBPs) to generate the new bond involved in the cross-linking. As vancomycin sequesters the remaining pentapeptide precursors, tetrapeptide precursors would be accumulated. Thus, bacteria would be incapable of building a functional cell wall. This would lead to lysis and death due to osmotic pressure.⁹

SProC5 activity is still too modest to be used in the clinical setting. However, it is possible that SProC5 could be more effective in combination with teicoplanin, a more potent glycopeptide against enterococci in general. Nevertheless, SProC5 is a model compound with room for improvement. More diverse and targeted combinatorial libraries can be used to find new compounds with better activity.

Our strategy has several advantages. By targeting the product D-Ala-D-Lac and not the proteins involved in the alternative metabolic pathway, the chances of developing resistance are reduced. The penicillin-binding proteins impose structural constraints for the peptidoglycan precursor's termini used for cell wall assembly, limiting the number of valid alternatives. The VanC (or VanE) phenotype is the only described alternative where the terminal D-Ala residue is replaced by a D-serine residue.² Fortunately, these are not transferable via plasmids as are the *vanA* or *vanB* clusters, thus limiting the appearance of new resistance mechanisms.

Conclusion

The false impression that antibiotics were infallible resulted in a perverse situation where no new class of antibiotics is even in advanced stages of clinical trials. Therefore, new innovative approaches to deal with the increasing problem of antibiotic resistance are desperately needed. The described approach, using a designer molecule to resensitize bacteria to an existing antibiotic, represents a new strategy for disabling the antibiotic-resistance mechanisms.

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Antibiotic-associated diarrhea

The largest literature providing evidence for probiotic efficacy is the concurrent use of probiotics with antimicrobials to decrease antibiotic-associated diarrhea. Antibiotic-associated diarrhea can indirectly lead to increased antimicrobial resistance by necessitating premature cessation of therapy or prolonging exposure to antimicrobials due to the need to switch medications. Poor patient compliance due to diarrhea can result in failure to eradicate the pathogen. Several probiotics have shown efficacy in preventing antibiotic-associated diarrhea, for example, in hospitalized adults (*Saccharomyces boulardii*)^{5,6} and in ambulatory pediatric patients (*Lactobacillus rhamnosus* GG)^{7,8} (Table 1). Particularly noteworthy are the two recent clinical trials of *Lactobacillus* GG showing a significant decrease in antibiotic-associated diarrhea in the context of a primary care pediatric setting.^{7,8} The lack of reported effect of *Lactobacillus* GG in preventing adult antibiotic-associated diarrhea in a hospital setting⁹ might relate to the inhibition of this bacterial probiotic by the IV antimicrobials used.

Pediatric nosocomial diarrhea

The etiology of nosocomial (hospital-acquired) acute diarrhea in pediatric patients is largely rotoviral in developed countries. Nosocomial diarrhea can prolong hospital stays thereby enhancing risks for other nosocomial infections.¹⁰ Inappropriate use of antimicrobials for acute diarrhea can lead to nonefficacious antibiotic exposure. Szajewska et al. recently showed that use of *Lactobacillus* GG could decrease acquisition of diarrhea in hospitalized infants.¹¹ This is consistent with an earlier study by Saavedra et al.¹² using a different probiotic preparation (Table 1). The mechanism here would seem to be probiotic enhancement of the immune response rather than a direct effect on rotovirus.

