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MINIREVIEW

Impact of *Antimicrobial Agents and Chemotherapy* from 1972 to 1998

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The antibiotic era began with the discovery, in 1939 and 1940, of the first three significant antibiotics, namely, tyrothricin (of bacterial origin), penicillin (a rediscovery of an antibiotic of fungal origin), and actinomycin (a product of actinomycetes). Within the first 18 years of the antibiotic era, about 30 antimicrobial agents had come into use, as noted by Selman Waksman, the discoverer of streptomycin (20). Included among these, in addition to streptomycin, were chloramphenicol, chlortetracycline, oxytetracycline, bacitracin, erythromycin, novobiocin, oleandomycin, vancomycin, and antimycotic agents such as nystatin and griseofulvin.

ANTIMICROBIAL DRUGS

To put in perspective this total of 30 antimicrobial agents introduced in the span of the first 18 years of the antibiotic era, it should be contrasted with the number of antimicrobials discovered or studied during the past 27 years (1972 to 1998). The best resource for such information has been *Antimicrobial Agents and Chemotherapy* (AAC) since its establishment in 1972 as a monthly journal published by the American Society for Microbiology (11). A compilation of the number of antimicrobial agents from a review of titles of papers published in AAC (1972 to 1998) totals more than 1,220 compounds. These include compounds described in any of the stages of development, from descriptive chemistry, susceptibility testing, mechanisms of action, and pharmacology to the various phases (I to III) of clinical trials. Antibacterial drugs account for 46% of the total, followed by antiviral drugs at about half of this percentage (Table 1). The smallest category, that of antimycobacterial drugs, may be slightly underrepresented, since only drugs described in articles dealing with their use against mycobacteria have been included, although some drugs (e.g., certain aminoglycosides) function as both antibacterial and antimycobacterial agents.

For an infectious disease clinician, AAC has provided an ongoing resource for information on interesting and important new antimicrobial agents. At any given time, some of these may be near approval by the U.S. Food and Drug Administration (FDA) and others may be only in preliminary stages of in vitro testing. While totals for the different categories of antimicrobial agents described over the past 27 years provide the "big picture," an examination of changes over time offers insight into changes in the field of antimicrobial chemotherapy (Table 2). The percentage of new antibacterial drugs among all new antimicrobial agents has declined over this period, dropping from 62% in 1972 to 1973 to 26% in 1997 to 1998. The number of new antibacterials described in AAC articles peaked at 57 in 1988 to 1989 and subsequently declined. While the number and percentage of new antiviral drugs cited by title remained very similar between 1972 and 1989, they subsequently rose to a total of 43 new antivirals and 31% of all antimicrobials in 1997 to 1998. To a large extent, articles on antiviral drugs introduced during the past decade detail investigations of nucleoside and nonnucleoside inhibitors of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and HIV-1 protease inhibitors. However, in the last few years they have described novel drugs aimed at respiratory viruses (influenza virus and rhinoviruses), hepatitis B virus (HBV), and picornaviruses. In the 1970s, reports of early antiviral drugs with activity against herpes simplex virus (HSV), i.e., drugs such as adenine arabinoside, idoxuridine, bromodeoxyuridine, and acyclovir, began appearing in AAC. In the 1980s, newer antiviral drugs with greater activity against cytomegalovirus (ganciclovir for parenteral use and its orally deliverable prodrug famciclovir) appeared in the pages of AAC. In the 1990s, among the antiviral agents introduced through preclinical and clinical studies in AAC were valacyclovir, an L-valyl ester of acyclovir (requiring less frequent dosing for treatment of genital herpes and herpes zoster), and lamivudine, which can serve in treatment of chronic HBV infection and as part of a multiple-drug program against HIV.

In the past 27 years, drugs directed primarily at parasitic diseases have comprised 13% of the 1,220 antimicrobials given prominence in AAC. Such drugs have included antimalarial agents (mefloquine, artemether, and halofantrine); drugs for the treatment of infection with *Pneumocystis carinii* (probably a fungus) (pentamidine and atovaquone); drugs with activity against *Toxoplasma gondii* (spiramycin and paclitaxel); drugs tested for activity against *Cryptosporidium* (paromomycin, halofunginone lactate, and nitazoxanide); antihelmintic agents such as avermectin, an antifilarial agent (particularly effective in onchocerciasis), albendazole, and oxfendazole in treatment of infection with *Echinococcus granulosus*; drugs such as allopurinol and dinitroanilines tested for antileishmanial activity; and drugs tested for antitrypanosomal activity, such as difluoromethylornithine, 2-acetylpyridine thiosemicarbazone, diaminotriazine derivatives, and nifurtimox (against *Trypanosoma cruzi*). As with newer antibacterial drugs described in AAC, most of the antiparasitic agents studied have been tested initially in in vitro cell culture systems or in animal models. The number of new antiparasitic drugs described in AAC has increased steadily. In the period from 1974 through 1978, 7 antiparasitic drugs were described; in 1984 through 1988, 22 were described; and in 1994 through 1998, the number had risen to 70.

