

Clinical Choices of Antibiotics: Judging Judicious Use

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Presentation Summary

Scientific literature widely documents the current overuse of antibiotics but often does not address the issue of the judicious use of antibiotics. Multiple analyses of prescribing patterns consistently reveal inappropriate prescribing of antibiotics, even when the clinician is aware of appropriate antibiotic use. In addition to overprescribing antibiotics, providers frequently address therapy failures by switching to same-class antibiotic agents.

Additional investigations report that prescribing of antibiotics at the first office visit tends to increase, rather than decrease, costs and has marginal impact on patient outcomes. Patient education interventions, delivered prior to illness, can significantly reduce inappropriate use of antibiotics and reverse resistance trends. A variety of developments in antimicrobial use and resistance and newer antibiotic and respiratory infection management strategies are discussed.

Media news reports warning against antibacterial cleaning agents coupled with the Centers for Disease Control and Prevention's (CDC) recent position on judicious use of antibiotics are influencing the public's ideas regarding antimicrobial overuse and resultant increased bacterial resistance. However, this new awareness has not substantially affected changes in the antibiotic prescribing culture of the provider; antibiotics are highly demanded and freely prescribed. Moreover, across the US borders, antibiotics are widely available over the counter to a population who is largely unaware of the seriousness of the resistance issues, which are of great concern to the medical community.

Broad spectrum effects of an antibiotic allow the clinician to provide empiric treatment for infection without as much diagnostic and microbiologic discovery, yet the effects can also negatively impact other microflora in the body by encouraging resistance in untargeted pathogens. Dosing of antibiotics is critical. Attempts by systems or individual patients to minimize doses to reduce costs will reduce effectiveness and potentially prolong therapy. Dose minimization can encourage resistance via a variety of mechanisms expressed under subminimum inhibitory concentration (MIC) conditions in the infection milieu, affecting the activity of tetracyclines, macrolides, and fluoroquinolones. Table 1 summarizes the

factors promoting the development of resistance.¹

Problems in Antibiotic Prescribing

Data from the National Ambulatory Medical Care Survey reveal that the leading infection diagnoses precipitating a care visit were upper respiratory tract infection (200 visits/1000 population), otitis media (80/1000), and lower respiratory tract infection (74/1000).² However, the top International Classification of Diseases (ICD)-9 codes for each category were *unspecified* upper respiratory tract infection, *unspecified* acute otitis media, and *unspecified* bronchitis. Clinicians seem to be treating many unspecified diseases with specific antibiotics. From an earlier survey, approximately half of the episodes of common cold and upper respiratory infections (URIs) and 75% of acute bronchitis cases were treated with an antibiotic (Figure).^{3,4} In a meta-analysis of clinical outcomes for patients with acute bronchitis receiving antibiotic therapy, Bent et al report marginal therapeutic benefits.⁵ Cough, purulent sputum, and work lost were decreased. In spite of this lack of data defending antibiotic use, 63% of patients with acute bronchitis seek care within less than a week of symptoms, 63% reported that they always received an antibiotic for this condition, and 69% believed the therapy was effective.⁶ Prescription of antibiotics for self-resolving viral conditions perpetuates patient and clinician perceptions that the antibiotic, not the natural course of the disease, was the factor in symptom resolution. This also greatly increases the likelihood of an antibiotic prescription the next time the patient visits the clinician for the same problem. In Saskatchewan, Canada, despite a more conservative stance on antimicrobial prescribing, 51% of prescriptions for infections in children were considered inappropriate.⁷ Although another Canadian study suggested nearly 90% appropriateness

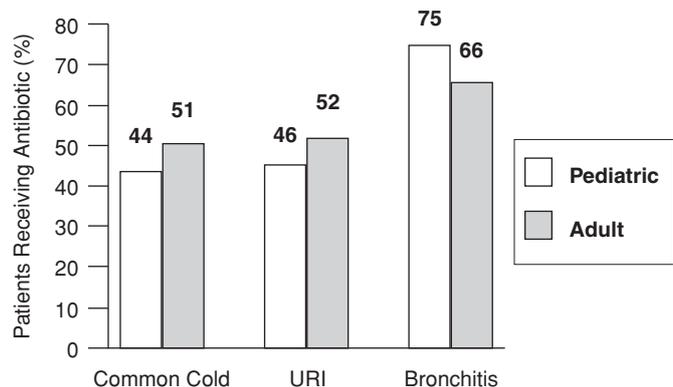
for such prescribing in pediatrics, 41% of the ICD-9 codes did not match the chart-documented diagnosis.⁸ Therefore, ICD-9 code shifting toward more antibiotic-justified diagnoses (eg,

