

Macrolide overuse for treatment of respiratory tract infections in general practice

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ABSTRACT

INTRODUCTION: High consumption of macrolides has been linked to increased macrolide resistance in the common pathogens of respiratory tract infections (RTIs). According to Danish recommendations, penicillin is the first-choice treatment for RTIs and macrolides should only be prescribed when a patient is allergic to penicillin or for treatment of mycoplasma pneumonias. The aim of the present study was to explore the prescription of macrolides for different RTIs to patients without penicillin allergy in general practice in Denmark.

MATERIAL AND METHODS: This was a cross-sectional study. Data were collected during a three-week period in January 2008 as part of the EU-funded project Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of Respiratory Tract Infections (HAPPY AUDIT). A total of 102 Danish general practitioners participated and registered patients with RTIs according to the Audit Project Odense method.

RESULTS: A total of 3,904 patients with RTIs were registered and 1,351 patients received antibiotics. Among these, 198 patients received a macrolide. In all, 136 patients received a macrolide without being allergic to penicillin. This proportion was highest for patients diagnosed with acute otitis media (71%), acute bronchitis (71%) or pneumonia (76%).

CONCLUSION: Overall, there was a considerable overuse of macrolide for treatment of all types of RTIs. The macrolide overuse found in this study cannot be explained by the aetiology of *Mycoplasma pneumoniae* since there was no epidemic in 2008.

FUNDING: Data for the macrolide study were collected from the HAPPY AUDIT study which was funded by the EU. The two first-authors each received DKK 30,000 from the PLU foundation for their work on the article.

TRIAL REGISTRATION: The HAPPY AUDIT method was registered and published in the BioMed Central.

Antimicrobial resistance is a major concern to the public health and has been associated with inappropriate consumption of antibiotics in ecological studies as well as individual patient-level studies [1, 2]. In Denmark, 90% of all antibiotics are prescribed in general practice, and 60-70% of antibiotics are prescribed to patients with respiratory tract infections (RTIs) [3, 4]. The majority of the

community-acquired RTIs are harmless, self-limiting and often of viral aetiology [4, 5].

Streptococcus pneumoniae and *S. pyogenes* are the most common and virulent bacterial pathogens in community-acquired RTIs [3]. According to Danish national recommendations, beta-lactam antibiotics are the first-choice treatment for these types of infections as both pathogens are highly susceptible to beta-lactam antibiotics [6] (see **Table 1**).

Macrolide antibiotics have a broader spectrum than penicillin. According to national Danish recommendations, they should only be prescribed for RTIs if a patient is allergic to penicillin or for pneumonia caused by *Mycoplasma pneumoniae* [6]. Macrolides are efficient in the treatment of RTIs caused by atypical pathogens due to the intracellular accumulation of macrolides [6]. However, the atypical pathogens are less frequent in Denmark and RTIs caused by *M. pneumoniae* primarily occur in epidemics, approximately every five years [7]. Macrolides are not recommended for upper RTIs caused by *M. pneumoniae*. Macrolides should only be prescribed to patients with pneumonia when the aetiology of *M. pneumoniae* has been confirmed by a laboratory test. However, during epidemics, macrolides are indicated for the treatment of pneumonia on clinical suspicion of *M. pneumoniae* aetiology [6].

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TABLE 1

Danish national recommendations for antibiotic treatment of respiratory tract infections in general practice. Data obtained from the Danish guideline Medicin.dk [6].

Diagnosis	First choice	Penicillin allergy	Comments
Acute otitis media	Penicillin V	Macrolide	Start treatment when child < 6 months or in case of ear secretion
Acute sinusitis	Penicillin V	Macrolide	Often self-limiting High CRP indicates treatment
Sore throat	Penicillin V	Macrolide	Often self-limiting Start treatment when positive StrepA test + clinical symptoms
Acute bronchitis	No antibiotics		Viral aetiology and self-limiting
Pneumonia	Penicillin V	Macrolide	Treatment with macrolide: verified <i>Mycoplasma pneumoniae</i> or suspected during epidemics
Exacerbation of COPD	Combination of amoxicillin and clavulanic acid	Tetracycline	Start treatment only when there is dyspnoea and coughing with increased purulent sputum

COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein.

