ANTIMICROBIAL MANAGEMENT: PAY NOW OR PAY LATER

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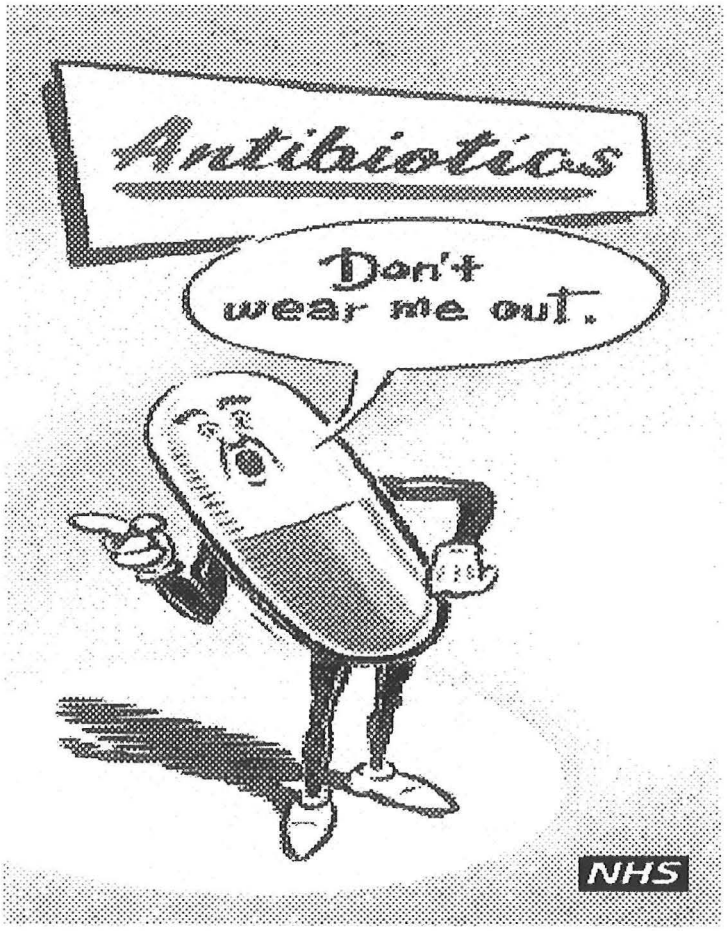

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This is to acknowledge that Dr. Skiest has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Skiest will be discussing off label uses in his presentation.

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Interests:

Opportunistic Complications of HIV/AIDS

Timing of Antiretroviral Therapy

Antimicrobial Management Programs

Antimicrobial Management: Pay Now or Pay Later

I. Overview of the Problem

Antimicrobials have led to dramatic advances in medical care in the past 65 years. The discovery of penicillin by Alexander Fleming in 1928 followed by its first clinical use in the 1942 dramatically altered the course of modern medicine [2]. The practice of medicine can be divided into the pre-antibiotic era and the post antibiotic era. Many infections, which were untreatable and sometimes lethal in the pre-antibiotic era, are easily treated with relatively simple antibiotics in the post antibiotic era. However, shortly after antibiotics came into widespread use, antibiotic resistance emerged. Bacteria and other organisms quickly evolved mechanisms to evade killing and containment by antimicrobials. The pharmaceutical industry has responded by developing and marketing new, more expensive antimicrobial agents. Invariably however, a vicious cycle develops. After the introduction of new antibiotics it is only a matter of time before resistance develops. Then another new antibiotic is introduced, which is again followed by resistance to the new agent(s). A corollary of this phenomenon is that antimicrobial costs continue to increase.

II. Reasons for Increased Costs of Antimicrobials

In recent years the costs of pharmaceutical agents have risen dramatically- a trend which is expected to continue at an even greater rate in the next decade. In 1980, the nation spent $12 billion on drugs, amounting for 4.9 percent of total health care spending. By 2000, the nation's medication costs had risen to $121.8 billion, or 9.4 percent of total health care costs (http://www.allhealth.org/sourcebook2002). Prescription drug costs increased 18 percent in 2000 and 17 percent in 2001 [3].

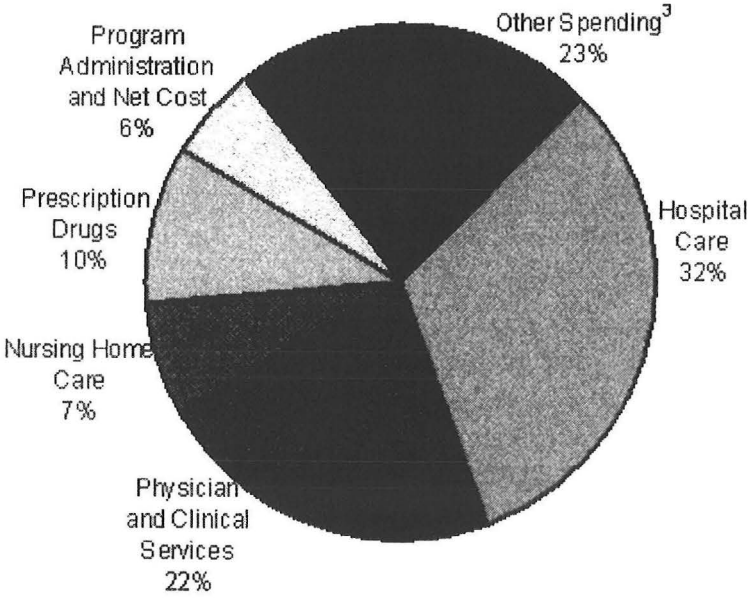
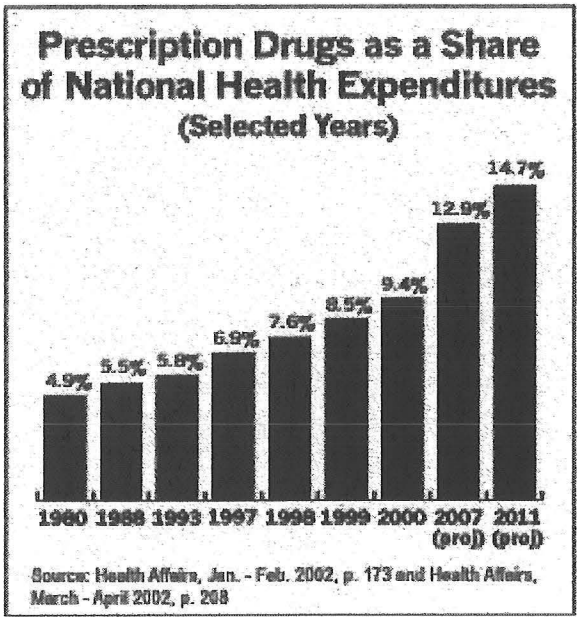


