Analysis of Guidelines for Treatment of Community Acquired Pneumonia (CAP) in Outpatients

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Abstract

Background:

CAP, usually treated by General Practitioners (GPs) without precise knowledge of the offending organism and of its susceptibility (if bacterial), remains an important cause of morbidity and mortality. Guidelines are supposed to help in selecting safe and effective drugs, taking local epidemiology and resistance data into account while avoiding unnecessary costs. Our aim was to analyze current guidelines for non-hospitalized CAP patients in this context.

Methods:

Guidelines (published or updated after 2004; written in English or another major European language) were identified from www.guideline.gov, by systematic search of pertinent literature, and by direct contact. Resistance data for *S. pneumoniae* (most critical organism in this context) were obtained from the literature and main congresses abstracts (2007-2008), and from the main surveillance networks (EARSS, PROTEKT and ALEXANDER). Safety of the recommended drugs was assessed from the warnings mentioned in their respective official labeling (package insert). Costs were estimated by using the recommended dosages and treatment durations, and using lowest [generic] and highest [branded product] prices in Belgium.

Results:

13 guidelines for adults and 6 for children were reviewed. Major differences were noted between North American (favoring beta-lactam/macrolides combination and/or fluoroquinolones [adults]) and European guidelines (mainly recommending amoxicillin alone as 1st line therapy). Current resistance patterns of *S. pneumoniae* were often only poorly taken into account in guidelines (typical examples: macrolides and tetracyclines). Safety issues with several of the recommended antibiotics could also be identified (typical example: cotrimoxazole in children). Acquisition costs of the 1st line drugs often reached that of 2d line antibiotics (considered as most costly) because of the necessity to use larger doses (beta-lactams, e.g.) and longer durations of treatment.

Conclusion: In spite of the efforts made to construct effective guidelines, several issues were identified that may explain why GPs often do not follow them. The main problem seems to be a difficulty for guidelines to keep in pace with the ever moving bacterial resistance patterns and too much focus on the use of low cost drugs.

References

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Introduction

Community-acquired pneumonia (CAP) is an important cause of morbidity (1-9 cases per 1000 adults; [1-3]). The majority of these infections are treated in ambulatory patients. Despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available (4). In about half of the cases, no pathogen is identified. *S. pneumoniae, Mycoplasma pneumoniae and Chlamydia pneumoniae* are the most frequent bacterial pathogens encountered in non-epidemic settings. General practitioners (GPs) play an important role in CAP management by avoiding unnecessary hospital admissions and, consequently, curbing national health costs. This can only be achieved if the first line therapy is efficient and safe. Otherwise, treatment failures or untoward effects can occur, leading to hospital admissions. The aim of our review is to assess whether guidelines proposed to GPs are valid, since bacterial resistance patterns are evolving, new drugs are introduced, and new information related to older antibacterial agents become available.

Methods

Multi-steps approach examining the following sets of data

Treatment guidelines (2005 and after): identified from (i) the US National Guideline Clearinghouse (NGC) website (www.guideline.gov), (ii) systematic search through SCIRUS and search engines; (iii) direct contact with key opinion leaders in specific countries.

Susceptibility patterns: (i) search through original papers in PubMed (2007-2008) in the the 18th (2008) ECCMID; (ii) and EARSS (European Antimicrobial Surveillance System), TRUST (Tracking Resistance in the United States Today), GLOBAL (Global Landscape On the Bactericidal Activity of Levofloxacin), PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin),and Riedel (Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90) antimicrobial resistance surveillance programmes.

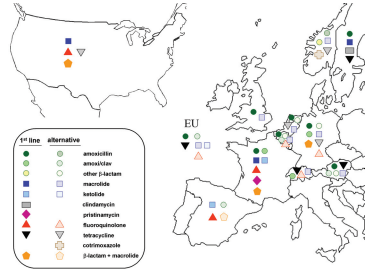
Safety of recommended antimicrobials: PubMed search (name of main antibiotics in guidelines + ""safety", "side effect", "adverse effect", or "toxicity"", and "community-acquired pneumonia"). Additional information from FDA website and the Belgian Center for Pharmacotherapeutic Information (CBIP/BCFI; http://www.cbip.be).

