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MANAGING ANTIBIOTIC RESISTANCE

Resistance Patterns and Effects on Practice

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Introduction

Antibiotic resistance is not a new phenomenon. It has been observed for as long as antibiotics have been in use. Initially, resistance was not considered a problem; it was rare and easily overcome by the use of higher doses or more potent agents. However, as antimicrobial use proliferated, so did resistance. Finally, in the early nineties, it began to be recognized as a cause for alarm. Resistant pathogens became increasingly difficult to treat and it seemed that antimicrobial efficacy, as a whole, was at risk.[1]

In recent years, however, there have been some positive developments on the resistance front.[2,3,4] First and foremost, clinicians have responded to the rise of resistance by pulling back on the volume of antibiotic prescription.[1,3] They have demonstrated growing vigilance to ensure that only select infections, i.e., those with bacterial etiology are treated with antibiotics.[1] In Canada, over the past decade, there has been a significant decrease in outpatient use of antibiotics, in spite of the addition of six new agents during that time period.[3] This seems to confirm a positive shift in attitude towards antibiotic prescribing, away from widespread use to a more sparing approach. Best news of all, resistance rates have been observed to decline in areas where antibiotic use has decreased.[1]

Not only do clinicians need to be able to determine which cases warrant an antibiotic, but when an antibiotic is required, they need to know which agent is going to be the most appropriate choice.

Nonetheless, antibiotic resistance remains a concern, particularly when we look at *S. pneumoniae*.[4]

Using fewer antibiotics is not the only strategy to reduce resistance and indeed, in many cases, sparing an antibiotic is absolutely inappropriate. Not only do clinicians need to be able to determine which cases warrant an antibiotic, they need to know which agent is going to be the most appropriate choice when it is required.

In many cases, the causative pathogen will not be resistant and so will respond to most of the available agents.[5,6] On the other hand, if a resistant pathogen is present, a more potent or specifically targeted agent may be necessary. However, since most antimicrobial prescription is empiric[7] and the causative pathogen is unknown, identifying the right antimicrobial remains a challenge. In the absence of a lab culture, we cannot definitively determine the pathogen or know for sure whether or not it is resistant. However, as research continues, new strategies are emerging to determine the likelihood of infection by a resistant pathogen which will help direct optimal therapy.

How Does Resistance Impact Your Patients and Practice? [1,7]

Infection with a drug-resistant pathogen could lead to:

- treatment failure and repeat physician office visits
- increased drug costs
- increased time to symptom resolution
- increased days off work
- increased morbidity, hospitalization and mortality
- increased resistant bacterial strains throughout the region

In respiratory tract infection (RTI), for example, current treatment guidelines offer some direction as to the most appropriate therapy.[5,6] However, it has been called into question whether current empiric treatment guidelines, which are based on general principles, are adequate to direct therapy given rapidly evolving and geographically disparate resistance patterns.[7,8]

The use of emerging predictive factors to specifically direct empirical therapy are explored here. Efficacy predictors based on drug pharmacodynamic characteristics are assessed, as well as risk factors including origin of infection, previous antibiotic therapy and the presence of underlying disease. These indicators may be used as tools by the clinician to evaluate the risk of infection with drug resistant organisms.

There is much at stake. Mounting evidence suggests that discordant therapy is responsible for increased morbidity and mortality,[9-13] so there is a clear need to 'get it right.'

Discordant therapy is responsible for increased morbidity and mortality.

It is reasonable to hope that as ongoing research reveals tools to help clinicians continue to "fine tune" antibiotic therapy, matching the most appropriate agent to each case of infection, the greater the chance of keeping resistance at bay.