Studies have shown that countries with a high consumption of macrolides have experienced a rapid increase in macrolide resistance in the common pathogens of RTIs [8, 9]. The macrolide resistance rate in Denmark remains low and macrolides are therefore a good alternative for the treatment of RTIs in patients who are allergic to penicillin. However, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) has registered a higher resistance against macrolides than penicillin in the most common RTI pathogens despite the lower consumption of macrolides [3]. This indicates that the use of macrolides in-

volves a greater risk of developing resistant bacteria than the use of penicillin when treating RTIs.

The use of macrolides in general practice in Denmark appears to be relatively high considering the treatment indications and the prevalence of patients with penicillin allergy [10]. The aim of the present study was to explore the prescription of macrolides to patients without penicillin allergy in different RTIs in general practice in Denmark.

MATERIAL AND METHODS

Design

This cross-sectional study was conducted as part of the EU-funded project Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of Respiratory Tract Infections (HAPPY AUDIT) [11]. A total of 1,971 general practitioners (GPs) from the five Danish regions were selected randomly and invited by letter, and 102 doctors volunteered to participate.

Population

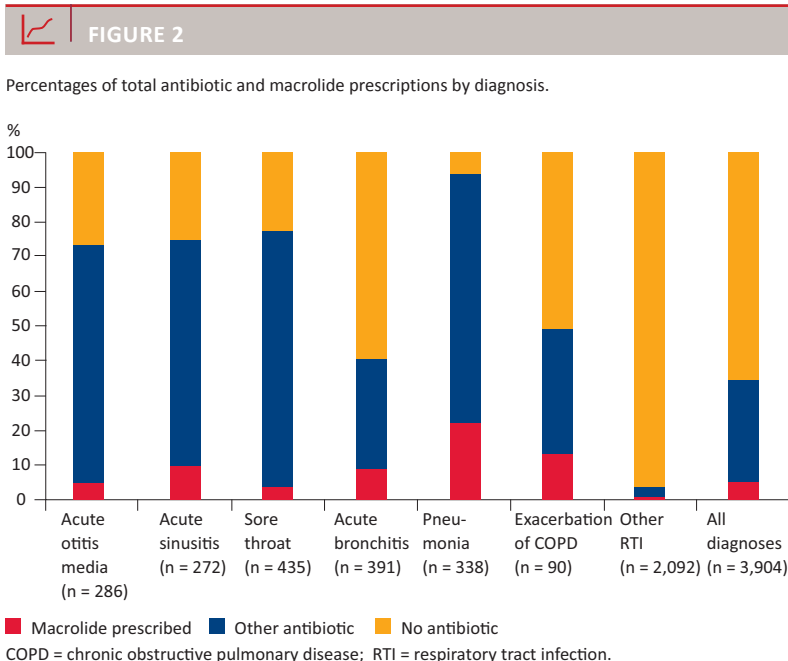
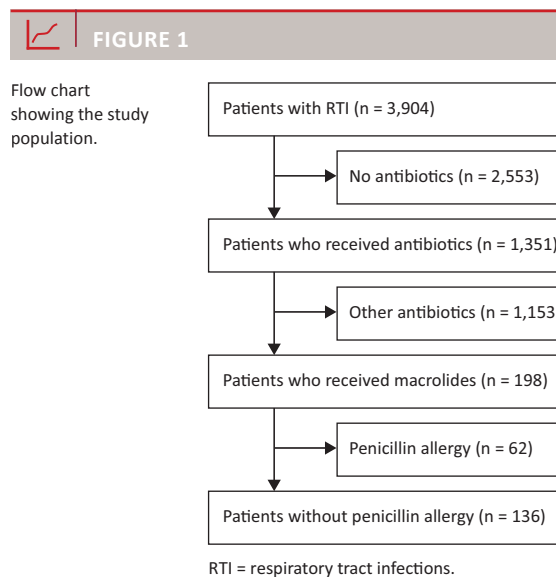
All patients with suspected RTIs attending primary care within normal working hours were registered. The GPs registered the patients during or shortly after the consultation. Only first contacts for the actual disease were registered and patients who had been receiving antibiotics prior to the consultation were excluded. Home visits and telephone consultations were not included.

Data collection

Registration took place during a three-week period in January 2008. Patients were registered using a prospective self-registration methodology based on a registration chart completed by the GPs according to the Audit Project Odense (APO) method [12]. The following variables were registered: age, gender, symptoms and signs, duration, diagnostic test, presumed aetiology, diagnosis, treatment with antibiotics, type of antibiotic, penicillin allergy, patient demand for antibiotics and hospital admittance. RTIs were coded according to the International Classification of Primary Care (ICPC-1) diagnoses: common cold (R74), acute otitis media (H71, H72), acute sinusitis (R75), acute pharyngitis (R72, R74), acute tonsillitis (R72, R76), acute bronchitis (R78), pneumonia (R81), exacerbation of chronic obstructive pulmonary disease (COPD) or chronic bronchitis (R95, R79), influenza (R80) and other respiratory tract infections (R71, R73, R77, R82, R83).