Antimycotic compounds have comprised about 10% of new antimicrobial agents described in AAC over the period from

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TABLE 1. Categories of antimicrobial agents described in AAC in 1972 to 1998

Category	Antimicrobial agents	
	No.	%
Antibacterial	567	46
Antiviral	293	24
Antiparasitic	158	13
Antifungal	110	9
Antimycobacterial	92	8
Total	1,220	100

1972 to 1998. All major antifungal drugs have been described in the journal, usually initially as reports of in vitro susceptibilities of various fungi to newly isolated or synthesized compounds and in animal models of infection. These drugs include amphotericin B (already long in clinical use), amphotericin B methyl ester, clotrimazole, miconazole, ketoconazole, itraconazole, terbinafine, and newer pneumocandin antifungals. As with antibacterial, antiviral, and antiparasitic drugs described in AAC, the number of new antifungal drugs has increased from 8 during the period from 1974 to 1978, to 12 in 1984 to 1988, and to 40 from 1994 to 1998, representing an overall fivefold increase.

AAC articles have provided infectious disease specialists with early indications of new antimicrobial classes well before they reach definitive clinical trials and approval by the FDA. For example, in 1987, the oxazolidinones, a new synthetic class of antibacterial agents with activity against gram-positive organisms, were described (16). The later finding that two of the oxazolidinones, linezolid and eperezolid, were active against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus faecium* made these drugs a subject of considerable interest when their in vitro activities were reported in AAC in 1996. Their mechanism of action was shown, also in AAC, to be inhibition of bacterial protein synthesis by prevention of formation of the *N*-formyl-methionyl-tRNA–ribosome–mRNA ternary complex (17). Eleven years after the first description of the oxazolidinone class, one of its members, linezolid, entered phase III clinical testing for skin infections, bacteremia, and pneumonia.

While the numbers of antimicrobial drugs described in AAC have increased considerably, the need for more clinically approved new drugs active against antimicrobial-resistant pathogens such as vancomycin-resistant *E. faecium*, methicillin-resistant *Staphylococcus aureus*, and β-lactamase-producing gram-negative bacilli is readily evident. A feature of each April issue of AAC since 1993 is a listing of the antibacterial, antifungal, antiparasitic, and antiviral drugs approved by FDA in the preceding year. This provides insight into the relation between the numbers of compounds that have had preliminarily favorable results (enough to warrant publication in AAC) and the numbers that achieve FDA approval for human use. For example, despite the many score of new drugs reported in AAC in the preceding half-dozen years, the number of new molecular entities approved by the FDA in 1992 was nine: three antibacterials (cefpodoxime, temafloxacin, and lomefloxacin), one antiviral (zalcitabine), one antimalarial (halofantrine), one antipneumocystis agent (atovaquone), two antifungals (itraconazole and topical terbinafine), and one antimycobacterial drug (rifabutin). In 1994 the number was 13, but of these, 10 represented new formulations (or routes of administration) or indications for use of previously accepted molecular entities, and only 3 were entirely new drugs. In 1997, while 37 entries were listed in AAC as antimicrobial agents newly approved by FDA, 25 represented new formulations, routes of administration, or indications for use of previously approved drugs. Of the remaining 12, 4 were topical antimycotic agents, 2 (the HIV protease inhibitor nelfinavir and the nonnucleoside reverse transcriptase inhibitor delavirdine) were used in treatment of HIV infection, one was a new lipid-associated form of amphotericin B, one was an antiviral drug (valacyclovir), and four were antibacterials belonging to either the cephalosporin (cefepime), fluoroquinolone (trovafloxacin and grepafloxacin), or macrolide (dirithromycin) families. Thus, apart from the four topical antimycotic drugs and the two drugs directed at HIV infection, new antiviral and antibacterial drugs approved in 1997 represent congeners or derivatives of existent agents, emphasizing the need for new drug discovery in an era of increasing antimicrobial resistance.

ANTIMICROBIAL RESISTANCE

The antibiotic era has been marked by cycles consisting of introduction of new antimicrobials and subsequent emergence of resistance to those drugs. In the past 27 years, AAC not only has provided early data on new antimicrobial agents but also has been a major source for information on drug resistance and its mechanisms among important pathogens. One might cite the widespread use in the 1960s and 1970s of semisynthetic penicillinase-resistant penicillins and cephalosporins and

TABLE 2. Distribution of categories of antimicrobials reported on in AAC in selected years

Category[a]	No. of antimicrobial drugs (% of total) in[b]:					
	1972–1973[c]	1978–1979	1982–1983	1988–1989	1992–1993	1997–1998
Antibacterial	56 (62)	27 (59)	41 (55)	57 (54)	54 (42)	36 (26)
Antiviral	17 (19)	10 (22)	14 (19)	19 (18)	37 (29)	43 (31)
Antiparasitic	7 (8)	6 (13)	5 (7)	20 (19)	21 (16)	36 (26)
Antifungal	6 (6)	2 (4)	12 (16)	7 (6)	12 (9)	20 (14)
Antimycobacterial	5 (5)	1 (2)	2 (3)	3 (3)	5 (4)	4 (3)
Total	91 (100)	46 (100)	74 (100)	106 (100)	129 (100)	139 (100)

[a] Drugs are listed only once in each category, but a few drugs, e.g., aminoglycosides and rifampin, fit into several categories (antibacterial and antimycobacterial) and are included in both.

