# Critical Analysis of the Risk/Benefit Ratio Related to the Use of Guidelines for the Treatment of Community-Acquired Pneumonia

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## Background

Resistance of the target organism(s) is a collateral effect of antibiotics that can lead to treatment failure. It should therefore be included, together with conventional adverse drug reactions (ADRs), in the analysis of the risk/benefit ratio of anti-infective drugs [1]. Although this is implicitly taken into account in the setting of national or regional guidelines, the ever changing pattern of resistance may make them rapidly less effective than expected.

## Objective

To assess to what extent most recent guidelines for the treatment of community-acquired pneumonia (CAP) in Europe and North America are safe and well-balanced with respect to the risk of bacterial resistance and to ADRs.

## Methods

Multi-step approach examining the following items:

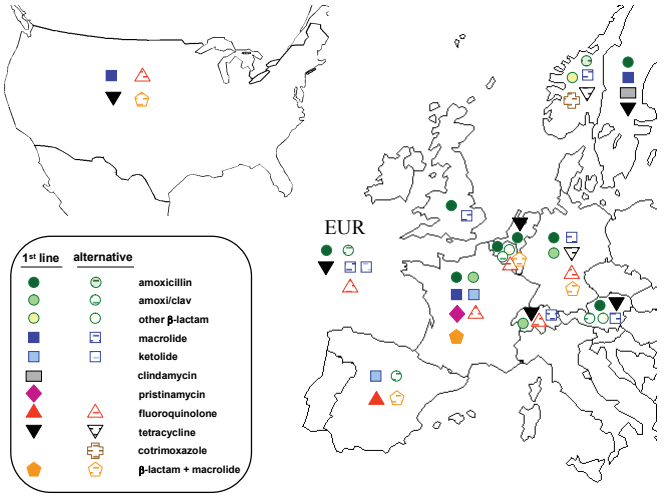
**Treatment guidelines:** identified from (i) the US National Guideline Clearinghouse (NGC; www.guideline.gov), (ii) systematic search through SCIRUS and search engines; (iii) direct contact with key persons in specific countries. Only guidelines published or updated after 2003 from European, national and North American organizations were selected.

**Safety of recommended antimicrobials:** compiled from the corresponding official labeling (EU SmPC if available; if not, Belgian and US labeling).

**Susceptibility patterns.** Resistance data concerning *S. pneumoniae* (most critical organism in CAP) as obtained from (i) systematic literature analysis (PubMed [2007-2008], (ii) abstracts of main congresses in 2008-2009 [ECCMID, ICAAC]); (iii) main antimicrobial resistance surveillance programmes/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], EARSS [European Antimicrobial Surveillance System]).

## Results

### 1. Treatment guidelines




Map concerning adult outpatients only

12 guidelines for adults (from EUR, DE, FR, GB, ES, NL, BE, SE, AU, CH, NO and the US) and 6 for children (from the WHO, FR, BE, AU, NZ and the US) were reviewed. Most European guidelines for patients without comorbidities recommended beta-lactams or macrolides as first-line therapy (tetracyclines in some countries), with fluoroquinolones as alternatives (except in ES).

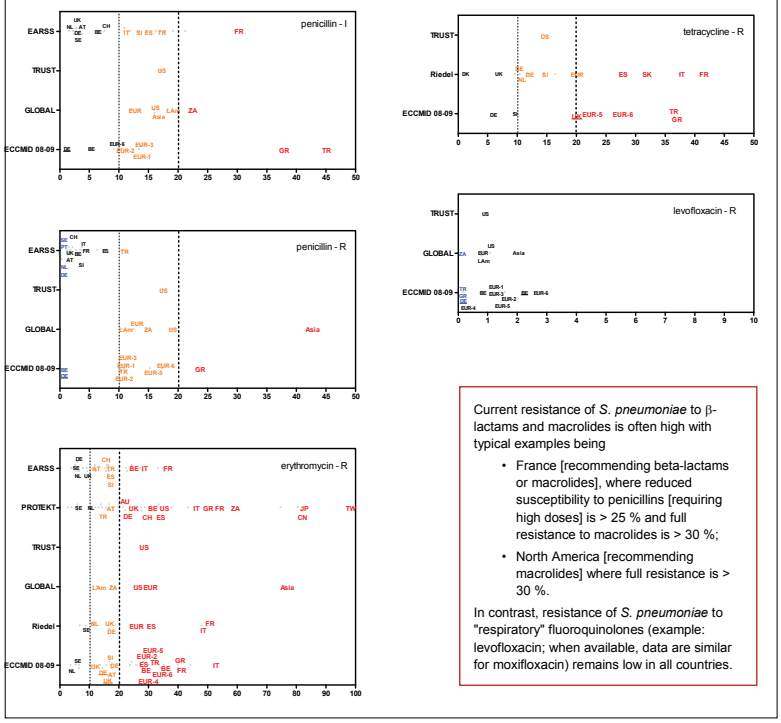
### 2. Adverse drug effects

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

Most frequent conventional ADRs are (i) allergy for beta-lactams (with hepatotoxicity if combined with clavulanic acid), (ii) impairment of hepatic metabolism of co-administered drugs for macrolides (with cardiac toxicity for IV forms); (iii) tendonitis (especially in elderly patients and those receiving corticoids) for fluoroquinolones (not registered for children; (iv) hepatotoxicity and photosensitivity for tetracyclines, and (v) hematologic disturbances for sulfamides .

### 3. Susceptibilities

% of *S. pneumoniae* isolates resistant to first-line antibiotics per country or region




Current resistance of *S. pneumoniae* to β-lactams and macrolides is often high with typical examples being

- France [recommending beta-lactams or macrolides], where reduced susceptibility to penicillins [requiring high doses] is > 25 % and full resistance to macrolides is > 30 %;
- North America [recommending macrolides] where full resistance is > 30 %.

In contrast, resistance of *S. pneumoniae* to "respiratory" fluoroquinolones (example: levofloxacin; when available, data are similar for moxifloxacin) remains low in all countries.

## Conclusions

Antibiotic classes commonly recommended (β-lactams, macrolides, and, in some countries, tetracyclines)

- may constitute rational choices for CAP in regions with low resistance rates but carry significant risks of conventional ADRs;
- expose patients to the risk of treatment failure in many other regions.

While antibiotics considered as alternatives have also their own conventional ADRs, integration of resistance pattern data, and continuous readjustment of guidelines based on a more global assessment of risk/benefit ratio may be necessary.

## Reference

1. Aronson JK. Drug therapy. In: Haslett C, Chilvers ER, Boon NA, Colledge NR, Hunter JAA, eds. Davidson's principles and practice of medicine 19th ed. Edinburgh: Elsevier Science, 2002: 147-63.

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