Figure. U.S. Health Care Expenditures in 2000, Source: Centers for Medicare and Medicaid Services http://cms.hhs.gov/statistics/nhe/historical/chart.asp



From reference [4]

Reasons for the increased costs of pharmaceutical agents are myriad. First, patients are taking more medicines. The average person had 10.3 prescriptions filled in 2000, compared with 8.3 five years earlier. For example the indications for cholesterol lowering agents have widened significantly in the past ten years. Second, conditions which were previously not treatable are now treatable with newer medications. Third, while new medications offer important benefits to patients the costs to develop new medications and to bring them to market are substantial. Most new drugs are actively promoted and advertised, which is associated with higher costs. The average price of the 50 top selling drugs in 2001 was $71.56 compared with an average price of $40.11 for all other prescription drugs. Sales of these drugs surged 34 percent in 2001. In addition, in order to reach the bottom line, companies may inappropriately promote medications for areas in which they are not required e.g. for upper respiratory infections.

Because a pharmaceutical company only has 20 years from filing a patent to have exclusive marketing rights, the company feels pressure to charge the maximal amount for each new medication, in order to recoup research and development costs and return maximal dividends for shareholders. Finally, generic medicines, which typically cost several -fold less than non-generic medications are usually not marketed to prescribing physicians and other health care providers. Physicians may are often convinced by pharmaceutical companies that "newer means better". Generic drugs accounted for 45 percent of retail prescriptions written in 2001, however, because they are so inexpensive they accounted for only 8 percent of spending on prescriptions.

Increasing Costs of Antimicrobials

The high costs of new pharmaceutical agents include antimicrobials, which are the second most commonly used class of drugs. Approximately 200-300 million antimicrobial agents are prescribed annually at a cost 7 billion dollars [5]. Antimicrobials constitute a significant portion of inpatient and outpatient pharmaceutical costs. It has been estimated that 25-50% of inpatients receive antibiotic therapy [6], a figure which is significantly higher for ICU patients. In most hospitals, approximately 20-50% of hospital pharmacy expenditures are for antimicrobials [6, 7]. Thus, given the high costs of antimicrobials a solid argument could be made to limit their use. However, costs are not the only reason to limit the use of antimicrobial agents.

III. Antimicrobial Resistance

Antimicrobial agents are unique with respect to other drugs in that the consequences of use and misuse have implications beyond the patient being treated. If the incorrect or sub-optimal drug is used to treat hypertension in an individual patient there may be consequences for that patient, e.g. the patient may have side effects or the blood pressure may not be adequately treated. However, these problems will not extend to other patients or to the population at large. The same cannot be said for antimicrobial agents (discussed below).

If a patient is treated inappropriately there are several potential consequences for that patient including side effects, super-infection, and the development of resistant organisms. Estimates are that approximately 5% of inpatients receiving an antibiotic experience an adverse reaction. Such adverse effects range from mild (nausea), to moderate (rash or diarrhea) to life threatening (anaphylaxis from a penicillin derivative). Due to the frequency of antibiotic use in the inpatient setting antimicrobials accounted for 23% of all adverse drug events in one hospital [8].

Societal Consequences of Resistance

Arguably a more important consequence of antimicrobial use and misuse are the consequences to the general population. Overuse or misuse of antibiotics may result in resistant organisms developing within a particular patient. This organism can then be transmitted to other individuals either within the hospital setting or in the community. Spread of resistant organisms thus can impact society at large. This results in increase in costs both directly and indirectly. Furthermore resistance is associated with substantial morbidity and mortality in instances where alternative agents to treat resistant organisms are not available or are more toxic compared with agents used to treat susceptible organisms.

Overuse of antibiotics is associated with both direct and indirect costs in terms of morbidity and dollars. Inappropriate peri-operative surgical prophylaxis is a common scenario. One study documented that surgical prophylaxis exceeded the recommended duration of one day in 61% of patients and resulted in an increase in bacteremias, catheter infections and cost [9]. Of the 2 million patients who experience a nosocomial infection per year, about one-fifth are caused by resistant organisms. Such infections result in significant morbidity and mortality [10, 11]. Nosocomial infections with resistant organisms result in prolonged hospital stays and a substantial economic cost, estimated at 4-4.5 billion dollars per year [11-13]. One estimate of the increased direct and indirect annual costs associated with microbial resistance was $100 million to $30 billion [14, 15].

While the most dramatic consequences of resistance are seen with hospitalized patients, outpatients are certainly not immune to the problem. In recent years in the outpatient setting we have witnessed the emergence of penicillin resistant pneumococcus, community acquired methicillin resistant *Staphylococcus aureus*, macrolide resistant streptococci, vancomycin resistant enterococci and urinary *E. coli*

isolates with resistance to trimethoprim-sulfamethaxozole. Most alarming is the recent report of vancomycin resistant *S. aureus* in a patient who received prolonged vancomycin therapy [16].

IV. Causes of Antimicrobial Resistance

In 1941 prior to the widespread use of penicillin, all *S. aureus* strains were susceptible to penicillin. Only three years later *S. aureus* were isolated which produced an enzyme capable of destroying penicillin (penicillinase). Alexander Fleming who discovered penicillin in 1928, was among the first to warn of the potential consequences of misuse of antibiotics e.g. the potential for resistant bacteria [2].

While antimicrobial resistance was noted shortly after the introduction of antibiotics, it is a problem, which is clearly increasing. What are the causes of the increase in bacterial and fungal resistance? There is a large body of evidence indicating that overuse and misuse of antibiotics play a substantial role in the increase in resistance [17-20]. Levy formulated five principles of antimicrobial resistance which emphasize the importance of antibiotic use as a risk factor [21].

