Respiratory tract infections: etiologic agents, therapy and the role of telithromycin

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Prior industry grants: Merck, pneumococcal vaccine, approx 1998-2001

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Infections of the respiratory tract

- A reductionist might view the respiratory tract as a single tube with outpouchings
- Regularly colonized by bacteria: pneumococci, *Haemophilus, Moraxella, S. aureus*
- Other organisms infect when they are acquired: viruses, Chlamydia, Mycoplasma, Legionella
- When treatable organisms are present, antimicrobial therapy is indicated
- The clinician often doesn't know and is left with decision to Rx based on clinical findings

Causes of pneumonia, preantibiotic era (Heffron, 1939)

Organism found	*Number of cases*	*Per cent*
Pneumococcus	3,189	96.1
Streptococcus	94	2.8
Friedländer's bacillus	17	0.5
Influenza bacillus	7	0.2
Staphylococcus	6	0.2
Mixed infections	6	0.2
Total	*3,319*	*100.0*

In the modern era …

Data are much more difficult to determine

a. Less emphasis on microbiologic diagnosis

b. More emphasis on prompt administration of antibiotics

Dr. Austrian, 1960's

In 2000-5, even when specimen submitted, pneumococci not detected by routine lab in >50% cases of proven (bacteremic) pneumococcal pneumonia Musher, Clin Infect Dis, 2005

IDSA/ATS guidelines: "S. pneumo most common cause of pneumonia → hospitalization"

Pneumococcal resistance: SENTRY (pediatric isolates) Jones et al, IDSA, Annual Meeting, Abstract #476 October 2006

- 1990's, most prevalent types in kids (4, 6B, 9V, 14, 18C, 19F, 23F) were also most likely to be antibiotic resistant.
- Protein-conjugate pneumococcal vaccine for children (Prevnar) introduced in 2000
- Widespread use Prevnar $\rightarrow$ 95% decrease in pediatric infections by these types
- "Replacement strains," not included in Prevnar (6 (non-B), 19 (non-F), 35, 11 and 15) , are increasing

Pneumococcal resistance: SENTRY, (cont'd)

- These replacement strains have been subjected to antibiotic pressure in day care centers, etc. and show ↑ antibiotic resistance
- Thus, overall rate of antibiotic-resistant pneumococci fell in the first yrs of PCPV, but has ↑ and is now back to the 2001 level
- In 2005, pediatric isolates, amoxicillin R 5-10%, erythromycin 30%, TM/SMX 40%
- Replacement strains are not targeted by 9- or 11-valent vaccines under development

Protekt study, Tom File et al IDSA, Annual Meeting, Abstract #253 October 2006

- Isolates from adults tend to be more susceptible than those from kids
- Not much difference in levels of antibiotic resistance 2003 vs 2005
- About 6% resistant to amoxicillin, 25% to macrolides and TM/SMX; 1% to quinolones; 0% telithromycin

Recommendations for Rx community acquired pneumonia of unknown etiology, outpatients

In 2000/2003, IDSA recommended, “in no particular order”:

- Azithromycin
- Doxycycline
- Amoxicillin OR amoxicillin/clav acid
- Respiratory quinolone

In 2006, IDSA + ATS joint guidelines: original version added telithromycin “if no risks for enteric gram-negatives”

Recommendations for Rx community acquired pneumonia… outpatients 2007, in press

In 2006, IDSA + ATS joint guidelines:

1. Telithromycin is active against *S. pneumoniae* resistant to other antimicrobials commonly used for CAP (including penicillin, macrolides, and fluoroquinolones)

2. Several CAP trials suggest that telithromycin is equivalent to comparators

3. Add telithromycin (level I) if no risks for enteric gram-negatives

Recommendations for Rx community acquired pneumonia… outpatients 2007, in press

4. In regions with ≥ 25% high-level macrolide-resistant *S. pneumoniae*, consider use of alternative agents

5. There have been reports of severe liver toxicity and the reader should refer to any new information regarding appropriate prescribing of this agent

6. At present the committee is awaiting further evaluation by the FDA of the safety of this drug before final recommendation

Macrolide resistance: is it clinically significant?

Small case series of patients failing treatment with azithromycin (Fogarty, CID 31:613, 2000; Kelly, CID 31:1008,2000; van Kerkhoven J Antimicrob Chemother 51:691, 2003)

Emergence of resistance and death during treatment with a macrolide Musher NEJM 346:630,2002

Case control series: patients with pneumococcal disease who were taking a macrolide at admission are infected with macrolide-R isolate Lonks et al, CID 33:556, 2002 Daneman, Clin Infect Dis 43:432, 2006, CDC presentation, ICAAC 2006

How would telithromycin do in these cases?

Based on data obtained in phase III studies, telithromycin cured 67 of 76 patients with bacteremic pneumonia including 8 of 10 caused by macrolide resistant pneumococci

Quinolone resistance Musher, Uptodate, revised 2006

- Quinolones are recommended as treatment options and widely used in respiratory infections
- Overall level of pneumococcal resistance to quinolones in US is only 1-2%
- Many isolates that are called susceptible already exhibit one mutation. Effect of mutations is additive; a second mutation is likely to lead to resistance
- Resistance in the community is associated with increased use of quinolones (Canadian experience) (Chen NEJM 341:233, 1999)

Quinolone resistance (cont'd)

Pockets of increased resistance, e.g. nursing homes, where levels approach 15%

Historically, such pockets of resistance herald spread to the community at large

Case reports of clinical failures associated with infection by resistant strains (Davidson, NEJM 346:747, 2002; Kays, Pharmacother 22:395, 2002; Fuller, CID, 2005)

Three important additional points:

1. Anticipated use of quinolones in children

2. Societal concerns over widespread use of quinolones and R of gram negative rods

***3. C. difficile* infections increasing in community and highly quinolone-associated**

Summary

- Telithromycin is broadly effective against respiratory pathogens including ‘typical’ and ‘atypical’ causes of community-acquired pneumonia, with a negligible rate of documented resistance to date
- Telithromycin has minimal activity against anaerobic flora and none vs. enteric bacilli, limiting undesired antibacterial effects
- Overall safety of telithromycin does not appear to be very different from other drugs used to treat the same respiratory infections

Summary (cont'd)

Resistance of pneumococci to macrolides, tetracyclines and trimethoprim/sulfa is widespread and clinically significant

Resistance of pneumococci to quinolones is low, but ↑ in proportion to use. Additional problems include impending pediatric use, ↑ resistance of enteric bacilli + predisposition to *C. difficile*

No other oral agents 'in the pipeline'

Conclusion

Telithromycin appears to be an important option for treating outpatients with upper and lower respiratory infections, including acute bacterial rhinosinusitis, acute exacerbations of COPD and community-acquired pneumonia