Outpatient Antimicrobial Therapy

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Role of Antibacterials in Outpatient Treatment of Respiratory Tract Infection

Acute Bacterial Rhinosinusitis

What is the treatment of choice for ABRS?

1. Antibacterials
2. Antibacterials + nasal steroids
3. Nasal steroids
4. Neither antibacterials nor nasal steroids

25% 25% 25% 25%
**Bacterial Etiology of ABRS**

- *S. pneumoniae* 30-35%
  - With 20-30% intermediate and high level resistance to penicillin
- *H. influenzae* 15-25%
  - With 30-40% beta-lactamase producers
- *M. catarrhalis* 5-10%
  - With 99% beta-lactamase producers

**Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data**

- Searched the Cochrane Central Register of Controlled Trials, Medline, and Embase, and reference lists of reports
- Individual patients' data from 2547 adults in nine trials were checked and re-analyzed

(Lancet 2008; 371: 908)

**Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data**

- 15 patients with rhinosinusitis-like complaints would have to be given antibiotics before an additional patient was cured
- Patients who were older, reported symptoms for a longer period, or reported more severe symptoms took longer to cure but were no more likely to benefit from antibiotics than other patients

(Lancet 2008; 371: 908)

**Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis**

Double-blind, randomized, placebo-controlled trial of 240 adults with acute sinusitis

Randomized to:
1. Amoxicillin 500 mg TID and nasal steroid
2. Nasal steroid and placebo amoxicillin
3. Amoxicillin and placebo steroids
4. Placebo amoxicillin and placebo steroids

(JAMA 2007; 298: 2487-2496)
Primary Outcome: Proportions of patients with symptoms lasting ≥10 days

- Amoxicillin: 29/100 (29%)
- No amoxicillin: 36/107 (33.6%)
- Nasal steroid: 32/102 (31.4%)
- No nasal steroid: 33/105 (31.4%)

(JAMA 2007; 298: 2487-96)

Amoxicillin for Acute Rhinosinusitis

- Randomized placebo controlled trial of adults with uncomplicated, acute RS
- Amoxicillin 500 mg TID or placebo for 10 days
- Symptom improvement:
  - Day 3: Amox (37%); placebo (34%) p=0.67
  - Day 7: Amox (74%); placebo (56%) p=0.02
  - Day 10: Amox (78%); placebo (80%) p=0.71

(JAMA 2012; 307:685-692)

2012 IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

Clinical presentations which best identify patients with bacterial vs viral (any one)
- Persistent symptoms for ≥ 10 days
- Severe symptoms: fever ≥ 39°C and purulent nasal discharge or facial pain lasting for at least 3-4 consecutive days
- Worsening symptoms (“double sickening”)

2012 IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

Antibacterial choice
- Children: amoxicillin-clavulanate>amoxicillin (strong, moderate recommendation)
- Adults: amoxicillin-clavulanate>amoxicillin (weak, low recommendation)
- Other agents
  - High dose amoxicillin-clavulanate: with severe infection, daycare, age<2 or ≥65, previous antibacterial use, immunocompromised
  - No fluoroquinolones, macrolides, TMP-SMX, or 2nd and 3rd generation cephalosporins
  - Doxycycline alternative to amoxicillin-clavulanate
Comparison of Care at E-visits and Office Visits for Sinusitis and UTI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sinusitis E-visit</th>
<th>Sinusitis Office visit</th>
<th>UTI E-visit</th>
<th>UTI Office visit</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designated PCP</td>
<td>39%</td>
<td>42%</td>
<td>40%</td>
<td>64%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotic prescribed</td>
<td>99%</td>
<td>94%</td>
<td>99%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preventive care</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>7%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

(Arch Intern Med Nov 19, 2012 E1-2)

Acute Otitis Media

What is the drug of choice for acute bacterial otitis media?
1. Azithromycin
2. Amoxicillin-clavulanate
3. Amoxicillin
4. Cefdinir
5. Cefuroxime

S. pneumoniae % resistance (1999-2000)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>INT</th>
<th>RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN</td>
<td>12.7</td>
<td>21.5</td>
</tr>
<tr>
<td>AMOX</td>
<td>4.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2.0</td>
<td>25.3</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>2.0</td>
<td>25.7</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>1.4</td>
<td>25.8</td>
</tr>
</tbody>
</table>

