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ORAL ANTIBIOTICS IN THE NINETIES: NEW DRUGS AND NEW CHALLENGES IN PRIMARY CARE

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TABLE OF CONTENTS

1. ABSTRACT

The primary care physician is faced with a bewildering array of new oral antimicrobials to treat common infections. These agents promise to be extremely effective as replacements for time-honored drugs, as prophylaxis, and for the treatment of infections previously requiring prolonged intravenous therapy. The overuse of the newer macrolides, quinolones, and beta-lactam beta-lactamase inhibitors may prove to be ecologically and economically costly. It is feared that the selective pressure from these broad spectrum agents may burden society with an even greater problem of multiply resistant community-acquired pathogens. The specific therapeutic and economic advantages and disadvantages of each class should be considered and the decision to employ these agents should be highly individualized.

2. INTRODUCTION

In the past three years, approximately 20% of the new drugs approved for release by the Food and Drug Administration (FDA) were antimicrobials. At present, pharmaceutical research firms have in development many new drugs and vaccines (1). Among the existing oral antimicrobials, the macrolides, fluoroquinolones, combination beta-lactam/beta-lactamase inhibitors, and advanced generation oral cephalosporins are marketed as major advances in the therapeutic armamentarium of the primary care physician. The newer drugs permit primary care physicians to treat a number of infections that previously required combination or intravenous therapy. Convenient dosing, improved bioavailability, fewer side-effects, and increased activity against a large number of pathogens are the advertised. These highly effective oral agents are promising direct cost savings by decreasing follow-up office visits and hospitalizations (2). Specific infectious syndromes, where these costly antibiotics are being used, are the common ambulatory conditions-upper respiratory tract infections (URIs), cellulitis, prostatitis and cystitis, as well as more serious infections such as community-acquired pneumonia, osteomyelitis, pyelonephritis, sexually transmitted diseases, Lyme arthritis, diabetic foot ulcers, and opportunistic infections in patients with Acquired Immunodeficiency Syndrome (AIDS). As a result a major concern for insurance carriers and pre-paid health plans is the widespread misuse of costly antibiotics in the ambulatory setting (2,3). Reports exist of up to 50% of antibiotic prescriptions being inappropriate with many patients receiving antibiotics for viral syndromes (4,5).

In the treatment of many infections encountered in the ambulatory setting there is scant evidence that more expensive drugs significantly improve outcome (6). Additionally, there is little agreement among physicians on which antimicrobial agents to use and when to treat specific infectious syndromes. The variability in practice styles begs that rational guidelines be constructed that will result in truly cost-effective medicine (7,8). Hence, it is imperative for practicing physicians to re-examine the rational use of oral antibiotics for common ambulatory infections. The specific indications for use of each new antibiotic instead of traditional, less expensive therapy must be critically examined. The opportunity to use these newer agents in certain settings should be exploited, not abused. In this analysis, we review the specific advantages and indications for certain new oral antibiotics so that the use of each drug is appropriate and the cost is justified.

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Table I. Antimicrobial Spectrum of Macrolide Antibiotics

BACTERIAL SPECIES
*Streptococcus pyogenes**
Streptococcus pneumoniae *
*Staphylococcus aureus***
Mycoplasma pneumonaie
Legionella pneumophilia
Chlamydia spp.
Borrelia burgdorferi
Ureaplasma urealyticum
Mycoplasma hominis
Mycobacterium spp.
Bortedella pertussis
Haemophilus influenzae
Camplybacter jejuni
Haemophilus ducreyi
Moraxella catarrhalis

* Strains of *S. pneumoniae* and *S. pyogenes* are resistant
** MRSA (methicillin-resistant *S. aureus*) is also erythromycin/macrolide resistant