Resistance Patterns

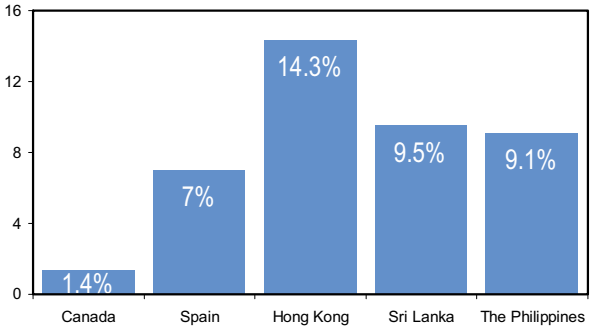
Historically, resistance rates have been directly correlated with antibiotic use: increased use seemed to promote increased resistance. This was clearly demonstrated in increased pneumococcal resistance to both the beta-lactam and macrolide classes.[1,4]

It's worth noting that an inverse pattern was observed in the Netherlands, when the policy of withholding antibiotics in children with all but the severest cases of otitis media resulted in exceptionally low resistance rates compared to other countries.[14]

Ciprofloxacin, the first fluoroquinolone to be released, was introduced in 1987 and uptake was swift. At first, resistance rates increased with use and fluoroquinolones seemed destined to follow in the footsteps of the beta-lactams and macrolides.[2]

In Canada, there was a small, but perceptible change in fluoroquinolone resistance as use increased. In 1993, the overall prevalence of non-susceptible ciprofloxacin isolates was 0%, but had risen to 1.7% in 1997-98 (p=0.01).[15]

The changes were more dramatic in other countries. For example, the prevalence of levofloxacin-resistant pneumococci in Hong Kong rose from 5.5% in 1998 to 13.3% in 2000.[18] These numbers seemed to indicate that the fluoroquinolone class was in jeopardy.



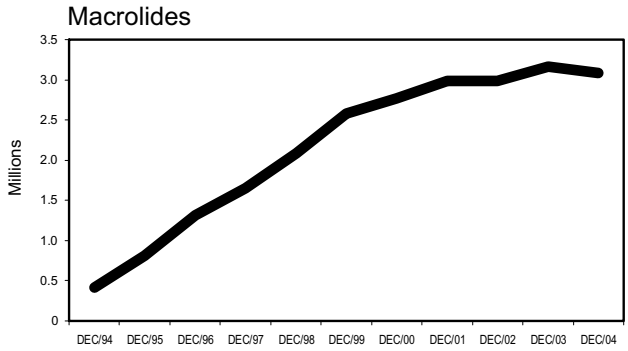
By 2000, fluoroquinolone resistance rates were strikingly high in some countries.[19-21]

However, the fluoroquinolone-resistant *S. pneumoniae* rate now appears to be stabilizing in North America.[2,4,22-25] This trend has a clear origin in the year 2000, and makes the fluoroquinolones an interesting exception to the increased use/increased resistance correlation previously observed. While use of the class has clearly increased, overall fluoroquinolone non-susceptibility rates remain low.[22-25] One report in the US actually identified a decline in levofloxacin-resistant *S. pneumoniae* isolates.[24] Incidence patterns in Canada have been found to parallel those in the United States.[23]

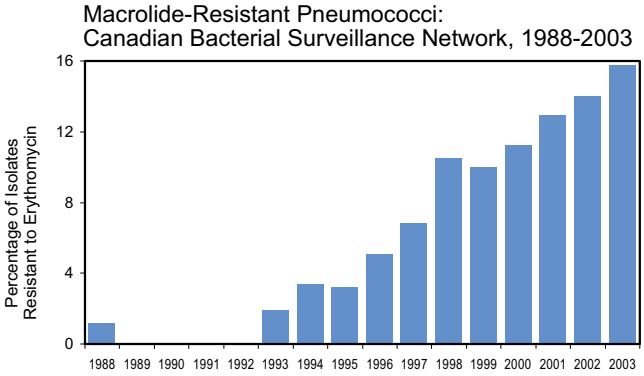
Fluoroquinolones are the Exception to the Rule?

What accounts for the fluoroquinolone class being able to maintain low *S. pneumoniae* resistance rates in spite of increased use?