[b] Twenty-four-month periods.

[c] The increased number of antimicrobial drugs in each category in 1972 to 1973 in comparison with the next several 2-year intervals is partially artifactual. An individual drug is listed only once, on its first appearance in a published article, even though it may be described in many subsequent articles in different types of studies. Thus, antimicrobials identified earlier (1950s and 1960s) may be the subjects of studies for the first and only time in 1972 to 1973 in this compilation.

the emergence of methicillin-resistant strains of *S. aureus* (MRSA), the extensive use of ampicillin and the development of ampicillin resistance in the 1970s in clinical isolates of *Neisseria gonorrhoeae* and *Haemophilus influenzae* and in *Escherichia coli*, the emergence of penicillin-resistant *Streptococcus pneumoniae* (due to stepwise changes in penicillin binding proteins) starting in the 1970s and subsequently spreading worldwide (5), the appearance among clinical isolates of *Enterobacter cloacae* of augmented levels of inducible (on exposure to drugs such as cefoxitin) chromosomally mediated β-lactamases causing resistance to β-lactam antibiotics like cefamandole and moxalactam (4, 19), and also selection of stably derepressed mutant strains.

In the 1980s the emergence of strains of *Enterobacteriaceae*, particularly *Klebsiella pneumoniae*, bearing plasmid-encoded extended-spectrum β-lactamases capable of inactivating extended-spectrum cephalosporins such as cefotaxime and ceftazidime became problematic (14).

Particularly troublesome problems of resistance have arisen in the treatment of severe enterococcal infections such as endocarditis. In the 1960s treatment required the synergistic combination of penicillin and streptomycin. Subsequently, when high-level resistance to streptomycin emerged, gentamicin replaced it. The initial report of high-level plasmid-mediated resistance to gentamicin among clinical isolates of *Enterococcus faecalis* in 1979 heralded further problems in subsequent decades (6, 10). In the early 1980s the first β-lactamase-producing strains of *E. faecalis* appeared, and sequencing data suggested the likely spread of this β-lactamase gene from *S. aureus* to enterococci. This problem augmented the already-present problem of resistance to penicillin among one-third of the *E. faecium* strains (15% of enterococci), precluding effective penicillin-aminoglycoside synergism (6). Such resistance to penicillin and penicillin-gentamicin synergism led in the late 1970s to widespread use of vancomycin in the treatment of life-threatening enterococcal infections. By the late 1980s vancomycin-resistant enterococci were reported, and in the mid-1990s these strains accounted for 13.6% of enterococcal isolates in intensive-care units in the United States.

Pneumococci with intermediate penicillin resistance began to be noted in the 1970s in South Africa; in the 1980s highly penicillin-resistant strains began to appear worldwide. By the mid-1990s the frequency of penicillin resistance in the United States had reached 20 to 25%. Most problematic has been the emergence of resistance to extended-spectrum cephalosporins in the 1990s, necessitating the addition of vancomycin in the initial treatment of pneumococcal meningitis. Resistance of pneumococci to β-lactams is based on production of penicillin binding proteins with decreased affinity for penicillin (21).

Following the release of ciprofloxacin in the United States in 1987, resistance began to be noted among highly susceptible species such as *E. coli* (and other *Enterobacteriaceae* and *N. gonorrhoeae*), among slightly less susceptible species such as *Campylobacter jejuni*, and among less susceptible species such as *Pseudomonas aeruginosa* and *S. aureus*. Resistance mechanisms have involved either of two mechanisms: altered target enzymes with reduced affinity of mutant enzyme-DNA complexes for fluoroquinolones (due to mutations in the gyrase A subunit or in the ParC subunit of topoisomerase IV) or altered drug permeation to the target site (in gram-negative bacilli due to reductions in porin proteins and due to energy-requiring efflux systems, sometimes with pleiotropic cross-resistance to tetracycline, chloramphenicol, and some β-lactams). Resistance among *S. aureus*, particularly MRSA, and among *P. aeruginosa* has been particularly troublesome. Although the frequency of fluoroquinolone resistance among isolates of *S. pneumoniae* is presently low, recent reports of resistance are disturbing in view of the extensive use of these compounds for community-acquired respiratory infections (8).

TABLE 3. Antimicrobial resistance papers in AAC

Period[a]	Total no. of articles (all types)	% Articles dealing with resistance
1972–1973	438	11
1978–1979	640	15
1982–1983	797	15
1988–1989	808	21
1992–1993	1,058	22
1997–1998	1,182	34

[a] Twenty-four-month periods.