Table 1. Factors Promoting Development and Spread of Bacterial Resistance

<ul style="list-style-type: none"> ■ Overuse or unnecessary use of antibiotics (URI, viral bronchitis, asymptomatic catheterized elderly, etc) ■ Use of newer antibiotics for simple common infections ■ Lack of recognition of risk of resistance to organisms colonizing patient but not direct targeted indication ■ Reluctance to narrow spectrum of antibiotics after culture and sensitivity results reported; ignoring susceptibility data ■ Over-the-counter availability of antibiotics outside the United States ■ Inadequate dosing leads to inadequate response, which leads to longer exposure ■ Inadequate dosing leads to subMIC concentration, which leads to resistance (gene expression, efflux, permeability mechanisms) ■ Inadequate infection control, agricultural use of antibiotics

MIC = minimum inhibitory concentration; URI = upper respiratory infection. Source: Reference 1.

Figure. Antibiotics in Ambulatory Care: Use and Misuse



URI = upper respiratory infection. Source: References 3, 4.

purulent rhinitis becomes sinusitis) may further blur the percentages of justified antibiotic usage. Factors involved in presumptive antibiotic use are shown in Table 2.

Need for Change in Practice Culture

The CDC has launched a tremendous crusade for judicious use of antibiotics and has documented the critical need for such efforts. A CDC-authored study of more than 7500 pediatric encounters with 366 pediatricians and family practitioners in Georgia reveals that 43% of the encounters resulted in an antibiotic prescription.⁹ Even 18% of all patient/parent telephone contacts with these physicians resulted in an antibiotic prescription. Acknowledgment that antibiotic overuse is a factor in resistance was reported by 97% of the physicians, and 83% believed there is a need to selectively use antibiotics in URIs because of concerns about resistance. Despite this awareness, the CDC investigators found in chart

review that 70% of these physicians prescribed antibiotics for purulent rhinitis and sinusitis. Eighty-one percent of pediatricians and 93% of family physicians prescribed antibiotics inappropriately for bronchitis, with β -lactams prescribed by 58% and 74%, respectively. Moreover, antibiotics were prescribed for the common cold by 30% of the pediatricians and by 58% of the family physicians.

Patient and parent expectations play a large role in this inappropriate prescribing culture. Investigators at the Institute for Clinical Symptoms Improvement, a consortium of 19 private practice groups in the Minneapolis/St. Paul area, surveyed symptomatic adult patients and the parents of symptomatic pediatric patients. All patients presented with common colds but were otherwise in reasonably good health.¹⁰ Eighty-five percent of the visits were prompted by the patient's/parent's concern that they might not be experiencing just a cold. Parents were 2 to 2½ times more likely to request an antibiotic if they believed antibiotics are helpful for colds, and if they perceived that relieving symptoms and their severity warranted an antibiotic. The symptomatic adults, in addition to the above factors, requested antibiotics if they felt confident about how to treat a cold, if symptoms lasted too long, or if they believed antibiotics would speed recovery. Those adults were also half as likely to believe that too many patients use antibiotics to manage colds. The huge gulf in knowledge and responsible prescribing must be narrowed for patients and clinicians to view demands and use of antibiotics in a more optimal and judicious light.

Many clinicians prescribe antibiotics for URIs at the first office visit, based on the assumption that early intervention will reduce subsequent visits and ultimately reduce costs. Clinical investigators have studied the impact of this practice on costs of care and found that, in fact, the

Table 2. Rationale for and Against Presumptive Antibiotic Use

<p>For</p> <ul style="list-style-type: none"> ■ Diagnostic uncertainty: viral or bacterial ■ Sociocultural and economic pressures ■ Malpractice litigation ■ Patient and parent expectations/satisfaction <p>Against</p> <ul style="list-style-type: none"> ■ Evidence of clinical efficacy lacking ■ No difference in rate of return visits if antibiotic is given ■ Encouragement of bacterial resistance ■ Avoidance of side effects ■ Avoidance of cost
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reverse is true. A review of 59,000 episodes of discrete respiratory illness (excluding pneumonia) from the Practice Partner and Research Network revealed that while statistically significant, the reduction in second visits when antibiotics were prescribed on the first visit was unimportant (15.4% with antibiotics, 17.4% without).¹¹ Assuming an average of \$35 per visit, the total cost of care was \$60.22 for those who received antibiotics on the first visit (one third of cost was for the antibiotics) and \$42.01 for the adults who did not receive antibiotics (2% of total for antibiotics prescribed at second visit). These findings demonstrate that prescribing antibiotics neither saved on the number of visits nor cost of care.