(Antimicrob Agents Chemother 2001; 45: 1721)
### PCN-I Pneumococcus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MIC&lt;sub&gt;50-90&lt;/sub&gt; (mg/Kg/D)</th>
<th>Time&gt;MIC (%)</th>
<th>Time&gt;MIC (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox 40*</td>
<td>0.25-1.0</td>
<td>55-80</td>
<td></td>
</tr>
<tr>
<td>Cefaclor 40</td>
<td>8-16</td>
<td>0-20</td>
<td></td>
</tr>
<tr>
<td>Cefurox 30</td>
<td>0.5-2.0</td>
<td>40-56</td>
<td></td>
</tr>
</tbody>
</table>

* 80-100 mg/Kg/day in children

(Clin Infect Dis 1998; 26:1-12)

### Pneumococcal Susceptibility

- From the 1999–2000 to the 2004–2005 respiratory illness season:
  - Prevalence of isolates with intermediate penicillin resistance (minimum inhibitory concentration, 0.1–1 µg/mL) increased from 12.7% to 17.9%
  - Prevalence of penicillin-resistant isolates (minimum inhibitory concentration, ≥2 µg/mL) decreased from 21.5% to 14.6%
  - Prevalence of isolates resistant to erythromycin increased from 25.7% to 29.1%
  - The prevalence of multidrug resistance among isolates did not change (22.4% in 1999–2000 and 20.0% in 2004–2005)

(Clin Infect Dis 2010; 48: e23-e33)

### Meta-analysis: Macrolide Treatment of AOM

- Included blinded RCTs comparing amoxicillin or amoxicillin-clavulanate to macrolides (azithromycin, clarithromycin) in AOM in children
- Primary outcome: clinical failure measured 10-16 days after starting antibiotics

(Ann Pharmacother 2010; 44: 471-478)

### Meta-analysis: Macrolide Treatment of AOM

- 10 trials with 2766 children 15 months to 15 years old included
- Macrolides associated with increased risk of clinical failure (RR 1.31; 95%CI 1.07-1.60; p=0.008)
- Rate of adverse event, particularly diarrhea, significantly less in macrolide group

(Ann Pharmacother 2010; 44: 471-478)
Acute Otitis Media 2011

- In 1932, AOM and suppurative complications accounted for 27% of all pediatric admissions to Bellevue Hospital
- Today, severe AOM and complications occur, but mostly in children living in regions with limited access to medical care
- It is argued that previous studies were limited due to varying diagnostic criteria and inappropriate antibacterials and dose

AOM in Children <2 Years

- 291 children with AOM diagnosed with strict criteria
  - AOM-SOS scale
  - Middle-ear effusion
  - Moderate to marked bulging of the tympanic membrane or slight bulging accompanied by otalgia or marked erythema of the membrane
- Randomized to amoxicillin-clavulanate (ES) 90 mg/Kg/day or placebo for 10 days (NEJM 2011; 364: 105)

AOM in Children <2 Years

- Initial and sustained resolution of symptoms significantly greater with antibiotics
- Rate of clinical failure (persistence of signs of acute infection on otoscopic examination) by Day 5 and Day 12 was significantly less with antibiotics (4%; 16%) compared with placebo (23%; 51%)
- Mastoiditis developed in one child receiving placebo; diarrhea and diaper rash were more common in children receiving antibiotics (NEJM 2011; 364: 105)

Streptococcal Pharyngitis
True or False? Penicillin is the drug of choice in the treatment of bacterial pharyngitis?

1. True
2. False

Streptococcus pyogenes (% Resistance)

- Penicillin: 0%
- Cefdinir: 0%
- Macrolides: 6.6-6.9%
- Clindamycin: 0.5%
- Telithromycin: 0.2%
- Levofloxacin: 0.05%


Cephalosporins vs Penicillin for Group A Strep Pharyngitis

- Meta-analysis of 9 randomized, controlled trials in adults
- Odds ratio for bacteriological cure (OR 1.83) and clinical cure rate (OR 2.29) significantly favored cephalosporins
  (Clin Infect Dis 2004; 38: 1526)

Cephalosporins vs Penicillin for Group A Strep Pharyngitis

- Penicillin is inexpensive, narrow spectrum and well studied in the prevention of rheumatic fever
- Absolute difference between cephalosporins was 5.4%, thus one would need to treat 19 adult patients to see 1 additional bacteriological cure
IDSA 2012 Guidelines Group A Streptococcal Pharyngitis

- Rapid Antigen Detection Test and/or culture should be performed because clinical features alone do not reliably discriminate between GAS and virus
- Penicillin or amoxicillin for 10 days
- Alternatives: 1st generation cephalosporin (if not “anaphylactically sensitive”, clindamycin, clarithromycin, azithromycin
  (Clin Infect Dis 2012; 55: 1279)