3. MACROLIDES AND AZALIDES

There has been a keen interest in the macrolide antibiotics as a result of their broad range of antimicrobial activity. These drugs are called "macrolides" because they possess a macrocyclic lactone nucleus (9). The primary targets of the macrolides include many respiratory and intracellular pathogens (Table I). Macrolides are both bacteriocidal (for *Streptococcus pyogenes* and *Streptoccus pneumoniae*) and bacteriostatic (for staphylococci). Erythromycin, the prototype macrolide, remains an inexpensive, effective, and time-honored therapy for the treatment of many community-acquired respiratory infections, uncomplicated skin and soft-tissue infections, and for group A streptococcal pharyngitis in penicillin allergic individuals (10). Newer macrolide derivatives promise to be effective against an even greater number of pathogens than erythromycin.

Macrolides available in the United States and Europe include erythromycin,clarithromycin, azithromycin, roxithromycin, dirithromycin, spiramycin, and josamycin.So far, only clarithromycin , dirithromycin and azithromycin are used in the United States. clarithromycin dirithromycin and roxithromycin are 14-membered ring compounds. Josamycin and spiramycin are 16 membered macrolides. Azithromycin is a fifteen membered ring azalide antibiotic (10).

Azithromycin and clarithromycin expand the spectrum of the macrolides to include Gram negative organisms such as *H. influenzae* (11,12). The excellent tissue levels of the new macrolides, less frequent dosing, and broad spectrum activity make them ideal agents in the treatment of community-acquired bacterial respiratory infections, uncomplicated soft tissue infections, and sexually transmitted diseases (11-17). In numerous clinical trials they have been found to be as effective as the currently available oral antibiotics. The most compelling indications for the use of the new macrolides in the community setting is in documented bacterial infections such as sinusitis and community-acquired pneumonia especially when Gram stains or cultures confirm the presence of a potentially beta-lactamase positive organism such as *Haemophilus influenzae* or when the concern for *Mycoplasma*, *Legionella* and *Chlamydia* is very great. Using azithromycin to treat sexually transmitted diseases in the office, the primary care physician can be visually certain that the entire therapy for gonorrhea and uncomplicated *Chlamydia* cervicitis can be administered without the concern for noncompliance.

Important new applications for the macrolides have been in the treatment of the disseminated *Mycobacterium intracellulare* and *Mycobacterium. avium* complex (MAC) infections (18-22). Both clarithromycin and azithromycin penetrate phagocytes and have been shown to effectively inhibit the replication of MAC in macrophage cell lines (21). Used alone, clarithromycin and azithromycin were initially very effective in treating disseminated MAC in AIDS (18,19,20). In AIDS patients treated with azithromycin or clarithromycin as monotherapy, there was a significant reduction in viable mycobacteria detected in blood cultures. Relapse with resistant strains was seen with both agents (18,19,20). Although the *in vitro* minimum inhibitory concentrations are not as low as with clarithromycin , the high degree of penetration of azithromycin into phagocytes makes this drug uniquely effective (21). In combination with other agents, clarithromycin and azithromycin have now assumed a central role in the treatment and prophylaxis of MAC (18).

A body of experience is emerging regarding the effectiveness of the macrolides (particularly clarithromycin) in the treatment of other nontuberculous mycobacterial infections(23). *In vitro,* clarithromycin is the most effective macrolide against *M. chelonae* and *M. fortitutum* (22). As part of a multi-drug regimen the macrolides are recommended either as primary agents or as alternatives in the treatment of *M. kansasii*, *M. chelonae* (subspecies *abscessus* and *chelonae*), *M. scrofulaceum*, *M. simiae*, *M. malmonese*, *M. szulgai*, and *M. fortuitum* (22).

The macrolides azithromycin or spiramycin in combination with pyrimethamine have superior activity *in vitro* against several stages of *Toxoplasma* (24). A number of studies demonstrate that this combination shows promise in treating acute toxoplasmic encephalitis in AIDS (25,26). This alternative therapy is of major importance since the side effects of clindamycin and sulfadiazine in AIDS patients are substantial.