Education Is Key

Restriction policies for antibiotics can reverse resistance patterns in some situations. In Finland, more than a 50% decrease (from 19% to 8.6%) in macrolide-resistant Group A β -hemolytic streptococcus (GABHS) infections was realized over 3 years after a national program was enacted to reduce outpatient usage of macrolides.¹² The role of education in promoting judicious use of antibiotics and consequent reductions in resistance is documented in a controlled study performed in rural Alaska.¹³ Providers and the public were educated regarding appropriate antimicrobial use; prescribing was monitored, and, subsequently, nasopharyngeal swabs were obtained from children to determine culture and sensitivity. The intervention group demonstrated a 22% decrease in antibiotic prescriptions per respiratory illness in children under the age of 5 years. Although investigators did not observe a change in the proportion of children carrying pneumococcus, they noted a 28% decrease in nonsusceptible *Streptococcus pneumoniae* in the intervention group. Furthermore, a reduction in fully resistant

strains (from 25% to 11%, $P = 0.007$) was obtained in the intervention group, but no statistical difference was seen in the control group (from 16% to 10%).

Integrating these educational benefits into the individual practice setting is often challenging: Patient education generally occurs at the worst possible time—when a patient is ill and least likely to be receptive to messages about antibiotics and resistance. Recognizing this issue, researchers at Kaiser-Permanente in Denver conducted a study of approximately 2000 patients.¹⁴ In one group, practitioners received education with prescriber profiling and academic detailing and educational materials regarding CDC guidelines for recognition and nonantibiotic means of self-support for URIs were sent to the patient's home. In the limited intervention group, patients received office materials only. Usual practice initiatives were used with 2 control groups. Antibiotic prescribing dropped significantly only in the full intervention group from 74% to 48% ($P = 0.003$) versus 82% to 77% and 78% to 76% for the limited intervention and control groups, respectively. Table 3 offers a detailed listing of interventions to promote optimal antimicrobial use.¹⁵

Trends in Antibiotic Use and Resistance

Increases in population antibiotic consumption generally lead to commensurate increases in bacterial resistance. In a 1991 to 1997 CDC surveillance study on pneumococcal infection, which involved 37 counties and 14.9 million people, those patients with the highest quartile of macrolide use were 2.1 times more likely to develop pneumococcal resistance to these agents—by National Committee for Clinical Laboratory Standards (NCCLS) breakpoints—and had a 1.6-fold greater likelihood of penicillin nonsusceptibility than

those in the lowest quartile of β -lactam use.¹⁶ However, the relationships between resistance and antibiotic-use patterns may not always be straightforward. In a multinational analysis, Baquero found that countries with the highest cephalosporin-to-penicillin use ratio have the higher pneumococcal resistance rates, presumably because of the intrinsically weaker activities of most oral cephalosporins against pneumococcus than those of penicillin, ampicillin, and amoxicillin.¹⁷ Use of cephalosporins increased 9-fold nationally between 1980 and 1992, but more disconcerting is the repeated use of this same class of agents after failure or intolerance of prior cephalosporin usage.¹⁸ An examination of 3 months of claims data (39,000 pharmacies and 630,000 prescriptions for cephalosporins) revealed that 62% of the prescriptions were for agents with lower activity

against *S pneumoniae* (eg, cefaclor, loracarbef, ceftibuten), and 53% of prescription switches were to another cephalosporin.¹⁹ Similarly, data from a New England health plan demonstrated that cephalosporins were prescribed 51% of the time in follow up to a prior episode of otitis media in which a cephalosporin was utilized.²⁰ Such prescribing patterns further contribute to *S pneumoniae* resistance. Furthermore, although penicillin-nonsusceptibility of pneumococcus decreased by 24% between 1998 and 1999 in association with the prior 3-year reduction of 9% in penicillin usage in Canada, an unexpected 12% decrease in resistance to macrolides occurred despite a 31% increase in macrolide use.²¹ The "driver" and "passenger" in multiple antibiotic resistance, encoded for by multiresistance transposons, may correlate more with the consumption patterns of primary "driving" antibiotics, eg, β -lactams. Additional data of this type are required to delineate these relationships more clearly, particularly for clonal spread of multiresistant strains.²²