“Expand the pharyngitis paradigm for adolescents and young adults”

- *Fusobacterium necrophorum*, cause of Lemierre Syndrome, causes pharyngitis in adolescents and young adults with an approximate incidence of 10%
  - GAS: 5 cases of complicated acute rheumatic fever and 1 death per 1,000,000 patients
  - *F necrophorum*: 20 cases long term disability and 11 deaths per 1,000,000 patients
- Penicillin or a cephalosporin, but not macrolides, are active in vitro

Antibacterial Options for Outpatient Treatment of Community Acquired Pneumonia

Etiology Outpatient-Treated CAP (in order of association)

- *S. pneumoniae* (most common organism in older patients and those with significant underlying disease)
- *M. pneumoniae* (most common in patients <50 yo and no co-morbidities)
- *C. pneumoniae*
- Viruses
2007 IDSA/ATS Recommendations: Outpatient Treatment of CAP

• Healthy, no use of antimicrobials within the past 3 months:
  – A macrolide (level I evidence)
  – Doxycycline (level III evidence)

• Presence of co-morbidities or receipt of antimicrobials within the past 3 months in which case an alternative from another class should be used:
  – A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, 750 mg levofloxacin): strong recommendation and level I evidence
  – Beta-lactam plus macrolide: level I evidence

• “In regions with a high rate (>25%) of infection with high level (≥ 16 mcg/ml) macrolide-resistant S. pneumoniae, consider the use of alternative agents.”
Azithromycin is least likely to be active against which of the following pathogens?

1. Chlamydia
2. Legionella
3. Mycoplasma
4. H. influenzae
5. S. pneumoniae

Pneumococcal Susceptibility

- From the 1999–2000 to the 2004–2005 respiratory illness season:
  - Prevalence of isolates with intermediate penicillin resistance (minimum inhibitory concentration, 0.1–1 µg/mL) increased from 12.7% to 17.9%
  - Prevalence of penicillin-resistant isolates (minimum inhibitory concentration, ≥2 µg/mL) decreased from 21.5% to 14.6%
  - Prevalence of isolates resistant to erythromycin increased from 25.2% to 28.1%
  - The prevalence of multidrug resistance among isolates did not change (22.4% in 1999–2000 and 20.8% in 2004–2005)

(Macrolides: Gram-negative activity)

- Azithromycin/clarithromycin in vitro superiority vs erythromycin against H. influenzae (98-99% of isolates susceptible to doxycycline)
- All agents are adequate in the treatment of Moraxella (but this is not a significant pathogen in most patients)

(Macrolides: Other pathogens)

- Reliable coverage of atypical pathogens, including Mycoplasma, Chlamydia, Legionella. Respiratory fluoroquinolones and doxycycline also with comparable coverage against these organisms
Macrolides in CAP

- Primary strength is atypical coverage and azithromycin/clarithromycin additionally appear to be adequate in their coverage of *H. influenzae* and *M. catarrhalis*
- Macrolides are unpredictable in pneumococcal susceptibility in certain high risk patients and resistance has been associated with clinical failure; widespread use of macrolides in other indications is contributing to this decline in susceptibility

Macrolide: adverse effects/interactions

- Upper gastrointestinal: less with sustained release products of erythromycin and with azithromycin, clarithromycin
- Ototoxicity: dose-related, cochlear, reversible. Risk factors: elderly, renal failure, liver failure

Macrolide: drug interactions

- Drug interactions: erythromycin and clarithromycin potent inhibitors of CYP 450 with associated increased warfarin, cyclosporine effect
- Azithromycin has little to no CYP 450 interaction

Azithromycin and CV Death

- Patients taking azithromycin, as compared to those who took no antibiotics, had increased risk of CV death (HR 2.88)
- Compared to amoxicillin, azithromycin was associated with increased risk of CV death (HR 2.49)
- Risk of CV death significantly greater with azithromycin compared with ciprofloxacin, but did not differ significantly from levofloxacin
Doxycycline

• Spectrum of activity is equal to or superior to extended spectrum macrolides vs *S. pneumoniae, H. influenzae, M. catarrhalis*, atypical pathogens
• Twice-daily (once-daily?) dosing regimen results in favorable adherence

S. pneumoniae Susceptibility (1999-2002)

<table>
<thead>
<tr>
<th></th>
<th>Blood (n=2459)</th>
<th>Pneum (n=1443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>88.4%</td>
<td>76.9%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>81.9%</td>
<td>73.4%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>92.6%</td>
<td>87.4%</td>
</tr>
<tr>
<td>Penicillin</td>
<td>76.6%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>97.0%</td>
<td>95.8%</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>99.6%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