Protozoan infections such as cryptosporidiosis, giardiasis, and *Entamoeba histolytica*, and even *Plasmodium falciparium* have been successfully treated with the new macrolides (27,28,28a,28b). Azithromycin has been identified as particularly promising in the treatment of severe cryptospoidial diarrhea and may prove to be an effective alternative to paromomycin (29).

In the treatment of Lyme disease, azithromycin also was shown to be more effective than amoxicillin or doxycycline-as measured by the response time to resolution of erythema chronicum migrans (30-32).

An unappreciated quality of macrolide antibiotics is their tendency to augment host immune function and their ability to exert significant anti-inflammatory effects. Normal human serum has been shown to potentiate the antibacterial effect of azithromycin (33). Incubating polymorphonuclear leukocytes with erythromycin influences phagocytic activity. This has been shown with Gram negatives as well as streptococci (34,35). *In vitro*, clarithromycin has been shown to inhibit production of interleukin-1 (36). This immunomodulatory effect may have important implications in the modulation of cytokine activity and in the treatment of infections in immunocompromised hosts (37).

Gastrointestinal intolerance has been the primary disadvantage of erythromycin. This is due to the motilin-like effect of the antibiotic (38). Approximately 14-19% of patients taking erythromycin experience gastrointestinal side effects that lead to discontinuation of the drug while only 2-5% of patients taking the newer macrolides have significant gastrointestinal intolerance (10,39). This side effect has been exploited in treating patients with disorders of gastric emptying (39,40). All macrolides have the potential to increase levels of carbamazepine, digoxin, theophylline, terfenadine and astemizole and to decrease the effectiveness of oral contraceptives. These considerations should be kept in mind.

Although clarithromycin and azithromycin have superior bioavailability, pharmacokinetic properties, and are better tolerated, it is uncertain under what circumstances the increased cost is justified when compared to erythromycin in the treatment of many infections encountered in primary care. In cases of treatment of acute bronchitis in young patients, a disease which is predominantly viral in origin, antibacterial therapy has not been shown to improve the outcome of acute bronchitis in otherwise healthy individuals (6). When the patient remains symptomatic for more than 7-10 days and the suspicion for *Mycoplasma* or *Chlamydia* infection is present, treatment with erythromycin or doxycycline is appropriate. The efficacy of any antibiotics in the treatment of "bacterial bronchitis" is controversial at best and then only in a subset of patients with chronic pulmonary conditions and with the most severe symptoms. Despite the superior *in vitro* activity of the newer macrolides against beta-lactamase producing *H. influenzae*, there is no clinical evidence that this difference is significant in the treatment of acute or chronic bronchitis. In fact, traditional therapy with amoxicillin is still the clinical standard. Trimethoprim-sulfamethoxazole remains an inexpensive broad spectrum alternative for the treatment of upper respiratory infections due to community-acquired bacterial pathogens. Clinicians should not anticipate that the newer agents will be more potent than erythromycin to treat macrolide resistant Gram positive pathogens (41).

4. QUINOLONES

The quinolone class of antimicrobials are proving to be one of the most important antimicrobials used in the management of outpatient infectious diseases. These broad spectrum agents are easily administered, have excellent gastrointestinal absorption and tissue penetration, and lack many unwanted side effects. An important feature of this class of drugs is the ability of medicinal chemists to manipulate the nucleus of the 4-quinolones. This has permitted an explosion of derivative compounds with differing antimicrobial activity, pharmacokinetics, and metabolic properties (42).