Principles of antimicrobial resistance

1. Antibiotic resistance is progressive, evolving from low levels through intermediate to high levels.
2. *Organisms that are resistant to one drug are likely to become resistant to other antibiotics.*
3. Once resistance appears, it is likely to decline slowly, if at all.
4. *The use of antibiotics by any one person affects others in the extended as well as the immediate healthcare environment.*
5. The use of antibiotics by any one person affects others in the extended as well as the immediate healthcare environment.

From Levy, S [21]

The recent trends toward broader spectrum antibiotics in the inpatient and outpatient settings is likely to worsen the problem. Physicians frequently prescribe antibiotics to adults with viral upper respiratory tract infections despite numerous studies demonstrating a lack of benefit. A study by Steinman and colleagues found that the use of broad spectrum antibiotics in the outpatient setting in adults increased from 24% in 1991-92 to 48% in 1998-99 [22]. Furthermore, 22% of prescriptions were for viral respiratory infections, which did not require antibiotics. The new broad spectrum fluoroquinolones appear to be especially overused. A recent study suggested that of 100 consecutive emergency department patients who were discharged on a fluoroquinolone, only 19 were treated appropriately [23]. In the inpatient setting a recent study demonstrated increasing resistance of gram negative bacteria in ICUs in the U.S. [24]. The largest increase in resistance of the gram negative bacilli in this study was to ciprofloxacin which was noted to be coincident with the marked increased use of fluoroquinolones.

Mechanisms of Resistance

Selective pressure caused by the use of certain antimicrobials leads to the emergence of mutant organisms with specific resistance mechanisms. Bacteria have evolved various mechanisms of resistance over the years but most involve three major mechanisms: alteration of the target site, preventing access to the target site and inactivation of the antibiotic. Specific examples of bacterial resistance mechanisms are shown in the table below.

An example of an altered target site is MRSA in which a bacterial gene known as mecA, produces an altered penicillin-binding protein (the usual B-lactam antibiotic binding site), such that it will not bind penicillin or any B-lactam antibiotic. An example of preventing access to the target site is demonstrated by *Pseudomonas aeruginosa.* Resistant organisms can lose porin channels , thus not allowing penetration of certain antibiotics such as carbapenems and aminoglycosides. The classic example of inactivation of antibiotics occurs with B-lactam antibiotics in which the production of an enzyme (B-lactamase) cleaves the B-lactam ring of B-lactam antibiotics.

Examples of resistance mechanisms (adapted from Shlaes, reference [19])

Antibiotic	Mechanism	Genetic basis	Examples
B-lactams	Altered penicillin binding targets	Chromosomal	S. aureus
Penicillins			S. pneumoniae
Cephalosporins			S. epidermidis
Carbapenems			H. influenzae
Monobactams			N. gonorrhoeae
			N. meningitides
			E. coli
			P. aeruginosa
	B-lactamase inactivation	Chromosomal and plasmid	S. aureus
			Enterococci
			Enterobacteriaceae
			S. epidermidis
			N. gonorrhoeae
			N. meningitides
			P. aeruginosa
	Reduced permeability	Chromosomal	S. marcescens
			Klebsiella spp.
			Enterobacter spp.
			P. aeruginosa
Macrolides and lincosamides	Methylation of rRNA target	Chromosomal and plasmid	Streptococci
			Enterococci
Erythromycin			S. pneumoniae
Clarithromycin			Staphylococci
Azithromycin			
Clindamycin			

	Modifying enzyme inactivation	Plasmid	Streptococci Enterococci Staphylococci
Aminoglycosides Amikacin Gentamicin tobramycin	Reduced permeability	Chromosomal	Enterobacteriaceae P. aeruginosa
	Altered ribosomal target binding	Chromosomal	Streptococci
Tetracyclines	Efflux	Plasmid	Streptococci Enterococci Staphylococci Bacteroides Haemophilus Enterobacteriaceae
	Altered ribosome target	Plasmid	Bacteroides N. gonorrhoeae
Folate inhibitors Trimethoprim- sulfamethaxazole	Altered targets	Chromosomal and plasmid	Streptococci Staphylococci S. pneumoniae Enterobacteriaceae Neisseria
Glycopeptides Vancomcyin	Altered target	Chromosomal and plasmid	Enterococci
Fluoroquinolones Ciprofloxacin Levofloxacin	Altered DNA gyrase target	Chromosomal	Staphylococcus Enterobacteriaceae
Rifampin	Altered DNA polymerase target	Chromosomal	Streptococci Staphylococci M. tuberculosis Enterobacteriaceae Neisseria

V. Relationship between antibiotic (mis)use and resistance

The problems associated with misuse of antibiotics have been recognized by opinion leaders for at least three decades [25]. It was recognized that physicians often view antibiotics as "drugs of fear" which leads to overuse [25]. A study from 1973 from a University teaching hospital suggested that antibiotics were used inappropriately in over half of patients [25].

There are numerous studies, which suggest a casual relationship between antibiotic use and the development of resistance [20, 26, 27]. Changes in antimicrobial usage are paralleled by changes in resistance prevalence. Antimicrobial resistance is more prevalent in nosocomial strains compared to community-acquired strains. Patients with resistant infections are more likely to have received prior antibiotics. There is a correlation between the areas of the hospital with the highest resistance rates and the highest rates of antimicrobial use. There is also a correlation between patient exposure to antimicrobials and the chances of colonization with resistant organisms [19]. However there are additional factors which contribute to the increase in antimicrobial resistance including prolonged hospital stays, severe illness, more immunocompromised patients,

the high rate of invasive devices, inadequate infection control practices, and antibiotic use in farm animals [28].

Factors Contributing to Increased Antimicrobial Resistance
Sicker inpatient population
Larger immunocompromised population
New procedures and instrumentation
Emerging pathogens
Ineffective infection control and compliance
Complacency regarding antibiotics
Increased antibiotic use

From Murthy et al [1]

A number of factors contribute to inappropriate use of antibiotics and thus to resistance [29]. The most significant resistant problems usually involve the intensive care units because of the severity of illness of these patients. These patients have more infections and are more immunocompromised and thus end up on antibiotics frequently. Frequently, patients are treated empirically either because cultures are not obtained or cannot be obtained for certain infections. Even when cultures are obtained there is a typical delay of several days warranting use of antibiotics up front to improve outcomes. However, antibiotics are often continued despite negative cultures and despite lack of objective evidence of infection. This leads to prolonged antibiotic exposure, thus increasing the risk for resistance as well as the costs. In the modern healthcare system with an emphasis on outpatient treatment and shorter hospital stays there is tremendous pressure to keep patients out of the hospital and to discharge admitted patients early. This also leads to overuse of antibiotics especially broad spectrum antibiotics, because of the prevailing belief that broad spectrum antibiotics are more potent and will treat the infection more quickly, allowing faster hospital discharge and/or allow the patient to be treated at home.