Table 3. Multifaceted Interventions to Promote Appropriate Use of Antibiotics

Administrative	Denial of claims for inappropriate use Financial incentives and penalties
Antibiotic Control	Order forms, stop dates, restriction for class/indication, culture evidence, prior authorization
Point-of-Care Support	Computer-assisted management programs Clinical Pharm/ID specialist recommendations
Provider Education	Academic detailing, peer education, local opinion leaders, multidisciplinary interactive meetings
Patient Education	CDC information, Web sites, reassurance, "preseason efforts," well-care/follow-up visits for other problems
Clinical Guidelines	Local, organizational, governmental
Audit and Feedback	Internal membership and review External governing body

CDC = Centers for Disease Control and Prevention.
Source: Adapted from reference 15.

Impact of Macrolide Susceptibilities and Disposition on *In vitro* and *In vivo* Pharmacodynamics and Clinical Outcomes of Respiratory Infections

Although the percentages of *S pneumoniae* isolates considered by the NCCLS to be resistant to macrolides (MIC \geq 1) have increased throughout the 1990s, this increase is almost entirely observed in low-level resistance encoded for by efflux-mechanism gene expression. Efflux, expressed by the *mef* genes, can be encouraged by subMIC concentrations and involves active pumping of an antibiotic from inside to outside of the microbe. The high-level resistance, via methylation of ribosomal binding sites (by *erm* gene products), has remained stable at 6.5%, according to CDC surveillance.²³ A similar

percentage of high-level resistance can be derived from the data of Thornsberry et al, who observed that of 301 macrolide-resistant pneumococci (23.6% of tested isolates), 74% were susceptible to clindamycin (which is not subject to the efflux mechanism of resistance)—leaving only 6.1% of the total isolates with high-level resistance to macrolides.²⁴ The cumulative 93.6% susceptibility to clarithromycin at an MIC of 8 µg/mL in this analysis would be a more relevant breakpoint MIC for this drug, corresponding to a greater likelihood of methylation-type resistance at MICs above this breakpoint (ie, 100% - 93.6% = 6.4%). This analysis assumes that the pharmacokinetics and pharmacodynamics of macrolides and clinical outcome of pneumococcal infection treated with macrolides are less affected by efflux-related resistance than by methylation. Several pieces of evidence are pertinent to this consideration.

Prospective community-based evaluation of pneumococcal macrolide resistance provides for relatively low prevalence of a resistance problem. A multicenter study of community-acquired pneumonia (CAP) in 405 adult outpatients (immunocompetent, noninstitutionalized) with a quality sputum specimen and culture revealed 56 *S pneumoniae* isolates; 23% and 11% were penicillin and macrolide nonsusceptible, respectively.²⁵ These percentages are less than those reported in microbiology laboratory-based surveys in which isolates are collected, in part, from sites where higher resistance is expected (eg, sinusitis and otitis from recalcitrant disease after repeated antibiotic courses).

Maintaining concentrations of antibiotic within the space where the organism replicates allows the best opportunity for pathogen eradication and the least opportunity for resistance development. Therefore, differences between intracellular-

extracellular disposition play an intimate role in describing and predicting the static/cidal effects of various antimicrobials on intracellular and extracellular pathogens. The concentration of clarithromycin in the extracellular fluid of the parenchyma of the lung, such as epithelial lining fluid (ELF), has been measured at 34.5 mg/L after multiple doses.²⁶ This exceeds the MIC for virtually all efflux-mechanism resistant pneumococcal isolates, exceeds by more than 10-fold the ELF concentrations of azithromycin, and agrees with *in vitro* evaluations of these intra/extracellular disposition differences.²⁷ Additionally, the 14-hydroxy metabolite provides synergy not only against *Haemophilus influenzae* but also against one third of the isolates tested by Martin et al, with the remainder showing additive activity.²⁸ The metabolite is typically not accounted for in *in vitro* testing but is readily produced in the body and contributes to the overall drug effect.