With the introduction of the quinolones, clinicians are now able to orally treat chronic Gram negative bacillary osteomyelitis, *Pseudomonas aeruginosa* urinary tract infections, prostatitis, invasive otitis externa, bacterial gastroenteritis, mycobacterial infections in AIDS patients, sexually transmitted disease due to gonococcus and *Chlamydia* and respiratory infections in cystic fibrosis patients. These drugs have also been used as prophylactic agents in protecting against meningococcal meningitis (43). In preliminary studies, they have also been used as prophylactic agents in patients with hematologic malignancies (45), in bone marrow transplant recipients (46), in patients with recurrent urinary tract infections (47), in prophylaxis against travelers' diarrhea (48), and in the prevention of bacteremia and spontaneous bacterial peritonitis in cirrhotics (49). Quinolones have not been successful in treating *Helicobacter pylori* (50).

The quinolones are well absorbed and have a bioavailability from 30% (norfloxacin) to greater than 90% (ofloxacin and levofloxacin). Penetration into body fluids is quite good and the highest concentration of drug is found in the urine and genitourinary tissues.

In the United States, levofloxacin, trovafloxacin, enoxacin, sparfloxacin, clinafloxacin, and lomefloxacin are the latest quinolones to join the ranks of ciprofloxacin, norfloxacin and ofloxacin. Enoxacin is marketed for the treatment of urinary tract infections and for the single dose treatment of urethral and cervical gonorrhea. Lomefloxacin is indicated only for the treatment of UTIs, acute bronchitis due to *H. influenzae* and *Moraxella catarrhalis*, and is recommended for prophylaxis before transurethral surgical procedures. These two drugs are not superior to ciprofloxacin against *Pseudomonas*. Levofloxacin, the L-enantiomer of the racemic mixture of ofloxacin, is advertised as being more effective than the parent mixture with little or no side effects. It can be dosed once-a-day (500 mg) either orally or intravenously. Levofloxacin promises to be effective against penicillin resistant pneumococci, methicillin-susceptible *S. aureus*, atypical respiratory pathogens such as *Mycoplasma pneumoniae*, *Chlamydia*, and *Legionella pneumophilia*, and Gram negative pathogens. Sparfloxacin is a once a day oral quinolone that is targeted to treat community-acquired respiratory infections. This quinolone, like levofloxacin, has been shown to be more effective than ciprofloxacin

Table II. Factors important in choosing antimicrobials

POSITIVE FACTORS	NEGATIVE FACTORS	NEW ISSUES
1. spectrum of activity	1. lack of correlation between spectrum of activity and clinical outcomes for many common conditions	1. cost-effectiveness
2. tissue levels	2. increased cost without benefits	2. difficulty in reaching consensus on indications for antibiotic use
3. dosing and compliance	3. emergence of resistance more rapidly than necessary (Fried)	3. antibiotic monitoring and drug approval
4. cost benefit of effective outpatient therapy	4. increased side effects in use that i not indicated	

against penicillin resistant pneumococci. Phototoxicity (8% of patients) may prove to be an undesirable side effect of this drug and may limit its use. Both sparfloxacin and levofloxacin are somewhat active against anaerobes but the current drugs available are superior. Trovafloxacin will also cover the same organisms as ciprofloxacin but with enhanced Gram positive activity. Trovafloxacin has a broad spectrum of activity *in vitro* , especially against common respiratory pathogens including those causing the atypical pneumonia syndrome and penicillin resistant *streptococcus pneumonia*. This drug also has excellent antimicrobial activity against *Streptococcus pyogenes*, ciprofloxacin-susceptible staphylocci, and *Enterococcus fecalis*. clinafloxacin is among the newest of the quinolones to be investigated (51). This synthetic broad-spectrum fluroquinolone is available for parenteral and oral administration. Clinafloxacin demonstrates excellent Gram negative activity but is also very active against Gram positive pathogens and strict anaerobes. This drug is also active against bacterial strains that are highly resistant to structurally-related drugs. It promises to be effective against *Acinetobacter* and *Sternotrophomonas maltophilia*, methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*, as well as coagulase negative staphylococci, enterococci, and *S. pneumoniae*. It is hoped that this agent will establish itself as an effective alternative to intravenous vancomycin.