Treating physicians are motivated by several factors including wanting to provide the best care for each patient. They may be concerned about " not wanting to miss anything" which may stem from both a desire to provide the best care and a fear of litigation. This often leads to inappropriate prescribing of overly broad-spectrum antibiotics. Another factor which may lead to inappropriate prescribing practices is that physicians may have inadequate knowledge of the particular antimicrobial or the infection they are treating. Interestingly, although physicians perceive antibiotic resistance to be a very important problem nationally, they are less likely to believe it to be a major problem at the local level [30].

Often the most complicated patients, with the highest risk of infection and resistance are admitted to teaching hospitals. Ironically, in this setting the physicians with the least experience and knowledge (e.g. interns and residents) are often the ones making antibiotic decisions, which may lead to incorrect choices or incorrect dosing [31]. Knowing that prophylactic antibiotics have been shown to decrease infection rates in certain situations and desiring low infections rates in their patients some surgeons have a tendency to overprescribe antibiotic prophylaxis by extending the duration of prophylactic antibiotics for several days. This is despite numerous studies demonstrating that a single pre-operative dose is adequate [32].

In the outpatient setting other factors may be at play including pressure from a patient or parent to prescribe antibiotics for the common cold and other viral infections. As managed care and other insurers have shortened available time per patient and reduced reimbursement rates physicians feel the time constraints, which in many cases make it easier and less time intensive to write a Z-pack than to explain why antibiotics are not needed for the common cold. Physicians may also be concerned about losing patients to another health care provider who freely prescribes antibiotics.

Finally, the impact of pharmaceutical company promotion cannot be underestimated. The pharmaceutical industry spent 15.7 billion dollars on 2000 on promotion of their products. In addition, to the usual promotion methods such as giveaways e.g., pens, penlights etc, free lunches and dinners and "educational seminars", which increase use of new antimicrobials, pharmaceutical companies appeal to clinicians to use new potent broad-spectrum antibiotics to avoid missing any rare organisms. More recently direct marketing to consumer-patients by pharmaceutical companies may be resulting in more demand for new antibiotics.

Factors that (Mis)Shape Antibiotic Use in Hospitals

Complex patients with more acute illness/ immunosuppression
Pressure to decrease LOS and limit admissions
Inappropriate prophylaxis
Overly broad spectrum antibiotics
Use of antimicrobials in cases without infections
Lack of cultures/ timing of cultures
Pressure from patients/ parents
Time constraints of physicians
Desire to cover all potential scenarios/organisms
Fear of litigation
Pharmaceutical Promotion

Clearly antimicrobial resistance is not going to disappear in the era of modern medicine. However, a relevant question is can we do anything to limit resistance or even diminish current resistance rates or is it a lost cause? There is some evidence to suggest that with concerted efforts antimicrobial resistance can be limited and even reversed in some cases. In general these approaches have been most successful when they have addressed a particular organism in a particular unit [26]. Examples include a multi-drug resistant Acinetobacter in the SICU in a Houston teaching hospital and a decrease in Group A streptococci macrolide resistance in Finland [33, 34]. Other examples include restriction of Ceftazidime in response to an increase in multidrug resistant *Enterobacter cloacae* in an ICU setting. This intervention resulted in an increase in Ceftazidime susceptibility from 54% to 75% [35].

Since 1989 the Joint Commission of Accreditation of Healthcare Organizations, has required hospitals to track their use of antimicrobials [36]. More recently the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America

issued joint guidelines for the Prevention of antimicrobial resistance in hospitals [19]. Recommendations included establishing a system for monitoring bacterial resistance and antibiotic usage; establishing practice guidelines to control the use of antibiotics; adopt CDC isolation and infection control guidelines; hold hospital administration accountable for such policies; and measuring of outcomes to evaluate the effectiveness of such policies. These guidelines emphasize the central role of hospital epidemiologists, pharmacists, infection control practitioners, microbiologists and physicians.

VI. Potential Solutions

Can costs of antimicrobials be controlled and resistance limited in a manner which does not have a negative impact on patient care? Again, as in the case of resistance, there are several experiences which suggest this can be done successfully and rationally and can simultaneously alleviate resistance problems. A number of different approaches have been studied and are listed in the table. In general there strategies can be divided into three main categories: educational initiatives, restrictions of various forms and pharmacy initiatives.

Strategies to Prevent resistance and limit costs
Limit unnecessary antibiotic administration
Hospital formulary restrictions
Protocols and guidelines
Antibiotic "streamlining"- recommendations to change dose, route
Automatic stop orders/order forms
Limit prophylactic/empiric antibiotic use
Prior approval programs
Optimize antimicrobial effectiveness
Antibiotic cycling or rotation?
Practitioner education programs
Lectures
one on one interaction/ detailing
performance evaluation
newsletters
cost data information
local MIC data
Use of combination antimicrobials?
New antimicrobial agents
Pharmacy initiatives
Antibiotic bidding
Pharmacy contracts
Computer assisted antibiotic selection
Optimize infection control practices

The Role of Education

Although educational initiatives are probably the most well accepted by practitioners [30], they are probably the least effective method [37]. Studies have shown that changing physician behavior is often difficult. There are various types of educational initiatives including lectures (including formal CME conferences, informal conferences, small group sessions, teleconferences etc), physician performance evaluations (chart audits with direct feedback), newsletters and one on one interactions. Lectures and other passive methods of education have generally been relatively ineffective. Inappropriate vancomycin use was successfully reduced by 30% in one study using a combination of administrative changes (revising perioperative antibiotic prophylaxis orders) and physician education [38]. However, this study was short term and the effect of the educational component was not clear. Physician performance evaluations have also been relatively ineffective [5]. More effective educational activities include direct physician interactions, as well as patient and peer feedback [39]. One-on one interactions (academic detailing) have arguably been the most effective type of educational program [40].