Respiratory infections and otitis media

Treatment of pediatric respiratory infections and otitis media account for

Table 1. Probiotic, placebo-controlled trials for prevention of disease

Prevention of	Probiotic	# of subjects	Study Population	Frequency (%)		Reference
				Treated	Control	
Antibiotic-associated diarrhea	<i>S. boulardii</i>	180	hospitalized adults	9.5*	21.8	27
		193	hospitalized adults receiving b-lactams	7.2*	14.6	28
	<i>Lactobacillus</i> GG	267	hospitalized adults	29.3	29.9	29
		188	ambulatory children	8*	26	7
Nosocomial diarrhea	<i>Lactobacillus</i> GG	167	ambulatory children	5*	16	8
		81	hospitalized infants	6.7*	33.3	11
	<i>Bifidobacterium longum</i> & <i>Streptococcus thermophilus</i>	55	hospitalized infants	7*	31	12
Respiratory infections	<i>Lactobacillus</i> GG	571	children in daycare	39*	47	13
Recurrent otitis media	5 <i>Streptococcus</i> alpha	108	ambulatory children	58*	78	14
Traveler's diarrhea	<i>Lactobacillus</i> GG	225	tourists from NYC area	3.9/day*	7.4/day	30
		1016	tourists from Austria	28.7*	39.1	31
<i>C. difficile</i> disease recurrence	<i>S. boulardii</i>	124	patients with <i>C. difficile</i> disease	26*	45	32
		168	patients with recurrent <i>C. difficile</i> disease	16.7*	50	33

* p < 0.05

enormous antibiotic prescribing. A provocative finding of a diminished rate of respiratory infections compared to placebo in children in day-care centers given *Lactobacillus* GG in milk was reported by Hatakka et al.¹³ This single study needs to be independently confirmed by others to gauge the extent of efficacy and the appropriate dose and length of treatment. A second study involved use of an innovative nasal spray containing five strains of alpha streptococci selected on the basis of inhibitory activity against otitis media pathogens.¹⁴ Currently symptomatic children with recurrent otitis media were all given antibiotics for 10 days. The nasal spray was applied for two 10 day periods during the three month study. There were significantly fewer subjects that relapsed in the active spray group compared to placebo (58% vs. 78%). While the effect was modest, the large number of children affected by otitis media makes small treatment benefits potentially important.

Recurrent *C. difficile* disease

Early work showing efficacy of the yeast *S. boulardii* in the hamster model of pseudomembranous colitis¹⁵ led to studies of efficacy in humans. Established recurrent *C. difficile* disease is particularly difficult to arrest. Two clinical trials em-

ployed *S. boulardii* along with metronidazole or vancomycin in patients with *C. difficile* disease (Table 1). The yeast treatment was continued for 30 days after stopping the antimicrobial. Excellent results were identified using a 10-day course of high-dose vancomycin plus a 30-day course of *S. boulardii* (16% recurrence vs. 50% in placebo). A regimen of adjunctive use of this probiotic in patients with recurrent disease would reduce repetitive exposures to metronidazole or vancomycin. Placebo-controlled studies of other probiotics for *C. difficile* disease have not been reported, but a study using *Lactobacillus* GG is apparently underway.¹⁶

Traveler's diarrhea

Tourists traveling to areas of the world where the risk of traveler's diarrhea is high will often be given a prescription for an antimicrobial (e.g. a fluoroquinolone) for use if diarrhea develops. An efficacious probiotic that could be used while at risk would diminish antibiotic use. Both *S. boulardii* and *Lactobacillus* GG have been shown in placebo-controlled studies to have modest efficacy in preventing traveler's diarrhea (Table 1). However, more study is needed and other probiotics need to be tested before application of this approach can be routinely recommended.

Urogenital infections

While consumer use of probiotics (mainly as yogurts) to prevent vaginitis is popular, there is a surprising paucity of controlled trials evaluating this practice. Some preliminary findings indicate some potential for *Lactobacillus*-based probiotics to prevent recurrent urinary tract infections, bacterial vaginosis and *Candida* vaginitis. Recent reviews cover these studies.^{17,18}

Risks of probiotic use

The overall safety record of available probiotics is excellent. However, any exogenously administered microbe could be harmful to severely debilitated or immunosuppressed patients. A few cases of Lactobacillæmia¹⁹⁻²¹ and *Saccharomyces* fungemia²²⁻²⁴ have been reported. While there are many probiotic products on the market, they fall into the "dietary supplement" regulatory category in the USA and hence are not under tight Food and Drug Administration scrutiny. Problems with quality control with some products continue to be reported.^{25,26} For the present, only probiotic products shown to be safe and efficacious in larger controlled studies can be recommended.