The increasing frequency of microbial resistance has been emphasized in articles in AAC. Over selected 2-year periods between 1972 to 1973 and 1997 to 1998, the percentage of articles in which antimicrobial resistance was a principal focus increased from 11 to 34% (Table 3). In 1972 to 1973, 83% of papers on resistance concerned bacteria (Table 4). This percentage subsequently increased, reaching 96% in 1988 to 1989. Over the next decade this percentage declined to 77%, paralleled by increases in the frequency of papers concerned with drug resistance in mycobacteria, parasitic agents, fungi, and viruses. Whereas the focus of antimicrobial resistance among fungi in 1972 to 1973 was on resistance to 5-fluorocytosine in strains of *Cryptococcus neoformans*, *Candida albicans*, and *Candida glabrata*, in 1997 to 1998 it was on fluconazole resistance in *C. albicans*, *C. glabrata*, *Candida krusei*, and *C. neoformans* and on resistance to itraconazole and amphotericin B in *Aspergillus fumigatus*.

In 1972 to 1973 the few papers on resistance to antiviral agents dealt with resistance to cytosine arabinoside in HSV. In 1992 to 1993 the major focus was on HIV-1 and its emerging resistance to nucleoside reverse transcriptase inhibitors (RTIs) such as zidovudine, dideoxyinosine, and dideoxycytosine and to nonnucleoside RTIs and, to a much lesser extent, on HSV resistance to acyclovir. In 1997 to 1998 most papers dealing with viral drug resistance concerned HIV-1 (more often resistance to protease inhibitors than to either nucleoside or nonnucleoside RTIs) and, to a lesser extent, cytomegalovirus (resistance to ganciclovir, foscarnet, or cidofovir). Just appearing in the most recent period have been rare papers describing resistance to neuraminidase inhibitors of influenza virus and resistance to lamivudine in HBV.

Reports of drug resistance in parasitic organisms changed considerably in AAC articles over the past 27 years: whereas in 1972 to 1973 the only resistances (to chloroquine and antifolate drugs) described were in *Plasmodium falciparum*, by 1998 to 1999 resistances were noted not only in *P. falciparum* (to cycloguanil, to pyrimethamine-sulfadoxine, and multidrug resistance) but also in other protozoa such as *Leishmania* spp. (to pentavalent antimonials and amphotericin B) and *T. cruzi* (to benznidazole) and *Trypanosoma brucei* (to pentamidine and difluoromethylornithine). Between 1978 to 1979 and 1988 to 1989, fewer than 1% of articles in AAC dealing with resistance (Table 4) concerned mycobacteria. By 1992 to 1993 and 1997 to 1998 this had risen to 3 and 5%, respectively, coinciding with the resurgence of tuberculosis and AIDS-associated *Mycobacterium avium* complex infections. In the first four periods analyzed (Table 4), the mycobacterial species engendering resistance was *Mycobacterium tuberculosis* and resistances were to isoniazid, streptomycin, and pyrazinamide. In the last two periods, *M. tuberculosis* and atypical mycobacteria were involved

TABLE 4. Antimicrobial resistance papers in AAC: categories of organisms for which resistance is described

Organism category	% of total articles dealing with resistance relating to each category of organism in[a]:					
	1972–1973	1978–1979	1982–1983	1988–1989	1992–1993	1997–1998
Bacteria	83	94	93	96	87	77
Anaerobes	8	9	8	4	5	2[e]
Enterobacteriaceae						
E. coli	20[c]	12[c]	13	13[c]	6	7
Other	20[c]	16[c]	14[c]	18[c]	9	18[c]
Enterococcus spp.		7	5	11	31[c]	13[c]
H. pylori						4
H. ducreyi			4			
H. influenzae and *H. parainfluenzae*		7	4			
N. gonorrhoeae		9		3[e]		2
P. aeruginosa	20[b,c]	8	14[c]	11	10[c]	9
S. pneumoniae		4[e]	3		5	13[c]
S. aureus	17	13[c]	15[c]	12[c]	17[c]	15[c]
Staphylococci (coagulase negative)	6		4	6	2[e]	3[e]
Streptococci (group A)	6					2[e]
Streptococci (viridans type)			4			
Other[d]	3[e]	14	12	15	13	11
Fungi	4	1	1	1	2	7
Mycobacteria	4		1	0.5	3	5
Parasitic agents	4	3	2	0.5	2	4
Viruses	4	1	3	2	7	7

[a] Twenty-four-month periods.
[b] Numbers refer to the percentage of articles dealing with resistant bacteria.
[c] The three bacterial species with highest percentages in each 2-year period.
[d] All other species in the aggregate.
[e] Only species accounting for ≥4% in at least one 2-year period are listed.

almost equally; resistance in *M. tuberculosis* was most commonly to isoniazid, rifampin, pyrazinamide, or ethambutol or was multidrug resistance.