Academic Detailing

Academic detailing involves direct person-to person interaction between clinician specialists and prescribing physicians. Such an approach is similar to the very effective methods used by pharmaceutical company representatives to "detail" new medications to physicians. Typically the detailing presentation lasts about 10 minutes and involves an infectious disease physician or pharmacist and the prescribing physician. A recent example of a successful academic detailing program was reported from Brigham and Women's hospital [40]. In a randomized fashion investigators either provided academic detailing by clinician-educators, clinical pharmacists, or infectious disease physicians to Internal Medicine interns and residents (intervention group) or no detailing (control group) based on orders for either of two broad-spectrum antibiotics. The detailing consisted of information based on local hospital antibiotic guidelines, microbiologic results, local resistance data and cost data. Interns and residents were free to prescribe the antibiotic of their choice. The rate of unnecessary use of the 2 target antibiotics was 41% lower in the intervention group (95% confidence interval, 44%-78%). In addition, the antibiotic courses were significantly shorter in the intervention compared to the control group. No differences in outcomes (length of stay, readmission rates, mortality) were noted.

A somewhat similar educational approach involved an antimicrobial management team consisting of an Infectious Disease fellow and a clinical pharmacist at a teaching hospital [41]. Patients receiving one of 10 chosen parenteral antibiotics for at least 3 days were randomized to an intervention group or a control group (nonintervention group). Those in the intervention group received antibiotic suggestions from the antimicrobial team in the form of a removable note in the hospital chart. Antibiotic suggestions (choice, dose, route) were accepted 84% of the time and led to lower antibiotic costs

(almost $400 per patient, p = 0.05) with no negative effects on clinical or microbiologic response, in hospital mortality or readmission rates.

Academic Detailing Program:
Comparison of Mean Antibiotic Charges per Patient and Utilization

Variable	Intervention (n =141)	Nonintervention (n =111)	Difference
Antibiotic charges per pt $	1287.17	1673.97	-386.80
IV charges pt $	1232.49	1624.06	-391.57
PO charges pt $	54.69	49.91	4.78
Days of antibiotic therapy per pt	12.17	13.58	-1.41
Days receiving IV antibiotic per pt	9.8	11.41	-1.61
Defined Dailiy doses of IV antibiotics per pt	10.16	13.59	-3.43

From Fraser et al. [41]

As in other fields of medicine although educational programs are often effective in the short term; without continuous repetition the positive results are usually limited to the short term. Thus education is an integral component of an antimicrobial program but is ineffective unless combined with other aspects of an antimicrobial control program.

Antimicrobial Guidelines

Antimicrobial guidelines have been an important aspect of several antimicrobial management guidelines [42]. Typically a group of infectious disease clinicians, often in conjunction with one or more clinical pharmacists and other specialists, publish and distribute treatment guidelines for various clinical conditions. These guidelines take into account local MIC data, as well as local formulary considerations. Often there are educational sessions with prescribers, which emphasize the guidelines. One example of a successful such program was reported by investigators from Norway. The authors, who combined the guidelines with continuous educational efforts, direct feedback and consultation, reported reductions in the use of broad-spectrum antibiotics by 23% over the two years following the publication of guidelines [43]. Simultaneously the use of narrow spectrum agents increased. These changes were associated with substantial cost savings as well and the percent of the pharmacy budget spent on antibiotics decreased from 31% to 22%. However, to be successful guidelines usually need to be combined with other aspects of an antimicrobial management program.

Role of the Pharmacy

The pharmacy plays a crucial role in any antimicrobial management program. Specific areas in which the pharmacy is often proactive include antibiotic bidding (equivalent antibiotics are bid based on price and only the least expensive is added to the formulary), automatic stop orders, physician and pharmacist education, antibiotic streamlining and limited hospital formularies. Limitation of the formulary can be an effective method of cost containment. Principles of formulary development have been suggested: a. maintain a minimum number of agents to ensure effective therapy, b. eliminate duplicate agents within a class, c. choose agents partially based on local susceptibility data; restrict certain antimicrobials because of toxicity, resistance, or cost [44].

Streamlining

Antibiotic streamlining and substitution have been successful methods of controlling costs in some reports. Substitution usually involves a therapeutic switch program in which an order for one agent is switched to either a less expensive agent from the same class or to another class of antibiotic. Streamlining usually consists of simplifying antibiotic regimens (for example, from combinations to single drugs) and early switching of expensive parenteral antibiotics to less expensive oral antibiotics. A successful example of this strategy has been reported from Hartford Hospital [45]. Investigators placed a form on the patient's chart, which recommended changes which simplified therapy antimicrobial therapy. 83% of recommendations were accepted and significant savings were realized (over $100,000 per year).

Many published experiences describe a response to a particular resistant organism. In several instances restriction of a specific antibiotic or class of antibiotics has resulted in improved susceptibility for that organism [46]. However, there is a downside to this limited approach. By restricting only one class of antibiotics and thereby pushing use to a different class this approach can result in a new problem, e.g. resistance to the new class of antibiotics or resistance of another organism. This problem was reported by Rahal and colleagues. In response to resistant ESBL producing Klebsiella they restricted cephalosporins by requiring prior approval [47]. While they were successful in reducing cephalosporin use by 80% and Ceftazidime resistant Klebsiella by 44%, there was a simultaneous 69% increase in imipenem resistant *Pseudomonas aeruginosa*.

Use of pre-printed antibiotic order forms has been encouraged in several institutions in order to improve dosing, and empiric antibiotic choices. Some studies of antibiotic order forms have resulted in less inappropriate dosing and less broad-spectrum antibiotic use [31, 48]. However, a problem with this strategy is that the forms are not always completed [49]. Used in isolation order forms are unlikely to have a major impact; to be successful they must be part of a broader antimicrobial management program.