Conclusion

It is hoped that the recent promising results discussed will be a stimulus for priority funding in this area, not only with the goals to decrease morbidity, but also to decrease antimicrobial use. Once the role of probiotics in therapy is better understood, the next approach will then be to optimize probiotic action through genetic engineering. These "living drugs" may help in the fight to decrease antimicrobial resistance.

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Quinolone Resistance in Vietnam

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Antibiotics are widely used in Vietnam. Ciprofloxacin has been used in Vietnam only in the last decade. APUA-Vietnam has documented that over the last decade, resistance to the quinolone antibiotics Norfloxacin and Ciprofloxacin has increased dramatically (Tables 1-4).¹ To stop the increase in resistance of bacteria to these antibiotics, the widespread inappropriate use of antibiotics in Vietnam must be reduced. Doctors should not use such powerful antibiotics as the quinolones to cover all possible patho-

Table 1. *Neisseria gonorrhoeae* resistance to Ciprofloxacin

Year	n (# of tested strains)	% Resistant
1994	131	0.0
1994-95	283	5.6
1998	135	5.9
2000	50	74.0

Table 2. *Staphylococcus aureus* resistance to Norfloxacin and Ciprofloxacin

Year	Norfloxacin		Ciprofloxacin	
	n	% Resistant	n	% Resistant
1996	516	8.9	93	16.1
1998	242	21.5	68	20.6
1999	343	30.6	181	33.7

gens. Antibiotics should be sold by prescription only. In parallel to reducing antibiotic use, health care centers should improve their infection control measures through sterilization and disinfection to avoid spreading resistant microorganisms.

Table 3. *Escherichia coli* resistance to Norfloxacin and Ciprofloxacin

Year	Norfloxacin		Ciprofloxacin	
	n	% Resistant	n	% Resistant
1994	79	1.3	no data	
1996	614	21.0	82	17.1
1998	376*/291†	32.2/19.2	166*/198†	39.2/27.8
1999	264*/280†	38.6/13.6	286*/655†	41.9/37.8

*From UTI (urinary tract infection) †No UTI

Table 4. *Pseudomonas aeruginosa* resistance to Norfloxacin and Ciprofloxacin

Year	Norfloxacin		Ciprofloxacin	
	n	% Resistant	n	% Resistant
1994	42	7.1	no data	
1996	355	20.6	no data	
1998	254	37.0	255	42.7
1999	306	30.7	939	41.0

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APUA News

Non-pathogenic bacteria: ROAR

APUA is pleased to announce a multiyear research award from the National Institute of Allergy and Infectious Diseases to conduct the ROAR (Reservoirs of Antibiotic Resistance) II project. This project follows on the heels of a related subcontract three years ago to investigate how commensal organisms can serve as reservoirs of resistance in pathogenic organisms. The project's aims are:

1. Implementation of a bioinformatics database to profile resistance genotypes in commensal organisms.
2. Implementation of research projects by ROAR participants to use the collected data to address the hypothesis that the frequency of resistance genes in commensal organisms found in the environment can act as a predictor for the emergence of antibiotic resistance in pathogenic bacterial organisms.
3. Development of a mathematical model to serve as a tool for predicting the emergence of resistance in medically important bacterial species, using the analyses of the data gathered in Aim 2 (above) to test and refine the model.

For more information on ROAR, please see www.apua.org. Interested APUA members with a research specialty in bioinformatics and/or resistance in commensal organisms should contact APUA Research Manager, Karin Travers, D.Sc. (karin.travers@tufts.edu).

US Health Provider Education

APUA is spreading the word about how to use antibiotics effectively while minimizing resistance. Three major means include: educating healthcare practitioners, exhibiting jointly with the CDC at key professional conferences around the US, and developing Continuing Medical Education programs for physicians, nurse practitioners, and pharmacists. Over the next six months, APUA will conduct six plenary session lectures at major regional

Early resistance warning by GAARD

As part of its efforts to track antibiotic resistance patterns on a global basis, APUA's GAARD (Global Advisory on Antibiotic Resistance Data) project welcomed a new surveillance system member in 2001. AstraZeneca Pharmaceuticals' MYSTIC program joins GlaxoSmith-Kline's Alexander Network, Bristol-Myers Squibb's SENTRY program, and Focus Technologies' TSN program as part of the public/private partnership for which CDC and WHO act as advisors.