(Diagn Microbiol Infect Dis. 2004; 49:147)

Doxycycline

• Almost completely absorbed in the duodenum after oral administration
• Unlike tetracycline, food does not impair absorption (however, concomitant iron and bismuth does)
• Nonrenal clearance

Doxycycline: Adverse Events

• Upper gastrointestinal: nausea, heartburn, epigastric pain, vomiting
• Esophageal ulceration (particularly if administered just prior to bedtime)
• Photosensitivity
• Teeth/bone deposition
Summary: Doxycycline

- Role in outpatient-treated community acquired pneumonia similar to that of the macrolides
  - Same or better spectrum of activity
  - Inexpensive compared to macrolides
  - BID dosing (same as clarithromycin), but advantage to azithromycin
  - Upper GI side effects with both macrolides and doxycycline, but greater incidence of more “severe” upper GI effects with doxycycline

Fluoroquinolones

Respiratory Fluoroquinolone Spectrum of Activity

- Predictable vs beta-lactam and/or macrolide resistant *S. pneumoniae*
- Outstanding activity vs *H. influenzae* and *M. catarrhalis*
- Predictable activity vs atypical pathogens, including Legionella, Chlamydia, Mycoplasma

Fluoroquinolones and Superinfection
Epidemic, Toxin Gene-Variant Strain of Clostridium difficile

- Background: recent reports suggest rate and severity of C. difficile disease is increasing

Multivariate Antibacterial Risk Factors for C. difficile

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>3.8</td>
<td>2.2-6.6</td>
</tr>
<tr>
<td>Quinolone</td>
<td>3.9</td>
<td>2.3-6.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3.4</td>
<td>1.8-5.4</td>
</tr>
<tr>
<td>Moxi/gatifloxin</td>
<td>1.6</td>
<td>0.5-4.8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.6</td>
<td>0.2-1.9</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.2</td>
<td>0.7-2.3</td>
</tr>
</tbody>
</table>

(Fluoroquinolones)

- Five years ago fluoroquinolones were among those agents (cefepime, penems, aminoglycosides) that could logically be used in the treatment of resistant gram negative infection
- The decline in activity vs Pseudomonas, Enterobacter, and E. coli, including ESBL-producers have greatly diminished the role of these agents in the treatment of resistant gram negative pathogens, including E. coli

Quinolones in CAP: Pros

- Gemifloxacin, levofloxacin, moxifloxacin cover virtually all suspected pathogens (PCN R S. pneumoniae, H. influenzae, Moraxella catarrhalis, Legionella, Mycoplasma, Chlamydia)
- Once-daily dosing
Quinolones in CAP: Cons

- Quinolones are (were?) active versus multidrug-resistant nosocomial gram-negative organisms.
- Risk factors for the hypervirulent *C. difficile*
- Does it make sense to use these agents in uncomplicated outpatient infection?

Cost of Oral Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Price 1</th>
<th>Price 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpodoxime 200 mg q12h</td>
<td>56.20</td>
<td>68.20</td>
</tr>
<tr>
<td>Cefuroxime 500 mg q12h</td>
<td>76.20</td>
<td>143.80</td>
</tr>
<tr>
<td>Azithromycin (Z-pack)</td>
<td>39.06</td>
<td>55.20</td>
</tr>
<tr>
<td>Clarithromycin 500 mg q12h</td>
<td>36.20</td>
<td>53.30</td>
</tr>
<tr>
<td>Clarithromycin XL 1 gm q24h</td>
<td>55.50</td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin 320 mg q24h</td>
<td>112.30</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin 750 mg q24h</td>
<td>113.60</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 400 mg q24h</td>
<td>60.90</td>
<td></td>
</tr>
<tr>
<td>Doxycycline 100 mg q12h</td>
<td>11.00</td>
<td>55.80</td>
</tr>
<tr>
<td>Amoxicillin 1 g q8h</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate 2 g q12h</td>
<td>67.80</td>
<td></td>
</tr>
</tbody>
</table>

Choice of Antibiotic in the Outpatient Treatment of CAP

- Patients with no co-morbidities and not recently exposed to antibacterials:
  - First choice: doxycycline (however, if I lived in the UK, it would be amoxicillin!)
  - Second choice: azithromycin
- “High risk”:
  - First choice: respiratory fluoroquinolone OR combination β-lactam + macrolide/doxycycline

