Lifting the lid off CAP guidelines

Dr. Andrew M. Morris
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12:00 - 13:00

web.mac.com/IDologist
Objectives

1. To review the epidemiology of community-acquired pneumonia (CAP)
2. To explore the evidence supporting ATS and IDSA practice guidelines over the past 15 years (focusing on outpatient CAP)
3. To chronicle the potential interaction between market forces and CAP guideline development
Disclosures

1. I was previously the Chair of the Pharmacy and Therapeutics Committee at Hamilton Health Sciences, with a mandate that included cost-effectiveness.

2. I was previously the physician lead for drug utilization at HHS, and received a stipend equivalent to approximately 10% of my income.

3. I negotiated an Infectious Diseases Research Fellowship at McMaster University with Bayer Healthcare (maker of Avelox®) worth $120K.
Napping (snacking) slide

- outpatient community-acquired pneumonia (CAP) is a relatively benign disease
- there is no evidence that any agent or combination of agents is superior to amoxicillin for outpatient CAP
- the development of guidelines for CAP management correlates more with market changes than with epidemiological or evidential changes
- authors of CAP guidelines have been cavalier with regard to safety
- CAP guidelines have potentially cost billions of dollars to the N. American healthcare system
Acknowledgements

Dr. Karen To (McMaster)
Dr. Trevor Jamieson (UBC)
Dr. Allan Detsky (U of T)
The Cardiologist, the Microbiologist, the Dentist, and her Husband: Getting to the Root of the Problem

Dr. Andrew Morris
Research Fellow in Infectious Diseases
Mount Sinai Hospital
March 1, 2000
Pneumonia is a common disease

- approximately 4.5 million cases annually
- 80% of cases are managed as outpatients
- 62,000 deaths/year (adjusted mortality rate of 22/100,000) in US
- 1.4 million hospital discharges in US
- in Canada, the mortality rate for CAP hovers around 12/100,000

American Lung Association, July 2007
www.cdc.gov
www40.statcan.ca
Pneumonia mortality has not changed over the years


American Lung Association, July 2007
Outpatient pneumonia is a benign disease

A PREDICTION RULE TO IDENTIFY LOW-RISK PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Michael J. Fine, M.D., Thomas E. Auble, Ph.D., Donald M. Yealy, M.D., Barbara H. Hanusa, Ph.D., Lisa A. Weissfeld, Ph.D., Daniel E. Singer, M.D., Christopher M. Coley, M.D., Thomas J. Marrie, M.D., and Wishwa N. Kapoor, M.D., M.P.H.

“Among the 1575 patients in the three lowest risk classes in the Pneumonia PORT cohort, there were only seven deaths, of which only four were pneumonia-related.”

Only 1 of these 7 patients were managed as an outpatient.

NEJM 1997;336:243-50
In-hospital case-fatality is low in young people

- Administrative database from Alberta, looking at all CAP admission from 1994-1999 in adults 18-55
- In-hospital case-fatality: 3.2%
- 10-day case-fatality: 2.1% (most deaths attributed to macroaspiration)

Clinical Infectious Diseases 2003; 36:413–421
CAP is a costly disease

- 10 million US doctor office visits
- annual cost ~$8.4 billion
- in-hospital cost: outpatient cost 17:1

Clinical Infectious Diseases 2003; 36:413–421
Summary 1

- CAP is a very common disease, and associated with considerable mortality
- outpatient CAP is a relatively benign disease
- in-patient CAP, for most young adults, is also a relatively benign disease
CAP Guidelinography

1998: Infectious Diseases Society of America publishes its own CAP guidelines
2000: IDSA update
2001: ATS update
2003: IDSA update
2007: joint ATS-IDSA update
<table>
<thead>
<tr>
<th>CAP Guidelines (abridged)</th>
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<tr>
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<tr>
<td><strong>&lt;60, no comorbidity</strong></td>
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<td>Mac or Tet</td>
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<tr>
<td><strong>&gt;60 and/or comorbidity</strong></td>
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<tr>
<td>2nd gen ceph OR</td>
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<td>2nd gen cephalosporin OR</td>
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<tr>
<td>Resp FQ OR Doxy</td>
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<tr>
<td>β-lactam/β-lactamase</td>
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<td>inhibitor +/- Mac</td>
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2007 CAP Guidelines: Outpatient Rx

Previously healthy and no use of antimicrobials within the previous 3 months:
- **macrolide** (strong recommendation; level I evidence)
  - OR
- **doxycycline** (weak recommendation; level III evidence)