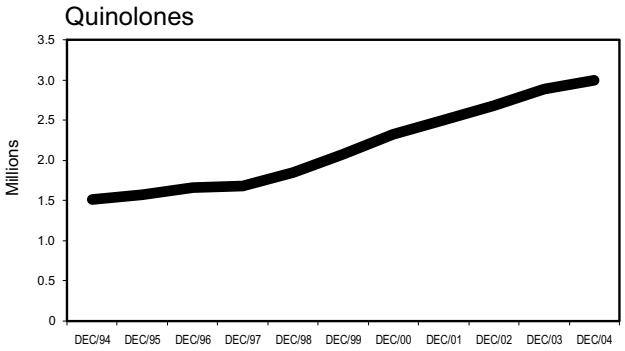
Two factors that emerged in 2000 may help explain this phenomenon and why it has happened in North America. First, the introduction of new fluoroquinolones with enhanced gram-positive activity and second, the introduction of the pneumococcal conjugate vaccine (PCV). These two factors may be acting synergistically to reduce selective pressure that would, unchecked, lead to the emergence of resistant *S. pneumoniae* mutations.[2]



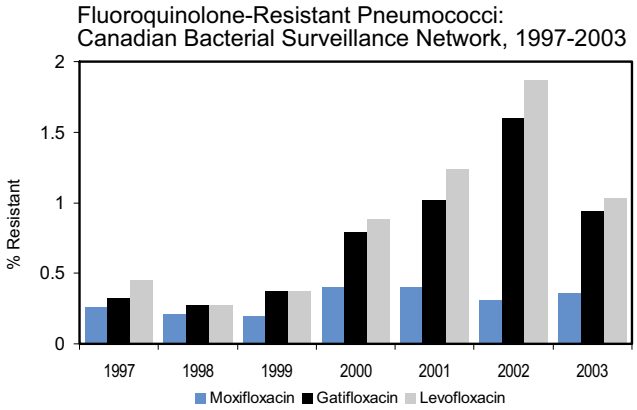
Increased use of macrolides in Canada to 2004.[3]



Escalating macrolide-resistant pneumococci in Canada to 2003.[4] Resistance levels increase with use and prevalence is high.



Increased use of fluoroquinolones in Canada to 2004.[3]



In contrast to macrolides, the prevalence of fluoroquinolone-resistant pneumococci in Canada remains low and has started to decline despite increased use.[4]

Effect of the Newer Fluouroquinolones

In 2000, two potent respiratory quinolones moxifloxacin and gatifloxacin, with their increased activity against *S. pneumoniae* were introduced in North America. These had a significant impact on the treatment armamentarium for pneumococcal disease.[2]

Before moxifloxacin and gatifloxacin, ciprofloxacin and levofloxacin had been widely used to treat respiratory tract infections but their borderline pneumococcal activity appeared to lead to poor eradication rates and increased pneumococcal resistance.[15-17] As ciprofloxacin and levofloxacin began to be replaced by the newer fluoroquinolones in the treatment of respiratory tract infection, pneumococcal resistance to the class as a whole began to stabilize.[2] When the respective pharmacodynamic properties of the fluoroquinolones are examined, significant differences become apparent and begin to explain the impact of the newer agents on pneumococcal resistance rates.

Pharmacodynamic Profile: Predictor of Efficacy

Evaluating pharmacodynamic/pharmacokinetic characteristics of antibiotics can be helpful in determining the potential for clinical success.

Recent research shows us that the ratio of the AUC to the MIC may be used as a predictor of efficacy.[7,17,26] An AUC/MIC ratio of >30 is needed for clinical success against pneumococci. The comparative chart below reveals that ciprofloxacin has a suboptimal AUC/MIC ratio against pneumococci, while those of gatifloxacin and particularly moxifloxacin are notably high. Although levofloxacin has adequate anti-pneumococcal activity, it is much less active against pneumococci than the newer fluoroquinolones.[17,20]

Newer fluoroquinolones predict better efficacy against S. pneumoniae

Since suboptimal therapy may result in insufficient eradication and the subsequent emergence of resistant mutations,[17] it is clear that PK/PD parameters such as the AUC/MIC ratio can act as a useful predictor of antibacterial efficacy.