Like the macrolides, the quinolones have established themselves as important partner antibiotics in the treatment of mycobacterial infections (18). Ciprofloxacin has been successfully employed in treating MAC and has established itself as an essential drug in the treatment of multi-drug resistant tuberculosis.

At present, quinolones should be used with caution in children. Adverse side effects and drug interactions include elevations of cimetidine levels (all quinolones), elevated theophylline levels (except for lomefloxacin), and prolongation of the prothrombin time (ciprofloxacin potentiates the effect of coumadin) (38). The co-administration of aluminum and magnesium antacids and iron sulfate interferes with the absorption of the quinolones. An important interaction can occur when quiniolones are used in AIDS patients taking didanosine (DDI). The magnesium and aluminum buffers that increase the absorption of DDI also interfere with the absorption of ciprofloxacin. Central nervous system side effects of quinolones include headache, agitation, dizziness and sleep disturbance. These are reported in 1-4% of patients. Seizures occur rarely. The neurological side effects are believed to be due to interference with gaba-aminobutyric acid receptors.

Balancing the positive impact of quinolones is their widespread inappropriate use (2). Although, It is well recognized that ciprofloxacin has a limited role in the treatment of upper respiratory tract infections (where pneumococci and group A streptococci are commonly involved) and in the treatment of skin and soft tissue infections (where streptococci and staphylococci are the major pathogens), they are often inappropriately used to treat bronchitis, sinusitis, and cellulitis in the community. When treating upper respiratory tract infections it must be emphasized that *S. pneumoniae* is more sensitive to the macrolide or beta-lactam antibiotics. In fact, there have been a number of failures when ciprofloxacin has been used to treat pneumococcal infections (52,53). Anaerobic organisms (found in the sinuses) are less susceptible to the action of quinolones perhaps due to their less susceptible DNA gyrase or by inactivation of the quinolones in the anaerobic environment.

A major concern of primary care practitioners is the use of quinolones in the treatment of enterococcal infections. The quinolones as a class have varying activity against *Enterococcus faecium* and *Enterococcus faecalis*. Of all the quinolones, ciprofloxacin seems to be the most active. However, the MIC_{90} is very near the maximum achievable serum concentration. Hence, except for urinary tract infections where amoxicillin cannot be used, the quinolones are not considered to be clinically useful against the entercoccus (54).

It must be kept in mind that resistance to one quinolone means resistance to all quinolones. In the intrinsically less susceptible organisms, such as staphylococci and *Pseudomonas spp.*, the MICs following a single mutation can readily exceed the therapeutic breakpoint. This is responsible for the failure of quinolones in serious infections with *S. aureus* and *P. aeruginosa*. In addition, the number of community isolates of other Gram negative pathogens demonstrating resistance to quinolones is increasing (55).

Table III. Cost of drugs for treating community-acquired respiratory infections (10 day course)

ANTIBIOTIC	COST*
Erythromycin	$15.00
Azithromycin	$37.00
clarithromycin	$65.00
Cefuroxime axetil	$100.00
Ciprofloxacin	$100.00
Levofloxacin	$70.00
Ofloxacin	$80.00
Sparfloxacin	$75.00

* Cost per 10 days of treatment, based on average wholesale price (AWP or HCFA) listing in Drug Topics Red Book 1997 and April Update.

Clinicians should not forget the availability of cost-effective alternatives to quinolones for many uncomplicated infections. For example, trimethoprim remains an inexpensive choice for the treatment of simple cystitis in women, and trimethoprim-sulfa is an effective therapy for prostatitis and acute pyelonephritis (8).

5. ADVANCED GENERATION ORAL CEPHALOSPORINS

A new class of cephalosporin (the carbacephem, loracarbef) and number of new oral second (cefprozil) and third generation (cefixime and cefpodoxime proxetil) cephalosporins are available to primary care practitioners. These advanced generation oral cephalosporins have an expanded Gram negative activity with some compromise in Gram positive spectrum.