Presence of comorbidities OR use of immunosuppressing drugs OR use of antimicrobials within the previous 3 months:
- **respiratory fluoroquinolone** (moxifloxacin, gemifloxacine, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - OR
- **β-lactam*** plus a **macrolide** (strong recommendation; level I evidence)
  - *amoxicillin 1g tid or amox-clav 2g bid recommended
CAP guidelines’ use of evidence for outpatient therapy recommendations

- reviewed all guidelines and extracted studies looking at outpatient CAP
  - randomized and blinded
  OR
  - systematic review or meta-analysis of similar trials
  - excluded duplicate trials
- extracted study design, and looked at clinical cure on intention-to-treat basis
CAP guidelines’ use of evidence for outpatient therapy recommendations

- 815 references
- 10 trials were identified, with only 4 trials (involving 6 comparator antibiotics) meeting our criteria
- 3/4 trials were designed as equivalence trials
- drugs involved:
  - 2 cephalosporins (cefditoren, cefpodoxime)
  - 2 macrolides (erythromycin, azithromycin)
  - 1 FQ (levofloxacin)
  - 1 penicillin (amoxicillin-clavulanate)
CAP guidelines’ use of evidence for outpatient therapy recommendations

Pooled cumulative clinical success rates for outpatient-only CAP studies

- Amox-clav: 90.3%
- Cephs: 90.1%
- Macrolides: 89.9%
- Levofloxacin: 86.3%
Recommndations for outpatient CAP and evidence

Number of patients failing to achieve clinical cure or improvement with β-lactam antibiotics compared with antibiotics active against atypical pathogens in all cause non-severe community acquired pneumonia.


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Recommendations for outpatient CAP and evidence

- there are 4 unpublished, blinded, randomized outpatient CAP studies on FDA file for moxifloxacin
  - 1 with amoxicillin 3g/day
  - 3 with clarithromycin 500mg bid
- all 4 studies show absolute equivalence

www.accessdata.fda.gov/scripts/cder/drugsatfda
Recommendations for outpatient CAP and evidence

- there is ample evidence of FQ and macrolide failure for pneumococcal pneumonia
- a search of the literature only finds a single case of penicillin failure
  - pt. was from an area of high pneumococcal resistance to penicillins
  - pt. had an empyema on amox-clav, where *S. pneumoniae* was recovered from thoracentesis (amox MIC=8)

*NEJM* 2002;346:747-50
Pneumococcal resistance

Toronto Invasive Bacterial Diseases Network, 2005
Summary II

• citing the data used to construct the CAP guidelines, there is no evidence-based reason for recommending a drug other than amoxicillin for outpatient CAP
• the data supports continued use of amoxicillin for outpatient CAP
for each antibiotic, we calculated the difference in months between the date of FDA approval and the first publication date of guideline inclusion

we obtained FDA approval dates from the FDA website

www.accessdata.fda.gov/scripts/cder/drugsatfda
Relationship of CAP guidelines to changes in the antimicrobial market

- Gemifloxacin
- High-dose amox/clav
- Gatifloxacin
- Moxifloxacin
- Trovafloxacin
- Grepafloxacin
- Levofloxacin
- Sparfloxacin
- Azithromycin
- Clarithromycin
- Cefuroxime axetil

- ATS 1993
- IDSA 1998
- IDSA 2000
- IDSA 2003

- FDA-approved antibiotics
- Date

- Nov '93
- Nov '98
- Feb '01
- Jun '01
- Aug '03

- 8m
- 15m
- 16m
- 22m
- 24m
- 16m
- 8m
- 16m
- 16m
- 5m
- 4m
Relationship of CAP guidelines to changes in the antimicrobial market

- mean latency from FDA approval to guideline inclusion: 13 months
- gemifloxacin was actually included in the guidelines before getting FDA approval for CAP
- telithromycin (Ketek®) was included by name in the 2003 guidelines before being FDA approved, and was only removed from the 2007 guidelines at the 11th hour
CAP guidelines have jeopardized patient safety

- grepafloxacin removed in 1999 due to concerns regarding QT interval prolongation and fatal cardiac arrhythmias
- sparfloxacin removed in 2001 due to phototoxicity
- trovafloxacin removed in 2001 due to hepatotoxicity
- gatifloxacin removed in 2006 due to dysglycaemia
- gemifloxacin causes rash in 32% of women <40 yrs
- telithromycin carries a black box warning regarding hepatotoxicity
Relationship of CAP guidelines to changes in the antimicrobial market