The ebb and flow of drug-resistant pyogenic bacterial species over the past 27 years have been accurately captured in the pages of AAC (Table 4). In 1972 to 1973, four species categories (*P. aeruginosa*, *E. coli*, other *Enterobacteriaceae* spp., and *S. aureus*) were the focus of almost 80% of articles on antimicrobial resistance. By the next period, these species accounted for only 50% of articles on antimicrobial resistance, while those on resistance in *N. gonorrhoeae* (β-lactamase-II and non-β-lactamase-producing strains), *H. influenzae* (R-plasmid-encoded β-lactamase), and *Enterococcus* spp. (R-plasmid-containing strains mediating streptomycin resistance and an early paper describing R-plasmid-based gentamicin inactivation) began to appear. In 1988 to 1989 articles about the same organisms (*P. aeruginosa*; *E. coli*; *Klebsiella*, *Enterobacter*, and *Citrobacter* spp.; and *S. aureus*) for which antimicrobial resistance was most frequently cited in the preceding 2-year period were again most frequently published, accounting for just over half of the articles dealing with resistance. In the same period articles on coagulase-negative staphylococci (mainly methicillin resistant but a few gentamicin or macrolide resistant) peaked in frequency (6% of articles on drug resistance). Also, at the same time the number of articles dealing with resistance among *Enterococcus* spp. began to increase (11%), going on to peak at 31% of articles in 1992 to 1993 (Table 4). In the latter 2-year period the four organism categories most frequently noted for antimicrobial resistance in AAC articles were *Enterococcus* spp., *S. aureus*, *P. aeruginosa*, and other *Enterobacteriaceae* (*Klebsiella*, *Serratia*, *Citrobacter*, and *Salmonella* spp.), in decreasing frequency. In 1992 to 1993 the problem of resistance to penicillin and extended-spectrum cephalosporins and macrolides in *S. pneumoniae* became more evident, appearing as the focus of 5% of AAC articles dealing with bacterial antibiotic resistance. In 1997 to 1998 papers dealing with drug resistance in *S. pneumoniae* comprised 13% (penicillin in about two-thirds of instances and quinolones, macrolides, trimethoprim, and sulfonamides in the remainder). *S. pneumoniae*, *Enterococcus*, and *S. aureus* were the subject of about 40% of AAC papers concerned primarily with antibiotic resistance.

Mechanisms of resistance reported in AAC papers have changed over time, as judged by titles of articles (Table 5). In 1972 to 1973, articles describing R-plasmid-based resistances comprised the leading category (45%). Over the succeeding five periods this steadily declined, ultimately reaching less than 4%. This decrease is largely artifactual, since in the later periods the titles of many articles focused on expanded-spectrum β-lactamase mechanisms of resistance that, in fact, are often R-plasmid mediated. Similarly aminoglycoside resistance described in some articles is R-plasmid based, but it is included only under aminoglycoside resistance, based on the article title (Table 5).

The leading mechanism of resistance in articles in AAC has consistently been β-lactamase production (e.g., penicillinase in *S. aureus*, carbenicillin resistance in *P. aeruginosa*, and cephalosporinase activity in *Bacteroides fragilis*). By 1992 to 1993 and 1997 to 1998 the emphasis was predominantly on β-lactamases active on extended-spectrum cephalosporins, of both R-plasmid and chromosomal origins. These include a variety of plasmid-mediated extended-spectrum and other β-lactamases and transposon-associated OXA enzymes in *P. aeruginosa*. Plasmid-mediated metallo-β-lactamases with the disturbing ability to hydrolyze carbapenems such as imipenem, drugs resistant to most other β-lactamases, have appeared in *Aeromonas* spp. and had been noted earlier in *Serratia marcescens*, *P. aeruginosa*, and *B. fragilis*. In addition, chromosomal β-lactamases that hydrolyze extended-spectrum cephalosporins have been

TABLE 5. Antimicrobial resistance papers in AAC: types of resistance among bacteria

Resistance (drug or mechanism)[b]	% of articles in[a]:					
	1972–1973	1978–1979	1982–1983	1988–1989	1992–1993	1997–1998
Aminoglycoside	15	19	15	11	14	6
β-Lactam resistance						
β-Lactamase	15	23	17	29	26	22
Methicillin (new penicillin binding protein)	5	3	7	9	7	4
Outer membrane protein alterations (β-lactams)				5	12	1
Recombinant penicillin binding proteins (*S. pneumoniae*)						7
Chloramphenicol	12	4	1	2		
Ethambutol						1
Fluoroquinolone				15	10	19
Isoniazid	2				1	1
Macrolide-lincosamide-streptogramin	7	4	3	4	1	4
Multidrug efflux						5
Multidrug resistance (Mar)						2
Mupirocin					1	
Polymyxin-colistin	5		2			
Pyrazinamide			1			0.5
Rifampin					2	2
R plasmids	45	30	29	19	3	
Sulfonamides				2		1
Tetracycline	12	2		7	6	2
Trimethoprim			3	2	1	1
Transposons				4	3	
Vancomycin-teicoplanin				4	9	5

[a] Twenty-four-month periods.
[b] Gleaned from title of article.

described for strains of *P. aeruginosa* and *Burkholderia cepacia*. The overall functional classification of β-lactamases has been thoroughly reviewed by Bush et al. in AAC (1), as has the subject of carbapenem-hydrolyzing β-lactamases (15).