During the 41st ICAAC, the GAARD group submitted an abstract on emerging *H. influenzae* resistance. The GAARD analysis of *H. influenzae* data warned of the potential of emerging fluoroquinolone resistance in this organism. The large size of the GAARD database, and the use of genotyping and phenotyping assays, allowed the identification of a small but growing subset of *H. influenzae* isolates with decreased susceptibility to fluoroquinolones associated with single first-step mutations associated with resistance. This study warned of a potentially important resistance problem in this organism before its emergence (see the *APUA Newsletter* 19:3).

In December 2001, the GAARD Steering Committee met to consider new research study possibilities. The group renewed its commitment to continue tracking *H. influenzae* and *Streptococcus pneumoniae* susceptibility and agreed to expand the tracking of these organisms to four different classes of antibiotics.

and national conferences. In 2001, APUA forged new collaborations with important public health groups and professional societies, such as 1) the American College of Physicians/American Society for Internal Medicine to disseminate guidelines for antibiotic use in adult respiratory conditions and 2) the Coalition for Affordable Quality Healthcare (CAQH) to provide valuable information in CAQH's member newsletters.

New at APUA Website

Check out a new addition to APUA's website, geared to the public. A Question & Answer (Q&A) section, scientifically accurate, yet user-friendly, addresses questions such as: 1) How do antibiotics work? 2) Can bacteria lose their antibiotic resistance? and 3) How can antibiotic resistance harm humans?

The new Q&A section also contains a discussion of the relationship between bioterrorism and antibiotic use and information about antibacterials. In addition, the newly expanded 'ecology' section is an in-depth resource on the ecological impact of antibiotic use in animals, humans, and plants.

Invite your patients, colleagues, friends and family to learn more about antibiotic resistance through the expanded APUA website. Go to www.apua.org, then click on the 'Q&A' or 'Ecology' links.

Antimicrobials in Animals: FAAIR

In January 2002, APUA completed the first phase of the Facts about Antibiotics in Animals and their Impact on Resistance (FAAIR) project. The report of the findings has been accepted by *Clinical Infectious Diseases* (CID). The report, "The Need to Improve Antimicrobial Use in Agriculture," is the culmination of a two-year effort of APUA and the FAAIR Scientific Advisory Panel, comprised of the foremost scientific and clinical authorities on antimicrobial use in agriculture. The report, including a summary of scientific findings, conclusions, and policy recommendations, synthesizes scientific evidence on the human health risks and ecological consequences of the agricultural use of antimicrobials.

The report is scheduled to be posted on the CID and APUA websites on April 30 and will be available as a supplement to the CID journal subscribers in May. On April 30, APUA will conduct a press conference and congressional briefing in Washington DC. A stakeholder meeting is planned at the ASM 102nd General Meeting in May.

APUA Celebrates Its 20th Anniversary!



APUA President and Founder, Dr. Stuart B. Levy presents the first APUA Leadership Award to Dr. Rosamund Williams of the World Health Organization.

APUA celebrated its 20th Anniversary with a reception at the Hyatt Regency Chicago during the 41st annual ICAAC conference in December. APUA partners who attended included representatives from the FDA, CDC, USVA, and members from over 15 countries. Dr. Rosamund Williams of World Health Organization was presented with the first APUA leadership Award “for her tena-

cious efforts in the worldwide battle against antibiotic resistance.” Dr. Stuart B. Levy, President and Founder of APUA, addressed the group and read congratulatory letters from the current and past presidents of the American Society for Microbiology. Dr. Thomas O’Brien, APUA Vice President, and Kathy Young, APUA Executive Director, also addressed the group.