Activity of clarithromycin against *S pneumoniae* has been maintained in the lung as seen in the most recent comparative treatment trials of acute exacerbation of chronic bronchitis (AECB); the cumulative eradication rate is 111/124 or 90% versus 79/94 or 84% for fluoroquinolones versus 29/44 or 66% for loracarbef.²⁹⁻³¹ An equivalent clinical and microbiologic outcome has been presented or published for more than 1000 patients in each arm of 6 CAP study comparisons of clarithromycin (1113 clinical responses/1234 total completed patients = 90.2%) versus a variety of newer fluoroquinolones (1108/1228 = 90.2%), including moxifloxacin and gatifloxacin.³²⁻³⁴ In the latter study, this equivalency was sustained despite 19% pathogen resistance for clarithromycin versus 0% for gatifloxacin. That difference in resistance did not translate to differences in clinical or microbiologic response probably because of the lack of impact of

efflux on *in vivo* success. A more direct example of this comes from a rat model of pneumonia induced with pneumococci having 3 levels of susceptibility to the macrolides: sensitive (MIC = 0.015 to 0.03 µg/mL), efflux range (4 to 16 µg/mL), and methylation range (> 64 µg/mL).³⁵ With clarithromycin treatment, 50% kill time was evaluated and found to be longer (1 to 1.5 weeks) for the efflux range and fully susceptible pneumococci compared with rats with high-level resistance pathogens (1.5 to 2 days). Therefore, it appears that the microbiologic and clinical response to clarithromycin of *in situ* pneumococcal infection is largely not affected by the lower-range resistance, again emphasizing the need to reevaluate the established breakpoints for the macrolides relative to their clinical outcomes and distinctive pharmacokinetics.

Similar findings pertaining to this *in vitro/in vivo* discordance include infections with GABHS and *H influenzae*. In a multicenter trial of more than 400 patients randomized

to receive either clarithromycin or azithromycin for streptococcal pharyngitis (80% with moderate illness), clinical cure was achieved in 98% of patients with clarithromycin and in 90% with azithromycin ($P = 0.002$).³⁶ Moreover, the eradication rate for clarithromycin was 94% versus 77% for azithromycin ($P < 0.001$); nearly twice as many patients in the azithromycin group required additional antibiotics to achieve response or eradication than in the clarithromycin group. This is not as a result of *in vitro* differences in activity, but *in vivo* disposition differences. This is further supported by a paradoxically more rapid recolonization rate of GABHS seen after treatment for streptococcal pharyngitis with azithromycin compared with penicillin, despite vastly different tissue penetration and persistence profiles.³⁷ The sequestration of azithromycin inside the cell provides excellent activity against Chlamydia, Legionella, and Mycobacterium avium intracellulae but may not consistently provide concentrations above the MIC for extracellular pathogens. Studies evaluating middle ear fluid eradication of *S pneumoniae* and *H influenzae* in otitis media revealed only 68% and 36% eradication, respectively, after a 5-day course. Although concentrations of azithromycin exceeded the MIC several fold, the authors suggested that insufficient extracellular concentrations promote this curious failure.³⁸ In contrast, eradication of *H influenzae* was demonstrated for 28 of 33 isolates in secondary bacterial infection of acute bronchitis treated with clarithromycin, despite MICs of 8 to 32 µg/mL.³⁹ Bactericidal activity in lung tissue was likewise demonstrated for this organism at similarly high MICs in an animal model of *H influenzae* pneumonia.⁴⁰ Some comparative clinical and pharmacodynamic features of clar-

Table 4. Clarithromycin: Applied and Comparative Considerations

<ul style="list-style-type: none"> ■ Indications: Broader range for clarithromycin ■ PK/PD clarithromycin: More balanced extracellular pathogens <ul style="list-style-type: none"> – Maintain higher activity against extracellular pathogens – Higher ECF concentrations negates clinical influence of efflux – 14-OH metabolite provides additive/synergistic effects (but not accounted for in <i>in vitro</i> testing) – <i>In vitro/in vivo</i> discordance: <i>S pneumoniae</i>, <i>H influenzae</i> activity – Less likely to create resistance <ul style="list-style-type: none"> Excreted faster from tissue and serum than azithromycin No lingering of ECF concentrations at subMIC levels ■ Immunomodulation: Decrease adhesion/virulence actors, decrease cytokine expression and level, (chronic mycoplasma/chlamydia infection, asthma, and sinusitis)⁴¹ ■ Once-daily dosing provided, emphasis on second-line use
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PK = pharmacokinetics; PD = pharmacodynamics; ECF = extracellular fluid; MIC = minimum inhibitory concentration.