Agent	Ratio of $AUC_{24\ (\mu g/h/L)}$ to MIC_{90}
Ciprofloxacin (750 mg)	21
Levofloxacin (500 mg)	36
Gatifloxacin (400 mg)	83
Moxifloxacin (400 mg)	128

An AUC/MIC ratio of >30 is needed for clinical success against pneumococci.[2]

Effect of the Pneumococcal Conjugate Vaccine

The stabilization of fluoroquinolone resistance may also be supported by the introduction of the pneumococcal conjugate vaccine (PCV). Many resistant pneumococcal serotypes are covered by this vaccine and widespread vaccination programs, particularly among children, are thought to have played a role in preventing the spread of resistant pneumococci throughout the population.[2]

Identifying Risk Factors for Resistant Microbials in RTI

The case of pneumococci shows how evaluating PK/PD profile may help predict the efficacy of one drug over another.

Risk prediction factors are another useful means of fine-tuning empiric therapeutic choices. Environmental and individual patient risk factors may be used to assess the likelihood of infection by a drug-resistant pathogen. This would make the difference between prescribing an older agent, or a newer, more potent or specialized agent.

The following risk factors for carriage and infection with resistant pneumococci are emerging as predictive criteria to help select the optimal therapy: [1,5,6]

1. **Local resistance patterns:** Resistant isolates detected in the community.

   Practice Tip: Maintaining an up-to-date knowledge of resistance patterns in your geographic area may help direct therapy (e.g., local surveillance networks such as the Canadian Bacterial Surveillance Network http://microbiology.mtsinai.on.ca/research/cbsn.shtml).

2. **Presence of underlying disease:** COPD, FEV_1 impairment, cardiopulmonary disorder, immunologic compromise, chronic corticosteroid use; the sicker patient is more likely to be infected with a more virulent gram negative pathogen or resistant pneumococci.

   Practice Tip: Employ more aggressive treatment strategies in the compromised patient.

3. **Institutionalization (day care, nursing home, hospital):** Nosocomial and nursing home acquisition may be associated with greater probability of resistant infection.

   Practice Tip: Consider environmental factors to direct treatment decision.

4. **Recent antibiotic history (up to 3 months):** Prior use of an antimicrobial is associated with an increase in the likelihood that the infecting pathogen will be resistant to that agent.

   Practice Tip: Establish which antibiotic (if any) the patient has taken within the past three months and prescribe accordingly.

Conclusion

There are many reasons for hope in the management of antibiotic resistance. Physicians have already adopted more judicious prescribing habits, which are having an effect on resistance rates. Antibiotic selection may be fine-tuned by evaluating efficacy predictors and risk factors for infection with resistant organisms.

Most of the agents in the overall antibiotic armamentarium are still useful when resistance is not an issue. However, when resistance is a concern, it is important to prescribe the right agent for complete eradication. As with the case of *S. pneumoniae*, the newer fluoroquinolones (moxifloxacin or gatifloxacin) have enhanced potency and may be the optimal choice, particularly if resistance is suspected. And to assess the potential for resistant infection, it is advisable to pre-screen patients, taking into account local resistance patterns, any underlying health problems such as COPD, whether the patient has been in a hospital or nursing home and most importantly, if that patient has had antibiotic treatment within the previous 3 months.

In conclusion, while drug resistant pneumococci remain a threat, there is growing evidence to suggest that the progression of resistance may be slowed through building on the practice of judicious prescription of antimicrobial agents. Continuing research will uncover further means to assist the clinician in the difficult task of predicting infection with drug resistant organisms.

RTI case examples:

Woman, age 54

- presents with dyspnea, cough, purulent sputum
- no underlying illness
- FEV_1 > 50% predicted
- 2nd exacerbation within 3 months
- previous antibiotic: azithromycin

Treatment options:

a) no antibiotic; it will resolve on its own
b) erythromycin
c) a respiratory fluoroquinolone or ß-lactam/ ß-lactamase inhibitor
d) anti-pseudomonal agent (ciprofloxacin)

Man, age 32

- presents with dyspnea, cough, fever
- chest x-ray indicates pneumonia
- Type II diabetes
- no antibiotic use in past 3 months

Treatment options:

a) an advanced macrolide or a respiratory fluoroquinolone
b) an advanced macrolide plus a ß-lactam or a respiratory fluoroquinolone
c) macrolide or doxycycline
d) amoxicillin-clavulanate or clindamycin

Answers: *(a 2, c) 1*

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