Prior Authorization Programs

Prior authorization programs have been successful in several instances. These programs can exist in several formats. The most common programs involve the

Infectious Disease physician or clinical pharmacist and include one or more of the following: phone approval, antibiotic order forms, automatic stop orders, direct interactions between the clinician and Infectious Disease physician or pharmacist or a formal Infectious Disease consult. Two of the first prior approval programs occurred in the early 1970s [25, 50]. The Veteran's hospital in Madison, Wisconsin required infectious disease service consultation prior to use of cephalexin which was considered broad spectrum and expensive at that time. Use of cephalexin significantly decreased with this program [25]. The second published experience of requiring antibiotic approval was reported in 1974 by McGowan and Finland [50]. A decade later many teaching hospitals had some form of antibiotic restriction [51]. Many such programs have reported substantial cost savings [52].

A recent example of a successful prior approval program was Ben Taub Hospital in Houston [34]. They initiated a program in response to a large number of bacteremic patients with a highly resistant isolate of Acinetobacter and to rising antimicrobial costs. Their program required prior approval by an Infectious Diseases faculty member for several broad spectrum antibiotics. This person was available via a dedicated antibiotic pager 24 hours a day. The authors compared antibiotic expenditures, bacterial susceptibilities and clinical outcomes in patients with gram negative rod infections before and after January 1, 1994. They demonstrated a reduction in parenteral antimicrobial costs of 32%, which resulted in a total savings of $431,548 in six months. Outcomes including time to receipt of appropriate antibiotics, 30 day survival after gram negative bacteremia and length of hospitalization were not altered by the intervention, while susceptibilities to antimicrobials (restricted and unrestricted) improved. The authors suggested that the decrease in resistance may have partially resulted from more appropriate use of antibiotics by housestaff, who received more frequent advice and education from the Infectious Disease faculty member who carried the antibiotic pager.

While prior justification programs are arguably the most effective means of controlling costs and possibly resistance they are the most labor intensive and require continuous input from an Infectious Disease physician(s) and one or more clinical pharmacist. These types of program place the Infectious Disease physician and/ or pharmacist in the role of an enforcer. This approach has been studied mostly in teaching hospitals where housestaff write most antibiotic orders. There is less experience with this approach in non-teaching hospitals and some concern has been expressed that the physician in charge of enforcement may experience fewer patient referrals from his colleagues.

Antibiotic Cycling

Antibiotic cycling or rotation is another method, which has been proposed as a remedy for the problem of increasing bacterial resistance. The theory behind this strategy is that by regularly rotating the antibiotic(s) of choice in a specific setting e.g. the ICU, the selective pressure on bacteria is for a limited time. Before substantial resistance can develop another antibiotic is substituted at regular intervals. Several experiences, were

published in the 1980s and mostly involved aminoglycoside switches, e.g. from gentamicin to amikacin, in response to Gentamicin resistance [53, 54]. Some were successful but recurrences of gentamicin resistance were noted with reintroduction of gentamicin [53, 55].

More recently Dominguez et al. evaluated antibiotic cycling in a prospective non-randomized study in cancer patients with neutropenia [56]. They used the following regimens: vancomycin-ceftazidime, imipenem, aztreonam-cefazolin, and ciprofloxacin-clindamycin. They found no increase in adverse effects, resistance or decrease in efficacy and a lower incidence of gram-negative infections. However infections due to gram-positive infections increased. Kollef and colleagues substituted ciprofloxacin for ceftazidime for empiric treatment of gram-negative infections after cardiac surgery [57]. They found a lower incidence of ventilator-associated pneumonia due to gram-negative bacteria in the second period; however, they did not reinstitute ceftazidime and thus did not follow a true rotation schedule.

There are practical problems with antibiotic cycling. Once resistant bacteria are established in a hospital or a particular unit they may be very difficult to eradicate and may re-emerge when a particular antibiotic is reintroduced. The optimal drugs to use in the rotation cycle are not known. The optimal length of each cycle is also unknown. Many large hospitals negotiate long term contracts, which require a single drug to be the primary drug used in its class (certain percent of market share). Thus, cycling, with the requirement that more antibiotics be kept on the formulary is likely to lead to higher costs for antibiotics. Also, changing antibiotics too frequently may result in confusion. Hospital staff need to be reeducated with each switch since clinicians and pharmacists may not be familiar with all the drugs used in the cycling program. The lack of familiarity could lead to dosing errors and insufficient knowledge of adverse effects and drug-drug interactions. Antibiotic cycling is an interesting idea, but like other interventions it is unlikely to be successful if used in isolation and the problems cited above need to be ironed out before it can routinely be recommended.

Any single intervention is likely to fail in the long term and multiple components are required for a program to be successful. Infection control is a vital facet of any multidisciplinary program. Infection control measures include appropriate isolation procedures, implementation of barrier precautions when indicated, cohorting of patients, hand washing awareness campaigns and recently the use of waterless hand disinfection systems [1].

Multidisciplinary Antimicrobial Programs

Multidisciplinary antimicrobial control programs, which combine all or several aspects of the above cited interventions, have yielded the best outcomes in terms of cost and resistance [7, 29, 58]. Schentag and colleagues from Millard Filmore Hospitals in Buffalo reported on a successful multidisciplinary approach, which resulted in over $200,000 in savings per year [59]. In addition to formulary revisions, clinical pharmacists used real-time computer links between the pharmacy and microbiology laboratory. The computer

program automatically picked up mismatches between pathogens and antibiotics. Prescribing physicians were contacted by the pharmacist to make changes based on culture results and for dosage adjustments. The program achieved savings by focusing on narrowing empiric therapy once culture results were reported, choosing less expensive oral medications, and shortening antibiotic therapy courses.

In a randomized study, Gums and colleagues reported improved outcomes and cost savings of a multidisciplinary antibiotic consult team, consisting of a pharmacy fellow, a clinical microbiologist, and an infectious disease specialist [60]. The team left written antibiotic recommendations on the chart with a rationale, references, lists of appropriate culture results, and estimated creatinine clearance. Control patients did not receive any intervention. Antibiotic recommendations were followed in 89% of cases. The intervention group had a shorter length of stay and lower hospital costs. Overall the program was well received and resulted in education of the prescribing physicians.

Another study compared antimicrobial policies at 14 hospitals [61]. Hospitals with passive antibiotic management programs (educational programs, automatic stop orders, order forms etc) were compared to hospitals with active programs (passive procedures in addition to an antimicrobial management team which was involved in antibiotic approvals). The five hospitals in the latter group spent significantly less on parenteral antibiotics and more inexpensive antibiotics than the nine hospitals with only passive programs.