Statistical method

Data are presented as proportions with 95% confidence intervals. The diagnoses acute pharyngitis and acute tonsillitis were merged into "sore throat". The diagnoses with assumed viral aetiology such as common cold and influenza were merged with other RTIs into "others".



In total, the contacts were divided into seven diagnostic groups. The data were analyzed in Statistical Analysis Software (SAS) version 9.2 and Microsoft Office Excel 2007.

Trial registration: The HAPPY AUDIT method was registered and published in the the BioMed Central [11].

RESULTS

Figure 1 shows the study population of patients with RTIs in general practice during the three-week registration period. A total of 3,904 patients with RTIs were registered out of whom 1,351 (35%) received antibiotics. Among the patients receiving antibiotics, 198 (15%) received a macrolide. A total of 136 patients received a macrolide without being allergic to penicillin. This accounted for 69% of the macrolide prescriptions.

The number of patients in each diagnostic group and the proportion of patients with RTIs treated with antibiotics are presented in **Figure 2**. Between 70 and 75% of upper RTIs were treated with antibiotics. Among the lower RTIs, over 90% of patients with pneumonia received an antibiotic. The proportion of antibiotic prescription for acute bronchitis and exacerbation of COPD was 40 and 50%, respectively.

Table 2 shows the distribution of macrolide prescription to patients without penicillin allergy for the various diagnoses. The proportion of macrolide prescribed to patients without penicillin allergy varied from 41 to 79%. The proportion was highest for patients with acute otitis media (71%), acute bronchitis (71%) and pneumonia (76%).

Among patients treated with antibiotics, 63 patients (5%) were allergic to penicillin. Among these 63 patients, 62 (98%) received a macrolide.

DISCUSSION

Limitations and strengths of the study

This study was conducted as a cross-sectional study where GPs participated in an audit during a three-week period in January 2008. The collected data might therefore not represent prescription habits throughout the year. However, the overall proportion of macrolides sold in primary care in Denmark relative to penicillin is constant throughout the year [13]. GPs from all of the five regions of Denmark participated in the study. They were demographically similar to GPs in Denmark in general regarding age-distribution and type of practice. However, slightly more female than male GPs participated in this study.

The GPs participated in the audit on a voluntarily basis and their prescribing habits might therefore not represent the average prescriptions of antibiotics in Denmark. Each registration took approximately two



TABLE 2

Macrolide prescriptions to patients without penicillin allergy by diagnosis.

Diagnosis	Macrolide prescribed, n	Macrolide prescribed to patients without penicillin allergy	
		n	% (95% CI)
Acute otitis media	14	10	71 (48-95)
Acute sinusitis	27	15	56 (37-74)
Sore throat	17	7	41 (18-65)
Acute bronchitis	35	25	71 (56-86)
Pneumonia	74	56	76 (66-85)
Exacerbation of COPD	12	8	67 (40-93)
Other RTI	19	15	79 (61%-97)
All diagnoses	198	136	69 (62-75)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; RTI = respiratory tract infection.

minutes and the GPs had to reserve time to planned activities during the audit period. This could have resulted in some GPs not participating in the audit. The participating GPs might be more aware of rational antibiotic policies and be more interested in quality development. This might have caused an underestimation of the inappropriate use of macrolides found in this study. Participating in an audit might also influence the GPs' prescription habits. However, studies have shown that there is a good correlation between prescription patterns registered in an audit and the GPs' real prescription habits [11].

In general practice the diagnosis and decision to treat are often made simultaneously. The prescription of an antibiotic might therefore influence the GPs' diagnostic decisions, even though from a theoretical point of view, the diagnosis should be made before the choice of treatment. This might lead to a diagnostic misclassification bias.

Discussion of the main results

Despite the limited clinical benefit of antibiotic treatment for RTIs, 35% of the patients in this study received an antibiotic. More than 70% of the upper RTIs were treated with antibiotics although upper RTIs are often of viral aetiology and antibiotics have limited effect [5]. Acute bronchitis is mainly of viral aetiology and thus no antibiotic treatment is indicated; nonetheless, 40% received an antibiotic on this indication.