A proclamation issued by Senator Edward Kennedy of Massachusetts honored the work of APUA over the last two decades. Senator Kennedy noted, “The Alliance is an effective advocate and advisor in the development of new US and global strategies to contain antibiotic resistance. Your leadership has reduced health costs and improved healthcare throughout the world ... Our nation is counting on the continued efforts of the Alliance to strengthen all of our defenses against infectious disease.” Abigail Salyers, current President of ASM, noted,



From right to left: Kathleen Young, APUA Executive Director, Dr. David Bell, CDC, Dr. Elisabeth TS Houang and Dr. Margaret Ip, APUA member from Hong Kong.

“I congratulate APUA on its record of hard work and look forward to being part of its promising future.”

APUA thanks the many sponsors of this event. Major sponsors included: Bayer Pharmaceuticals, Inc.-LIBRA Initiative, Procter & Gamble Pharmaceuticals, Inc., GlaxoSmithKline, Lilly Research Laboratories-Infectious Disease Research Division, Roche Labs; see www.apua.org, for a complete list of sponsors.

APUA Chapter News

Congratulations to the following APUA chapter recipients of the 2002 APUA **Small Grants!** The objectives of the funded research projects are to describe and compare the cost implications of antibiotic usage patterns. **APUA-Moldova:** Analysis of sale and dispensing of antibiotics in Moldova; **APUA-Uruguay:** Cost of *Staphylococcus aureus* hospital-acquired infections, implications of methicillin-resistant and methicillin-susceptible isolates; **APUA-Ukraine:** Cost analyses of antibiotic usage patterns: estimation of an economic efficiency of microbiological researches in the ordinary city hospital; **APUA-Russia:** Cost-effectiveness analysis of miniVITAL automated system vs. routine microbiological procedures for blood cultures from ICU patients with sepsis; **APUA-Poland:** Cost-effectiveness of evolving antibiotic prescribing in primary care hospitals; **APUA-Brazil:** Epidemiology and treatment of persistent diarrhea in NE Brazil; **APUA-Peru:** Cri-

teria for defining a surgical site infection; **APUA-Colombia:** National survey on approach to the level of empirical use of antimicrobial agents and diffusion of basic rules for prudent use.

APUA/PAHO Survey

Funded by the Pan American Health Organization (PAHO), APUA conducted a survey in selected countries in **Latin America** with the objective of evaluating physician knowledge and practices with respect to antibiotic use and resistance. The survey was developed by PAHO/APUA staff and sent to physician study coordinators in **Bolivia, the Dominican Republic, Ecuador, El Salvador, Nicaragua, Paraguay, and Peru.** Highlights of the findings were:

- A significant need for the collection and dissemination of more local antibiotic resistance data to improve prescribing patterns and patient outcomes.
- An urgent need for consumer education as self-medication rates are high.

- A general lack of antimicrobial resistance information to enable physicians to appropriately treat ARI and ADI empirically.

APUA Co-Sponsors Conference in Latin America

The VI Dominican Congress on Infectious Diseases was held on December 1, 2001, in Santo Domingo, organized by the Dominican Society for Infectious Diseases and sponsored by the Panamerican Society for Infectious Diseases and APUA. Topics included the surveillance of drug resistance and antibiotic resistance patterns in the Dominican Republic. The “Declaración de Guadalajara” (Guadalajara Declaration), supporting the prevention of antibiotic resistance in the country, was signed and sent to the Ministry of Health to encourage the national health authorities to develop a national strategy for antibiotic resistance. For more information contact Dr. Anibal Sosa, M.D. (anibal.sosa@tufts.edu).

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... preserving the power of antibioticssm throughout the world.

Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society's defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA's mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. 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.



★ **Headquarters**

- **Chapters:** Argentina, Australia, Bangladesh, Belarus, Brazil, Bulgaria, Chile, China, Colombia, Cuba, Dominican Republic, Ecuador, El Salvador, Greece, Guatemala, India, Italy, Mexico, Moldova, Nepal, Peru, Russia, Senegal, Spain, Sweden, Turkey, Ukraine, Uruguay, Venezuela and Vietnam.

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