Computerized Programs

Computer based physician order entry has several potential advantages in terms of efficiency, quality assurance and error prevention, and cost efficacy. Many of the above cited interventions and objectives may be best realized with a sophisticated computer program. LDS Hospital, a community teaching hospital in Salt Lake City, has found computer assisted programs to be very helpful for anti-infective management [6, 62]. They developed a comprehensive computer program which uses decision support logic to suggest an antibiotic regimen for their 12 bed shock-trauma ICU (or no antibiotics if indicated by the clinical data). The program, obtains daily input from numerous sources including microbiology (including mean inhibitory concentration, pharmacy (drug allergies, interactions and cost data), the clinical laboratory (e.g. WBC, serum creatinine and hepatic function), radiographic reports, admission diagnosis, and pathology reports. This information is integrated and forms the basis of recommendations for appropriate antibiotic choices and dosing. In cases where empiric therapy is required, treatment algorithms developed by infectious disease clinicians are followed until susceptibility data is available. Physicians have the option of reviewing the rationale for the antibiotic recommendation made by the program and can override the program if they desire.

Investigators compared 1992-1994 (pre-intervention period) to 1994-1995 (intervention period). Approximatly two-thirds of patients in both groups used antibiotics. Physicians followed the computers suggestions including dose, route and interval 46%of the time, but 93% of the time they followed the recommendations for dose and interval [62]. During

the intervention period the number of adverse events, drug allergy alerts, and number of doses and number of days with excessive dosing were decreased. In addition, costs decreased by a mean of $71 per treated patient. Furthermore, within the intervention period the number of antimicrobial agents, days of excessive dosage, as well as antimicrobial costs, total hospital costs and length of ICU stay were lower in cases where the computer suggested regimen was followed compared the instances where it was overridden. In another study from the same institution, the authors reported an improvement in appropriateness of surgical prophylaxis and cost savings associated with the program [6]. The authors suggested that an additional advantage of this type of program is the amount of time saved for physicians which could potentially further improve quality of care. They estimated that it would take an infectious disease physician 14 minutes to retrieve the same patient specific data the computer program retrieved in 3.5 seconds. Despite the high initial investment in terms of dollars and manpower computer assisted antimicrobial management is a concept worth paying for now and is likely to lead to long term cost savings and improved outcomes if more widely adopted.

Results of a Computerized antibiotic ordering program at LDS Hospital [62]

Variable	Pre-intervention N=1136	Intervention N=545
Received anti-infectives, no. patients (%)	766 (65)	398 (73)
No. of defined daily doses/100 bed-days	185	170
No. of susceptibility mismatch alerts	206	12*
No. of drug allergy alerts	146	35*
No of excessive dosage alerts	405	87*
Adverse events 2° antibiotics	28	4*

*P < 0.05

For an antiimicrobial management program to be successful it must not result in adverse patient outcomes. Recent studies have suggested that inadequate initial antimicrobial therapy results in higher mortality rates in ICU patients [63, 64]. Thus, strategies which restrict antibiotics need to be permissive enough to allow critically ill patients appropriate empiric antibiotics at least until susceptibility testing results are know to clinicians.

One of the important factors in the development of antibiotic resistance is the total duration of antibiotic therapy or total antibiotic exposure. A successful approach to limit antibiotic exposure involved a protocol for limiting antibiotic use for possible ventilator

associated pneumonia in a surgical intensive care unit [65]. While prompt treatment of ventilator associated pneumonia is associated with improved outcomes; it is notoriously difficult to make a clinical diagnosis of ventilator associated pneumonia. Singh and colleagues used the clinical pulmonary infection score (CPIS) to stratify patients according to whether there was a high or low likelihood for VAP. Those with a high likelihood were treated with standard antibiotics while those with a lower chance of having VAP (but who would have received antibiotics anyways) were randomized to either standard care (antibiotics for 10-21 days) or study group (3 days of Ciprofloxacin). After three days patients were reassessed and a CPIS score was recalculated. If the repeat score was low ciprofloxaxin was stopped, while if it was higher standard antibiotics were given. The patients randomized to three days of ciprofloxacin fared better in all respects. Duration of antibiotics was much shorter (by two-thirds), duration of ICU stay was shorter, there was a trend towards lower 30 day mortality and costs were less than half.

It is often more difficult to control antibiotic prescribing in the outpatient arena than the inpatient arena. The CDC launched a national campaign to promote appropriate antimicrobial prescribing in 1999 [66]. This program, which partners with state and local health departments, provides educational brochures and posters for physicians' offices and free slide kits for local experts to use.

An antimicrobial management program has several goals. Arguably the most important objective of an AMP is to prevent antimicrobial resistance in the hospital setting and to some extent outside the hospital setting. A second goal is to hold down costs. A third objective is to improve patient care. A fourth objective is to encourage rational, evidence based decision making by health care providers in choosing appropriate antimicrobial agents.