In this study, macrolides accounted for 15% of the total antibiotic prescriptions given to patients with RTIs in general practice. In a similar country such as Norway, where the same antibiotic recommendations for treatment of RTIs are in place, Gjelstad et al found that macrolide prescriptions accounted for 28% of all antibiotic prescriptions for RTIs [14]. This indicates a possible underestimation of the macrolide consumptions in our study.

The proportion of patients treated with macrolide without penicillin allergy was high for all diagnoses. However, the confidence intervals are relatively broad, as there are few patients in each diagnostic group. Nevertheless, our results show a very high prescription rate of macrolides to patients without penicillin allergy, irrespective of the focus of the respiratory infection. The proportion of macrolides prescribed to patients without penicillin allergy was highest for patients with acute otitis media, acute bronchitis and pneumonia. This indicates that macrolides were prescribed to upper as well as lower RTIs, for severe as well as harmless diagnoses and independently of the fact that some diagnoses are more common among children while others are more common in elderly.

The high prescription rate of macrolides for patients with upper RTIs is problematic because a high macrolide resistance has been detected in *S. pyogenes* in countries with a higher consumption of macrolides [15]. Prescription of macrolides to patients with exacerbation of COPD is irrational due to the common viral aetiology and the fact that macrolides are inefficient against *Haemophilus influenzae* [6].

The majority of community-acquired pneumonias (CAP) in Denmark are caused by *S. pneumoniae* and penicillin is therefore the more efficient CAP treatment. Besides penicillin allergy, the other main reason for prescribing macrolides is a CAP caused by *M. pneumoniae*. This diagnosis should be verified by a diagnostic test. Since only first contacts were included in this study, a laboratory test result could not have been available at the time the GPs issued the antibiotic prescription. During an epidemic, a strong suspicion of *M. pneumoniae* aetiology and severe clinical symptoms indicate macrolide prescription for CAP. However, there was no *M. pneumoniae* epidemic in 2008 and therefore no reason for choosing a macrolide for patients who were not allergic to penicillin [7].

This study showed a very high prescription rate of macrolides for RTIs in patients without penicillin allergy, irrespective of the infection focus. This is not in accordance with the Danish recommendations for antibiotic prescription in general practice. When treating patients with RTIs, macrolide should be reserved for patients who are allergic to penicillin or cases in which CAP caused by *M. pneumoniae* is highly suspected.

Possible explanations for macrolide overuse

M. pneumoniae infections can be difficult to diagnose in general practice due to their mild symptoms and the lack of a specific point of care tests [16]. The difficulty in verifying the *M. pneumoniae* aetiology may explain the overuse of macrolide found in this study.

Many factors may influence GPs when they make

their decision on the treatment of patients with RTIs. The increased risk of resistance related to the use of macrolides may be overruled by other factors such as patients' wishes for a quick recovery, demands for an easy administration regime and previous experience with successful treatment with macrolides [17, 18].

Studies show that compliance when treating patients with RTIs improves with less frequent doses [19]. The newer macrolides have a longer serum half-life than penicillin and shall therefore only be consumed once daily. However, the longer half-life affects the extended post-antibiotic effect (PAE) which contributes to high resistance development against macrolides [8]. Some pharmaceutical companies have developed macrolides with a fruity taste; this increases compliance when treating children with RTIs. In comparison, penicillin has an unpleasant taste, which may decrease compliance. However, penicillin is a narrow-spectrum antibiotic and it affects the normal bacterial flora to a lesser extent than macrolides and causes less resistance development. Furthermore, penicillin is generally cheaper and has fewer side effects. The inappropriate overuse of macrolides in general practice in Denmark might also in part be due to aggressive marketing.

Globally, a growing development of resistance towards macrolides has been detected in *M. pneumoniae* [16]. This raises a concern for the future treatment of CAP caused by *M. pneumoniae*. Macrolide resistance has also been detected in the common pathogens causing community-acquired RTIs in Denmark [9, 15]. In 2009 the macrolide resistance in *S. pneumoniae* remained low (4%) in Denmark [3] compared with the United States where a high consumption of macrolides has resulted in a resistance rate above 30% [20].

In order to maintain a low macrolide resistance in Denmark and to ensure that macrolides continue being a good treatment choice in patients who are allergic to penicillin, and CAPs caused by *M. pneumoniae*, macrolides should be restricted to these two indications.

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