Although articles with a major focus on β-lactamases in 1992 to 1993 and 1997 to 1998 have dealt with these enzymes in gram-negative bacillary species, in the 1990s a number of articles dealing with the new problem of penicillinase-producing *E. faecalis* strains appeared. In 1992 to 1993 one-fifth of the 44 articles in AAC dealing with antibiotic resistance in enterococci involved penicillinase-producing strains. Vancomycin resistance among enterococci, an increasing problem clinically in the late 1980s and throughout the 1990s, was the subject of 4 to 9% of articles in AAC dealing with bacterial resistance to antimicrobial drugs (Table 5). Two phenotypes (Van A and Van B) with high-level inducible resistance in *E. faecalis* and *E. faecium* were described most often. This form of resistance can be transferred by conjugation and is often mediated by transposons. A low-level, constitutive (Van C) type of resistance carried on the chromosomes of *Enterococcus gallinarum* and *Enterococcus casseliflavus* appeared much less commonly in articles in AAC.

A potential problem with vancomycin resistance in a few nosocomial *S. aureus* strains was observed first in Japan in 1997 and subsequently in the United States. These strains have been methicillin resistant and characterized by intermediate levels of susceptibility to vancomycin and other glycopeptides and thus have been named vancomycin-intermediate *S. aureus* or glycopeptide-intermediate *S. aureus*. The evaluation of susceptibilities of such strains to other antimicrobials and drug combinations has already been reported in AAC (7).

Emergence of resistance to fluoroquinolones and delineation of their mechanisms in clinical isolates have been reported in ACC, comprising 10 to 20% of articles dealing with antimicrobial resistance in the past decade.

SUSCEPTIBILITY

Many studies on antimicrobial susceptibilities of various bacterial species in AAC in the past 27 years were included in the numerous articles describing new antimicrobials. AAC has also provided valuable information on antimicrobial susceptibilities of species less commonly encountered in the clinical microbiology laboratory: *Yersinia enterocolitica*, *Brucella melitensis*, *Pseudomonas pseudomallei*, *Chlamydia pneumoniae*, *Bartonella quintana* and *Bartonella henselae*, *Bacillus cereus*, *Mycobacterium marinum*, *Rhodococcus equi*, and *Ehrlichia chaffeensis* and human granulocytic *Ehrlichia*. Within a year or so of isolation of the bacillus of Legionnaires' disease, the susceptibility of extracellular and intracellular *Legionella pneumophila* to erythromycin and rifampin was described in AAC. This was followed by delineation of the susceptibilities of *Legionella micdadei*. Data were updated over subsequent years in articles describing susceptibility to fluoroquinolones, the newer macrolides, and azalides. In 1983, when antibiotic susceptibility testing of strict anaerobes was not reliably performed, AAC published the first of a series of articles from collaborating centers describing susceptibilities of strains of the *B. fragilis* group (18).

During its lifetime AAC has been a major resource for reporting state-of-the-art procedures for antimicrobial susceptibility testing. These have included interpretive criteria for disk diffusion susceptibilities, systems (time-kill, checkerboard, and E-test) for detecting antibiotic synergism, rapid testing for β-lactamase production utilizing chromogenic β-lactam substrates, attempts at standardization of susceptibility testing of fungi, use of isoelectric focusing and oligonucleotide probes for detection and characterization of β-lactamase-producing strains, radiometric methods for determining in vitro susceptibility, and rapid susceptibility testing of *M. tuberculosis* by bioluminescence assay of mycobacterial ATP. Postantibiotic ef-

fects of various antibiotics (β-lactams and aminoglycosides) on selected microorganisms utilizing electronic and viability counting and CO_2 generation methods have been described in AAC.

PHARMACOLOGY

AAC articles have been leading sources of information on the pharmacology of antimicrobial agents. Much of the data on pharmacokinetics of aminoglycosides (gentamicin, tobramycin, amikacin, and sisomicin) appeared in its pages during the 1970s. Articles on the use of blood gentamicin levels to avoid nephrotoxicity appeared during this period. Dosage schedules for aminoglycosides in patients with renal impairment were defined. The entry of aminoglycosides into bone, bronchial secretions, and synovial fluid after parenteral administration was described. The comparative ototoxicities of amikacin and gentamicin were studied in a feline model. In the 1990s careful pharmacokinetic studies provided a safe basis for use of once-daily aminoglycoside dosing (3).