<table>
<thead>
<tr>
<th>FDA-approved antibiotics</th>
<th>Date</th>
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<tbody>
<tr>
<td>High-dose amox/clav</td>
<td>Nov '93</td>
<td>Feb '98</td>
<td>Nov '00</td>
<td>Aug '03</td>
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<tr>
<td>Gatifloxacin</td>
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<td>Moxifloxacin</td>
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<td>Trovafloxacin</td>
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<td>Levofloxacin</td>
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<td>Azithromycin</td>
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<td>Clarithromycin</td>
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<tr>
<td>Cefuroxime axetil</td>
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Relationship of CAP guidelines to changes in the antimicrobial market

- Gemifloxacin (ATS 1993)
  - High-dose amox/clav
- Moxifloxacin (IDSA 1998)
- Levofloxacin (IDSA 2000)
- Gatifloxacin (ATS 2001)
- Sparfloxacin
- Azithromycin (IDSA 2003)
- Clarithromycin
- Cefuroxime axetil

Date:
- Nov '93
- Feb '98
- Nov '00
- Aug '03
Summary III

- there is a suspiciously short latency from FDA approval of a patented drug to its inclusion in CAP guidelines
- by readily including drugs that have not been reasonably tested in the field, CAP guideline authors have exposed their patients to unnecessary risk
Economic impact of CAP guidelines

- we estimated 3.6 million cases of outpatient cap/year
- we then calculated 3 possible total treatment costs per year:
  - first using the price of a standard regimen of amoxicillin
  - second using the average price of all recommended single antibiotic regimens listed in the guidelines
  - third using the price of the most expensive single antibiotic regimen listed in the guidelines
Economic impact of CAP guidelines

- we did not consider combination regimens
- we used a constant price for all years in U.S. dollars, taken from a 2005 issue of *The Medical Letter*
- chose the most expensive regimen listed, regardless of the existence of a cheaper equivalent
- we calculated both aggregate cost estimates for the US for each year from 1993-2006 and total cumulative aggregate costs from 1993-2006
### Cheapest possible cost of a course of CAP treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>US cost</th>
<th>CDN cost</th>
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<tr>
<td>cefuroxime axetil (generic)</td>
<td>$76.20</td>
<td>$20.07</td>
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<tr>
<td>azithromycin (generic)</td>
<td>$39.06</td>
<td>$33.23</td>
</tr>
<tr>
<td>clarithromycin (generic-US only)</td>
<td>$36.20</td>
<td>$16.59</td>
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<tr>
<td>levofloxacin 750mg</td>
<td>$113.60</td>
<td>$49.85</td>
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<tr>
<td>moxifloxacin</td>
<td>$60.50</td>
<td>$28.60</td>
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<tr>
<td>doxycycline (generic)</td>
<td>$11.00</td>
<td>$5.86</td>
</tr>
<tr>
<td>amoxicillin (generic)</td>
<td>$9.00</td>
<td>$6.03</td>
</tr>
<tr>
<td>amox-clav 2g bid</td>
<td>$67.80</td>
<td>$59.75</td>
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source: *The Medical Letter* 2007;249:62
Economic impact of CAP guidelines

Annual costs in US of CAP treatment according to published guidelines since the publication of the first CAP guidelines in 1993.
Economic impact of CAP guidelines

Estimated cumulative cost of treatment of all cases of outpatient CAP with amoxicillin and according to the IDSA and ATS guidelines, since the introduction of CAP guidelines in 1993.
Summary IV

• CAP guidelines have potentially cost the North American healthcare industries billions of excess dollars
• the specific dosing of amoxicillin-clavulanate 2g and levofloxacin 750mg, where no generic equivalent exists, is curious
Endocarditis guidelines and CAP guidelines

| Endocarditis guidelines recommended antibiotics without sound clinical evidence | CAP guidelines recommend antibiotics without sound clinical evidence |
| Endocarditis guidelines have been treated as the standard of care | CAP guidelines have been treated as the standard of care |
| Endocarditis guidelines received a re-tooling this year | CAP guidelines are in sore need of re-tooling: safety, economics, evidence |
Silenced

• we have tried to get our work/opinions published in peer-reviewed journals (NEJM, Lancet, JAMA, CMAJ) as a commentary/perspective, but have been unsuccessful
• reviews usually dichotomous: one reviewer loves and endorses, the other reviewer is scathing in his/her rebuke of our commentary
Waking up (serviette) slide

- outpatient community-acquired pneumonia (CAP) is a relatively benign disease
- there is no evidence that any agent or combination of agents is superior to amoxicillin for outpatient CAP
- the development of guidelines for CAP management correlates more with market changes than with epidemiological or evidential changes
- authors of CAP guidelines have been cavalier with regard to safety
- CAP guidelines have potentially cost billions of dollars to the N. American healthcare system
Time to take a breath and answer questions

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