Cefpodoxime proxetil is an orally administered prodrug of the third generation cephalosporin class (56). Cefpodoxime proxeti l is de-esterified in the gut to its active moiety, cefpodoxime. It is stable in the presence of beta-lactamases from *H. influenzae*, *Neisseria gonorrhea*, and *M. catarahallis* . Unlike cefixime, the other third generation oral cephalosporin, cefpodoxime has some activity against methicillin susceptible *S. aureus* . It should be kept in mind, however, that this activity is less than cephalexin. In both upper and lower respiratory tract infections as well as the treatment of uncomplicated gonorrhea, cefpodoxime proxetil was as effective as the currently available ceftriaxone. Oxacillin (methicillin)-resistant *S. aureus*, *P. aeruginosa*, *Serratia*, *Citrobacter*, *Enterobacter*, *Morganella* and the enterococcus are resistant to cefpodoxime.

Loracarbef is a carbacephem chemically similar to cefaclor (57). The sulfur group at position 1 of the dihydrothiazine ring in cefaclor has been replaced with a carbon in loracarbef. This substitution enhances drug stability in plasma. This drug is as effective as amoxicillin, penicillin and amoxicillin/clavulanate in the treatment of upper respiratory infections. The only therapeutic advantage offered by this drug is convenience in dosing and a lower incidence of serum sickness like reactions in children.

Cefprozil is very similar to cefadroxil- it has greater activity against penicillin resistant *S. pneumoniae*, *S. aureus* and *M. catarrhalis*. It can be dosed on a once or twice a day basis.

It is clear that the new cephalosporins are very similar to existing drugs and provide little advantage to what is already available. Oral cephalosporins are rarely the drug of first choice for any uncomplicated community-acquired infection.

Anaphylaxis is uncommon with cephalosporins. Data regarding the cross-reaction rate of oral cephalosporins and penicillins is scant, but evidence from intravenous use suggests that third-generation cephalosporins may cross-react less with penicillin allergic patients than first generation cephalosporins.

6. BETA-LACTAM BETA-LACTAMASE INHIBITOR COMBINATIONS

Amoxicillin/clavulanic acid is the current oral beta-lactam beta-lactamase inhibitor combination antibiotic available for use. Clavulanate permanently inactivates the beta-lactamase so that the beta-lactam can reach its target, the penicillin binding proteins (PBPs). Amoxicillin/clavulanate is effective against methicillin-susceptible *S. aureus*, plasmid determined beta-lactamase producing *Escherichia coli*, *Klebsiella spp.*, *Neisseria spp.*, as well as anaerobic organisms such as *Bacteroides spp*. Specific indications for use of amoxicillin/clavulanate include upper respiratory infections, human and animal bites (especially due to cats) and skin and soft tissue infections involving anaerobic organisms such as complicated oral-pharyngeal infections, and beta-lactamase producing respiratory infections due to *H. influenza*.

Amoxicillin/clavulanic acid is effective in therapy of bacterial otitis media, sinusitis or bacterial lower respiratory infections where beta-lactamase producing organisms such as *H. influenzae* or *M. cattarhalis* may be involved (58). Amoxicillin/clavulanic acid is not appropriate as a single empiric therapy for community-acquired pneumonia where *Legionella*, *Mycoplasma* or *Chlamydia* are suspected. Although amoxicillin/clavulanic acid is an effective therapy for acute pyelonephritis, it has no obvious advantages over other agents (8). A promising application for amoxicillin/clavulanate has been entertained in the treatment of *M. tuberculosis* and *M. fortuitum* infection. Both species possess beta-lactamase enzymes that are constitutively expressed. Inhibition of this mycobacterial beta-lactamase may prove to be therapeutically useful (59,60). Unfortunately, beta-lactams do not penetrate phagocytes well.