ithromycin (including immunomodulatory characteristics) are noted in Table 4.⁴¹

These concepts serve as an underpinning for the recent recommendations for the management of CAP published by the CDC.⁴² The guidelines delineate the 2 different mechanisms of macrolide resistance and the stated potential to overcome this resistance with higher concentrations of drug in the tissue. Macrolides are recommended as first-line therapy for outpatient treatment, along with other choices (doxycycline, β -lactams with good antipneumococcal activity). Macrolides are also included in combination with a potent parenteral cephalosporin for CAP in hospitalized and critically ill patients. Similar discussions of resistance and first-line recommendations for the macrolides appear in the recently revised Canadian Infectious Disease Society and Infectious Diseases Society of America CAP guidelines.^{32,43} However, in the CDC guidelines, flu-oroquinolones are suggested to be reserved for patients who have an allergy to other drugs or who have failed on the prior regimen, or for the treatment of a penicillin-resistant *S pneumoniae* isolate (redefined for CAP as MIC ≥ 4 $\mu\text{g/mL}$). This reservation in first-line use recommendation of quinolones is, in part, because of reported increases in pneumococcal resistance with increased usage, and the reduction of sensitivity of other pathogens (eg, pseudomonas) with higher use profiles in institutions.⁴⁴

For example, in 1999 at Long Beach Memorial Medical Center, 773 isolates of *Pseudomonas aeruginosa* obtained from adults were only 62% susceptible to levofloxacin and 57% susceptible to ciprofloxacin (antibiogram; T. Rushing, PharmD, personal communication, 2000). However, 119 tested isolates of pseudomonas cultured from children yielded 93% sensitivity to these quinolones. Because the burden of use of fluoroquinolones

is much less in children than in adults, this differential susceptibility pattern from the same institution demonstrates the notable impact of increased class usage on changing organism susceptibility.

Once-Daily Macrolide Therapy

Ease of use and potential improvements in compliance are incentives for the development and clinical use of once-daily dosage forms of antimicrobials. An extended-release form of clarithromycin was approved by the Food and Drug Administration (FDA) in March 2000. This form maintains serum concentrations and area-under-the-curve above the MIC for most of the dosage interval for susceptible bacterial strains.⁴⁵ The tissue concentration and active 14-hydroxy metabolite profiles are similar to the rapid-release drug. An *in vitro* model mimicking levels over time based on human pharmacokinetics suggests pharmacodynamic superiority for the once-daily clarithromycin formulation compared with azithromycin for *S pneumoniae* and for *H influenzae* when achievable concentrations of the 14-hydroxy metabolite were included.⁴⁶ In head-to-head comparisons with the rapid-release form, extended-release clarithromycin provided equivalent clinical, microbiologic, and radiologic cure rates in patients randomized for treatment for AECB and sinusitis.^{47,48} The gastrointestinal and taste adverse effects are suggested to be less in number and severity ($P = 0.020$) when compared with the rapid-release version.⁴⁹ Statistical equivalency of these outcome measures was also demonstrated for extended-release clarithromycin in a comparative study versus trovafloxacin for CAP, which was stopped early because of FDA restrictions placed on this fluoroquinolone.⁵⁰ Bacterial eradication of *S pneumoniae* by clarithromycin was excellent, as seen in other recent quinolone comparisons, with 12 of 13 patients who

had pneumococcus culture responding completely to therapy. Additional data demonstrating equivalency between a fluoroquinolone (levofloxacin) and extended-release clarithromycin in clinical cure, radiologic success, bacterial cure rate, and eradication have been recently submitted to the FDA for expected approval in the treatment of CAP.⁵¹

Conclusion

Multifaceted interventions must be taken to limit antibiotic resistance. Changes in practice culture that result in a reduction of antimicrobial use and a shift away from therapeutic nihilism within prescribing patterns is a major thrust of current disease management. Better diagnosis, judicious use of antibiotics, education, and vaccination must be encouraged. Monitoring of local and national resistance patterns and linking these patterns to antibiotic consumption, both institutionally and globally, must be ongoing efforts. Consideration of reserving newer antibiotics for established infection or failure of more time-tested efficacious choices, particularly in low resistance-prevalence areas, is strongly advised. Yet in order to encourage completion of therapy, compliance and ease of use of antimicrobials are necessary. Balancing of antibiotic drug formularies, with an emphasis on retaining potent members of each class of agents, and choices driven primarily by optimal disease management are necessary in managed care to preserve the antibiotics we have, or they may be prescribed into obsolescence. Many of these initiatives can best be accomplished within managed care settings using applied academic and clinical information.

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