Amoxicillin for acute lower RTI when pneumonia not suspected

- 2061 patients with lower RTI randomized to amoxicillin 1.0 gm TID or placebo for 7 days
- Investigators and patients masked to treatment allocation
- Primary outcome: duration of symptoms rated “moderately bad” or worse
- Secondary outcomes: symptom severity days 2-4 and new or worsening symptoms
  (Lancet Infect Dis Dec 19, 2012)
**Amoxicillin for acute lower RTI when pneumonia not suspected**

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin</th>
<th>Placebo</th>
<th>Hazard ratio/Conf intervals/P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td>Duration of symptoms moderately bad or worse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 1.06, 95% CI 0.96-1.18; p=0.229</td>
</tr>
<tr>
<td>Mean symptom severity</td>
<td>1.62</td>
<td>1.69</td>
<td>-0.07 [95% CI -0.15 to 0.007]; p=0.074</td>
</tr>
<tr>
<td>New or worsening symptoms</td>
<td>15.9%</td>
<td>19.3%</td>
<td>Number needed to treat 30 (18-811); P=0.043</td>
</tr>
<tr>
<td>Nausea, rash, diarrhea</td>
<td>28.7%</td>
<td>24.0%</td>
<td>Number needed to harm 21, 95% CI 11-178; p=0.025</td>
</tr>
</tbody>
</table>

*(Lancet Infect Dis Dec 19, 2012)*

**Infant Antibiotic Exposures and Early-Life Body Mass**

- Antibiotic exposure during the first 6 months of life associated with significant:
  - Increased body mass
  - Increased weight for length scores
  - Overweight (OR 1.22; p=0.029) at 38 months

*(Intern J Obesity 2012; 1-8)*

**Less is More: UTI in Males**

- UTI in 4,854,765 outpatient male veterans in 33,336 index cases
- 35% received ≤ 7 days and 65% > 7 days
- Longer duration was associated with increased late recurrence compared with shorter duration therapy (10.8% vs 8.4%; p<0.001)
- C. difficile infection was higher in long duration vs short duration therapy (0.5% vs 0.3%; p=0.02)

*(Arch Intern Med Dec 3, 2012)*
Impact of Macrolide Therapy on Pharyngeal Carriage of Macrolide-Resistant Streptococci

- Randomized, double-blind, placebo-controlled trial
- Azithromycin 500 mg QD X 3 days, clarithromycin 500 mg BID X 7 days, or placebo
- Primary outcome: proportion of macrolide-resistant streptococci
- Secondary outcomes: variation in the carriage of macrolide and tetracycline resistance genes and changes in macrolide MIC
  (Lancet 2007; 369: 482-490)

Zinc for the common cold

- Meta-analysis RCTs comparing oral zinc with placebo or no treatment
- 17 trials with 2121 participants
- Efficacy
  - 1.65 day ↓ cold symptoms
  - ↓ symptoms in adults but not children
- Adverse events
  - Bad taste: RR 1.65 (95% CI 1.27-2.16)
  - Nausea: RR 1.64 (95% CI 1.19-2.27)
  (Can Med Assoc J 2012; 184: E551-61)

Probiotic Update

- Possible mechanism(s) of action
  - Inhibition of pathogenicity of bacterial toxins
  - Lower intestinal pH and inhibit growth of pathogenic bacteria
  - Physically or chemically prevent adhesion and colonization of pathogenic bacteria
  - Induction or enhancement of immune response
  (Med Letter 2013; 55: 3-4)
Probiotics and C. difficile: Meta-Analysis

- Twenty trials with 3818 participants
- Probiotics reduced the incidence of CDAD by 66%
- Assuming a 5% incidence of antibiotic-associated CDAD, probiotic prophylaxis would prevent 33 episodes per 1000 patients
- Of probiotic-treated patients, 9.3% experienced ADEs compared with 12.6% in controls
  (Ann Intern Med 2012; 157: 878)

Vicks VapoRub

- Eligible patients aged 2 to 11 years with symptoms attributed to URIs characterized by cough, congestion, and rhinorrhea that lasted 7 days or longer
- 138 children randomized to Vicks VapoRub, petrolatum, or no intervention
- Parents massaged into child’s neck and chest 30 minutes before bedtime

Vicks VapoRub “works”. True or False?

1. True
2. False
VR, petrolatum, and no treatment on (A) cough frequency, (B) cough severity, (C) severity of congestion, (D) severity of rhinorrhea, (E) child's ability to sleep, (F) parents' ability to sleep, and (G) combined symptom score.