There is a reported high incidence of diarrhea in patients administered amoxicillin/clavulanic acid perhaps reflects the depletion of normal bowel flora caused by this broad spectrum antibiotic. Surprisingly only 1-3% of

patients discontinue the drug due to diarrhea (38). The new twice-a-day oral formulation of amoxicillin/ clavulanate has gained widespread acceptance in the community, especially for the treatment of refractory otitis media in children. It may also reduce the incidence of diarrhea.

Resistance to beta-lactam beta-lactamase inhibitor combinations can arise by a variety of ways (hyperproduction of beta-lactamase, presence of a chromosomal beta-lactamase, alterations in the genes encoding beta-lactamases that are normally inhibitor sensitive making them inhibitor resistant, change in outer membrane proteins) potentially making this combination also ineffective. There are reports of clinical isolates bearing plasmid mediated beta-lactamases that are resistant to inactivation by mechanism based inhibitors (61,62).

7. PERSPECTIVES

Oral antibiotic therapy for complex conditions is now become possible for an expanded number of syndromes including serious infections such as community-acquired pneumonia, osteomyelitis, pyelonephritis, mycobacterial infection, and sexually transmitted diseases. Oral agents are finding a role as both initial therapy or as a means to complete initial parenteral therapy. Despite the initial successes, rigorous comparisons of oral and parenteral therapy are not always available. The efficacy of oral antibiotic therapy cannot always be generalized to high risk patients who are immunocompromised, pregnant, diabetic, chronically ill, or elderly. In addition, the duration of therapy for most infectious syndromes is unknown. For example, for the treatment of acute pyelonephritis, antibiotic therapy varied from seven days to six weeks (8). Most worrisome, the clinical trials using new agents in ambulatory settings with healthy adults involve limited and highly select patient populations.

The availability of new, effective oral antibiotics can be cost-effective when they provide the potential for increased adherence, continuation of parenteral therapy with oral agent, decreased need for retreatment, and low costs for monitoring and treatment of adverse reactions. Oral therapy can help avoid or reduce the cost of hospitalization and the potential nosocomial complications of hospitalization. Outpatient therapy may also improve patient satisfaction and convenience (Table II).

Despite the potential for cost-effective use, the availability of the newer antibiotics carries the potential for unproved or excessively expensive care (Table III). Currently, society is placing greater emphasis on the cost-effective practice of medicine. Some antibiotics may be used in infectious syndromes for which they do not provide optimal coverage for the suspected or typical organisms. Most importantly, complex and costly antibacterial therapy is not indicated when bacterial infection is present that can be treated simply. The overuse of antibiotics is not only expensive but may accelerate the emergence of bacterial resistance in the community setting. Fearing that antibiotic resistant community-acquired pathogens are endemic, clinicians will prescribe more potent and expensive antibiotics as first line therapy. This is most widely seen in long term care facilities. In this setting, the emergence of resistance can prove exceptionally far reaching. The favorable side effect profile of new antibiotics, consumer pressures, and the presence of drug promotional activity make it very easy to abuse these potent agents. Under the stress of meeting productivity quotas, the busy clinician is frequently unable to make a specific etiologic diagnosis in the ambulatory setting. Therefore, much of the treatment is empiric and may be influenced by both patient expectations and a provider unique approach (6). In the hospital, pharmacies have control over the use and misuse of antibiotics. In the community and nursing home, the only control is the practitioners' good sense. The influence of drug company "detailing" on prescribing practice of oral antibiotics also has a profound impact in this particular setting. Broad spectrum antibiotics may be prematurely used because of the fear of bacterial resistance to established antibiotics even when there is no evidence that this is a clinically important issue in the majority of cases. There is a need for clearly establishing indications for use of both old and new antibiotics. However, the difficulty in reaching consensus on indications for antibiotic use has been widely recognized (24). The role of guidelines and education on the promotion of cost-effective patient care need to be explored.

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