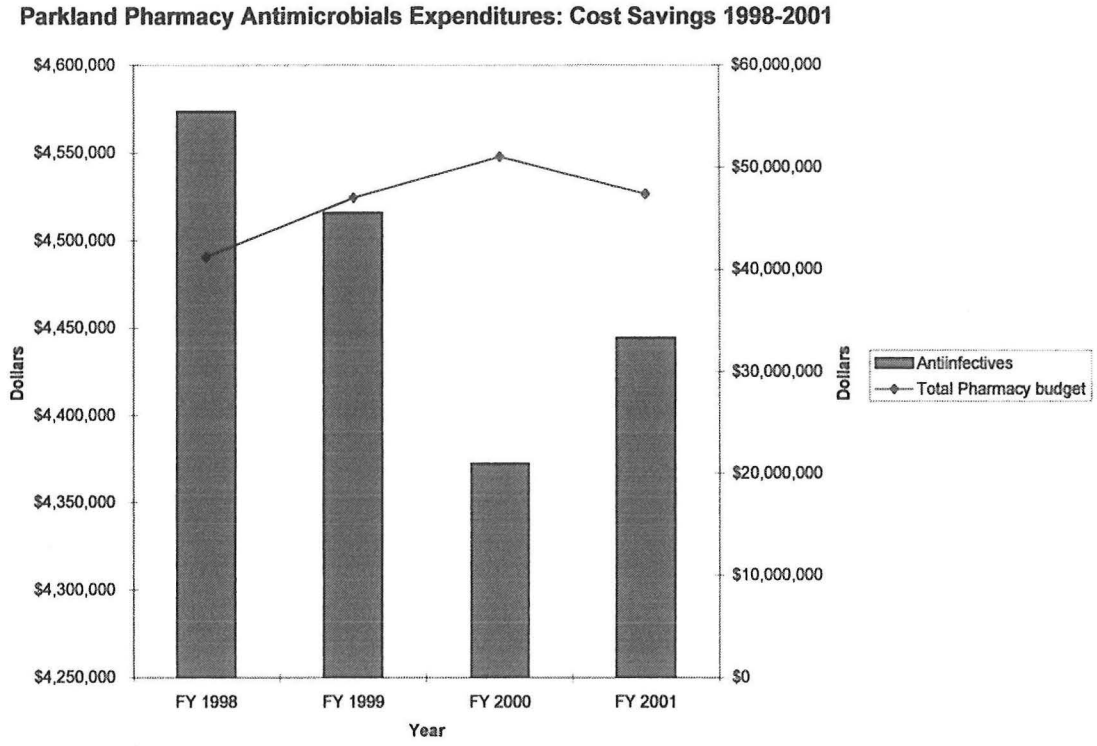
VII. The Parkland Hospital Experience

In the 1990s in response to the increasing prevalence of resistance and increasing antimicrobial costs, many hospitals, including Parkland, formed multidisciplinary antimicrobial control teams to organize and manage a local antimicrobial management program [29, 58]. The Parkland Hospital Antibiotic Subcommittee, which was organized in 1997, includes representatives from various clinical disciplines in addition to Infectious Diseases and Pharmacy such as microbiology, surgery, Ob-gyn, Pulmonary Critical Care, Infection Control and general Internal Medicine. The goals of the committee are to curb the development of antimicrobial resistance, maintain or minimize antimicrobial expenditures, and to promote the rational use of antimicrobial agents in the inpatient and outpatient settings. The committee has undertaken numerous initiatives in pursuit of these objectives.

Initiatives by the Parkland Hospital Antibiotic Subcommittee 1997-2003

Education Initiatives
Lectures
Surgery and medicine housestaff
COPC physicians
Quarterly newsletter
Pharmacy Initiatives
Therapeutic substitution
Formulary revision/interchanges
Aggressive contract pricing
Antibiotic bidding
Guidelines published
Empiric guidelines published for common infections
Community acquired pneumonia
Influenza treatment
Activated Protein C
Empiric fluconazole
Order Forms
Automatic stop order form (96 hours)
Vancomycin order form and stop form
Prior approval program (antibiotic pager)
Empiric Piperacillin-tazobactam in the SICU for Ventilator Associated Pneumonia

One of the main aspects of the Parkland antimicrobial program has been a prior approval program. An antibiotic approval pager is carried by a member of the antimicrobial management team (usually either the Chairman of the antimicrobial subcommittee or the Infectious Disease Clinical Pharmacist and occasionally the Infectious Disease fellow or another Infectious Disease faculty member). The pager is carried 24 hours per day. Antimicrobials are classified into one of several categories including unrestricted, restricted tospecific indications (e.g. cefepime for neutropenic fever), specific locations (e.g, ICU), or specific physicians (e.g. attending faculty or Infectious disease faculty) or restricted to the prior approval pager. Since inception the program has been successful in promoting rational usage of antimicrobials and saving money. Many of the calls received are for advice and are educational in nature. An audit of the pre-approval program in 2000 revealed that 59% of requests made to the pager were approved and alternative therapy was recommended in 29% of cases. Annualized cost avoidance from the prior approval program was estimated at $76,000. When combined with the other program initiatives approximately $220,000 in cost expenditures were avoided in the first year of the program. More recently another audit was performed with data from 2002. The most common diagnoses were nosocomial pneumonia and sepsis and the annualized cost savings were conservatively estimated at $40,000. (data compiled by Travis Waldrep, Pharm.D)



Another important objective of the program has been to improve appropriateness of vancomycin usage based on HICPAC/CDC guidelines. An audit revealed that vancomycin appropriateness increased from 50% prior to the program to 87% after first three years of the program. A recent survey comparing Parkland to comparable hospitals found that with a few exceptions, Parkland was in line with benchmark institutions and vancomycin use was appropriate in approximately 85% of cases. Ongoing and future projects include issuance of guidelines for outpatient antimicrobial therapy, an antibiotic detailing program, automatic dosage switch programs based on pharmocokinetic considerations, educational newsletters and expanded web-based antibiotic usage guidelines.

Conclusions

Antibiotic resistance and the increasing costs of antimicrobials are problems, which are here to stay. The causes of these problems are multifactorial; however, physicians are both part of the problem and critical to the solution. It is important for physicians to realize their central role in these problems and to recognize the implications not only for their patients but for the health care system as a whole. Rational use of antibiotics can be achieved with integrated approaches. While such approaches are not likely to reverse resistance, there is evidence to suggest that multidisciplinary solutions can limit resistance while simultaneously holding down costs. If we as physicians do not heed the advice to limit antimicrobial use now, we will all pay later.

Table. **Physician and Patient Resources Promoting Rational Antibiotic Prescribing** * From Avorn [31]

Focus	Organization (Web Site)	Content
Physician/patient	Centers for Disease Control and Prevention , Atlanta, GA (www.cdc.org)	"Judicious Use of Antibiotics" program contains information on appropriate antibiotic use
Physician/patient	National Institute of Allergy and Infectious Diseases, Bethesda, MD (www.niaid.nih.gov/factsheets/antimicro .htm	Antimicrobial Resistance Fact Sheet
Physician/patient	Alliance for the Prudent Use of Antibiotics, Boston, MA (www.healthsci.tufts.edu/apua)	Educational materials with links to a network of antibiotic resistance researchers
Physician	Infectious Diseases Society of America, Alexandria, VA (www.jounals.uchicago.edu/IDSA/guide /SE39_584.pdf)	References to the Society's guidelines on prevention of antimicrobial resistance in hospitals.
Patient	American Medical Association, Chicago, IL (www.ama-assn.org/insight/gen_hlth/Antibi01.htm)	Practical information on antibiotics and infectious diseases.

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