Studies in AAC reported on the comparative pharmacokinetics of the early oral cephalosporins and parenteral cefamandole, cefuroxime, cefoxitin, and cefotetan. Extensive studies of the pharmacokinetics of expanded-spectrum cephalosporins followed in the 1980s. Methyltetrazolethiol side-chain-containing cephalosporins (cefamandole, cefotetan, cefoperazone, and moxalactam) were reported to cause a bleeding diathesis (due to hypoprothrombinemia) and disulfuram-type reactions in patients taking alcohol. Demonstrations of bactericidal levels of ceftriaxone and cefotaxime in cerebrospinal fluid (CSF) were instrumental in initiating the use of these antibiotics in treatment of community-acquired bacterial meningitis.

With the increased use of vancomycin in the 1980s, further attention was paid to its pharmacokinetics, its tissue penetration, and the monitoring of levels in serum for efficacy and avoidance of nephrotoxicity.

The pharmacokinetics of the monobactam aztreonam was reported in the late 1970s in AAC. The carbapenems imipenem-cilastatin and meropenem, which are exceedingly resistant to most plasmid and chromosomal β-lactamases, have been studied in regard to pharmacokinetics, their penetration into inflammatory exudates, and particularly their penetration into CSF in cases of meningitis.

The fluoroquinolones, starting with norfloxacin in the 1980s, have been described in AAC in regard to pharmacokinetics, concentrations in specific tissues, oral bioavailability, and drug interactions. Congeners studied have included enoxacin, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin.

Reports in AAC have documented the pharmacokinetics of a new macrolide, azithromycin, with an extended half-life and excellent tissue distribution. Pharmacokinetics of β-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) alone and in combination with specific β-lactams (amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) have been described as well.

Newer antimycotic agents (ketoconazole, fluconazole, and itraconazole) have been reported on in AAC since the early 1980s in terms of pharmacokinetics, oral bioavailability, side effects, renal excretion, and penetrance into CSF. Pharmacokinetics of newer lipid formulations of amphotericin B with less toxicity and comparable efficacy have also been studied.

Starting in the 1980s the development of antiviral agents blossomed, and most of the important pharmacologic studies appeared in AAC. Initially, these involved studies of single-dose oral and intravenous pharmacokinetics of acyclovir, followed later by studies of famciclovir and ganciclovir. The outbreak of AIDS in the mid-1980s accelerated the development of agents active against HIV and against other opportunistic virus infections in patients with AIDS. Such antiviral drugs required pharmacologic studies, many of which were reported in AAC, before clinical evaluation. Early studies involved the pharmacokinetics of oral zidovudine in hemophiliacs with HIV infection. Pharmacokinetics of other nucleoside analogs (stavudine, lamivudine, didanosine, and zalcitabine) and nonnucleoside RTIs (e.g., nevirapine) in nonhuman primates and in humans were subsequently reported. The major addition to the anti-HIV armamentarium during the late 1990s has been that of the protease inhibitors (e.g., ritonavir, indinovir, saquinavir, and nelfinavir), all of which were studied pharmacokinetically in patients with HIV infection and described in articles in AAC. Importantly, their pharmacokinetics have been examined when used in combination with RTIs (e.g., the combination of saquinavir with zidovudine and zalcitabine). Pharmacokinetics in healthy individuals demonstrated interactions between the two protease inhibitors ritonavir and indinavir, where ritonavir appeared to inhibit metabolism of indinavir, substantially raising indinavir concentrations.

Lamivudine has a place in multidrug treatment of HIV infection, but it has also achieved a role in treatment of chronic HBV infection. To develop dosing programs, the pharmacokinetics of this drug were established for an animal model of chronic HBV infection in the woodchuck and for humans as well, both of which were reported in AAC.

EXPERIMENTAL THERAPEUTICS

Since the mid-1970s animal models of infection have been employed to investigate issues of pathogenesis and therapeutics in articles in AAC. Among the most frequently studied have been animal models of bacterial endocarditis and meningitis. One such study of experimental enterococcal endocarditis in the rabbit showed that the combination of penicillin with streptomycin or gentamicin increased the rate of bacterial killing in vegetations compared with the use of penicillin alone when the infecting strain was susceptible to streptomycin (9). When the infecting strain was highly resistant to streptomycin, only the combination of penicillin with gentamicin was more effective than penicillin alone. Over succeeding years newer antibiotics have been tested in the treatment of experimental endocarditis due to problematic microorganisms such as MRSA, penicillin-tolerant viridans streptococci, and, most recently, β-lactamase-producing enterococci. Such models have been helpful in suggesting which therapies might be effective clinically.

Animal models of bacterial meningitis have been helpful in providing insights into a variety of problems in therapy: the efficacy of newer drugs (e.g., expanded-spectrum cephalosporins in gram-negative bacillary meningitis; vancomycin, ceftriaxone, and meropenem alone and in combination in meningitis due to penicillin- and cephalosporin-resistant *S. pneumoniae*) and the influence of dexamethasone on efficacy of vancomycin therapy of experimental pneumococcal meningitis (2).