Pharmacoeconomics: Defined daily dose (DDD) from the World Health Organization (WHO) website (http://www.whocc.no/atcddd/).

Cost: calculated for treatments for antibiotics available in Belgium (http://www.cbip.be).

This poster will be made available for download after the meeting at http://www.facm.ucl.ac.be/posters.htm

Results



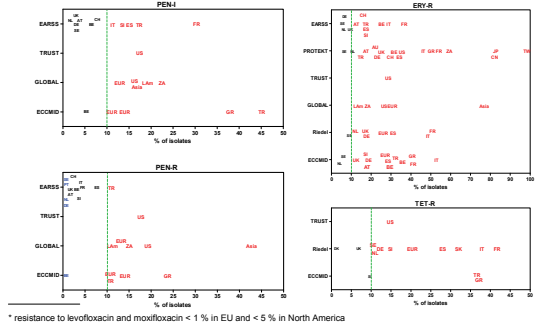
1. Analysis of guidelines:

With the notable exception of North-American guidelines (in which fluoroquinolones are included in first-line antibiotics),

- amoxicillin is the most commonly recommended antibiotic as first line therapy, but always with a large daily dose (2 to 3g);
- macrolides and fluoroquinolones (with doses of 0.5 to 1g for levofloxacin vs. 400mg of moxifloxacin) are proposed as alternatives or second line;
- amoxicillin-clavulanic acid or the combination of a beta-lactam and a macrolide is also but less often recommended as an alternative;
- major discrepancies between guidelines are observed for tetracyclines (first-line in several countries);
- the position of telithromycin (active against erythromycin-resistant *S. pneumoniae*) remains largely ill-defined;
- a few molecules are specific of some countries (cefuroxime-axetil in Belgium and Germany, pristinamycin in France or feneticillin in the Netherlands);
- recommended mean duration of therapy is 7 to 10 days (5 days only for ATS/IDSA; 3-days for azithromycin), but remains also unspecified in several guidelines.

2. Analysis of susceptibilities:

% of *S. pneumoniae* isolates resistant to first-lines antibiotics * by countries (country ISO code; EUR = European Union) – Countries in red are those where resistance > 10 % of isolates



* resistance to levofloxacin and moxifloxacin < 1 % in EU and < 5 % in North America

3. Analysis of side effects

Class	Drugs within the class	Most frequent or serious side effects	Populations at high risk / main contra-indication
β-lactams	amoxicillin	• anaphylactic reactions	• allergic patients
	clavulanic acid	• hepatic toxicity	• hepatic dysfunction
macrolides		• drug interactions (CYP450) • hepatic toxicity • cardiac toxicity (arrythmias, TdP)	• patients taking drugs metabolized by CYP450 • patients with antiarrythmics
fluoroquinolones		• musculoskeletal (tendinopathies) and cartilage toxicity • prolongation of the QTc interval and isolated cases of torsade de pointes	• elderly, patients taking corticoids, or with kidney, heart or lung transplants • patients taking other drugs with effects on QTc or antiarrythmics, or with hypokaliemia • pregnancy, lactation, infants
tetracyclines		• esophagitis and esophageal ulcerations • hepatotoxicity • photosensitivity	• pregnancy, lactation, infants
sulfamides		• agranulocytosis, anemia, thrombocytopenia, leukopenia, neutropenia, hypoprothrombinemia, methemoglobinemia, eosinophilia • metabolic and nutritional: hyperkalemia	• elderly patients or patients with preexisting folic acid deficiency or kidney failure. • pregnancy

4. Analysis of costs

The lowest treatment acquisition costs (in Belgium) for the doses and durations recommended are doxycyline (4 to 30 €) and amoxicillin (7 to 65 €) whereas a combination treatment of amoxicillin + clarithromycin is the highest (43 to 104 €). Fluoroquinolone acquisition costs are 31 to 63 €.

Conclusions

This study raises the question as to whether the use of "commonly recommended agents" such as amoxicillin is still scientifically sound, safe, and cost-effective if, as is often the case, it needs to be associated with clavulanic acid and/or a macrolide. Fluoroquinolones (for adults and with attention to side effects) might represent a better cost-effective approach but their wide use should be balanced with the risk of loosing "rescue" drugs that could become essential pieces of our armamentarium should resistance to penicillins and macrolides further increase.