Many other experimental models of infection have been described in the pages of AAC during the past quarter-century. These have included tetracycline-associated pseudomembranous colitis in the hamster (due to tetracycline-resistant, toxin-producing *Clostridium difficile*), ocular infections (*P. aeruginosa* keratitis and candidal endophthalmitis), cryptococcal meningitis and candidal pyelonephritis treated with fluconazole and itraconazole, *L. pneumophila* and *Legionella micdadei* pneumonia in guinea pigs, a murine model of toxoplasmic encephalitis

treated with clindamycin, and a rat model of foreign-body infection due to MRSA successfully treated with antibiotic combinations. Many animal models developed in recent years to study the chemotherapy of a variety of viral infections (HSV and cytomegalovirus in mice and influenza virus in mice and ferrets) have been reported on in AAC.

CLINICAL THERAPEUTICS

Reports of clinical trials have been included in AAC since its beginning. One of the earliest dealt with the long-term follow-up of chronic typhoid carriers previously treated with ampicillin plus probenecid for 6 weeks (12). During the 1970s, clinical trials of newer antibacterial drugs (e.g., cefazolin, cefoxitin, and netilmicin) in a variety of serious bacterial infections were reported. Starting in the 1970s and continuing to the present, AAC has reported trials of various regimens for empiric treatment of febrile granulocytopenic patients with cancer. These have encompassed studies of antibiotics based on changes in the major infecting species and their resistance patterns over time. In the 1970s these included comparisons of ticarcillin-tobramycin with cephalothin-tobramycin and ticarcillin-cephalothin. In the 1980s trials of cefoperazone versus cefoperazone-amikacin and of ceftazidime alone versus ceftazidime-flucloxacillin were included. In the past decade initial monotherapy of ceftazidime versus imipenem-cilastatin and meropenem monotherapy versus ceftazidime plus amikacin were studied.

Many clinical trials of antibiotic therapy of acute bacterial meningitis have been reported in AAC over the past three decades. In the 1970s these included trials of carbenicillin and ampicillin; in the 1980s, trials of cefuroxime and ceftriaxone compared with ampicillin plus chloramphenicol in childhood meningitis; and in the 1990s, vancomycin for therapy of adult pneumococcal meningitis and trials comparing meropenem with cefotaxime. In 1995 management of meningitis caused by penicillin-resistant *S. pneumoniae* was reviewed in AAC (13). These studies, and many others in AAC, have helped clinicians keep current with changes in antibiotic management in an era of evolving antimicrobial susceptibilities.

Other bacterial infections in which the etiologic agent has undergone successive changes in susceptibility have been reported often in AAC. These include gonorrhea and studies of ceftriaxone and trials of single-dose ofloxacin versus amoxacillin-probenecid. Other diseases in which resistance to previously used antibiotics has become problematic include bacterial endocarditis and typhoid fever. Among studies on the former is one evaluating teicoplanin in endocarditis caused by gram-positive bacteria; among studies on the latter are trials in the 1990s comparing ceftriaxone for 5 days with chloramphenicol for 2 weeks and a trial of ciprofloxacin in children.

Nasal colonization with *S. aureus* and nasopharyngeal colonization with *N. meningitidis* may be factors in dissemination of the infecting microorganism within the carrier host or dissemination to others. Trials of eradication of nasal carriage of MRSA in AAC have included use of minocycline-rifampin plus topical mupirocin. Studies of successful reduction of the meningococcal carrier rate in army recruits in Finland involved use of ciprofloxacin.

In the early 1980s, a number of articles describing clinical trials of antiviral and antifungal drugs began appearing in AAC. Initially, these included trials evaluating pharmacokinetics and side effects of interferon and adenine arabinoside in therapy of chronic HBV infection. Another reported on the safety of prolonged administration of rimantadine in prophylaxis of influenza A infections in nursing home patients. By the late 1980s reports on treatment of opportunistic viral infections (e.g., cytomegalovirus retinitis) in patients with AIDS began appearing in AAC. In the 1990s, after the widespread use of protease inhibitors in the treatment of HIV infections, articles describing the emergence of protease inhibitor resistance mutations in HIV isolated from patients appeared in AAC.

Among clinical reports of antifungal therapy in the past 15 years have been descriptions of toxicity of high-dose ketoconazole for treatment of nonmeningeal and meningeal coccidioidomycosis, high-dose fluconazole as salvage therapy for cryptococcal meningitis in patients with AIDS, and the response to antifungal therapy of patients with disseminated *Penicillium marneffei* infections. The occurrence of *Torulopsis glabrata* infections during fluconazole prophylaxis in patients with bone marrow transplantation was pointed out in another study.

Since its establishment 27 years ago, AAC has achieved a position of leadership among publications dealing with antimicrobial therapy of infectious disease. It has done so through its full coverage of all aspects of antimicrobial chemotherapy—chemical features of new drugs, their mechanisms of action, the spectrum of susceptibilities, the development of resistance (genetic and biochemical bases of such resistance), treatment of experimental models of infection, pharmacologic studies, and treatment trials. One can look forward in this new century to the continued development of new antimicrobial agents and to the description of their development in the pages of AAC as a leader in its field.

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