Antibiotic switch during treatment with antibiotics against respiratory tract infections in ambulatory care in Norway

Running title: Antibiotic switch in ambulatory care

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Abstract

***Objectives*:** To compare antibiotic treatment failure evaluated as switch from one type of antibiotics to another in ambulatory care.

***Methods*:** Data on all dispensed doxycycline, amoxicillin, phenoxymethylpenicillin and macrolides in Norway June 2013 - May 2015, was retrieved from the Norwegian Prescription Database. We computed switch rates for the selected antibiotics on day 1- 28 after initial dispensing, and the corresponding odds-ratios, adjusted for patients´ age and gender, and prescribers´ specialty.

***Results*:** Of 1.860.036 dispensed antibiotics, 103.076 (5.5%) were switched within 28 days. Within 10 days after the index date, the switch rate was highest for phenoxymethylpenicillin (4.1%), followed by amoxicillin (2.5 %), macrolides and doxycycline (2.2 %).

***Conclusions*:** The switch rate after initial dispensing of phenoxymethylpenicillin is higher than that of more broad-spectrum antibiotics. However, it is still low, supporting the recommendation of phenoxymethylpenicillin as first line treatment when an antibiotic is indicated for a respiratory tract infection in primary care.

Introduction

Antibiotic resistance is an increasing global health threat, and the need to keep a high relative use of narrow-spectrum antibiotics is essential.[1] In Norway, approximately 85 % of all antibiotics are prescribed in primary health care.[2] More than half of these prescriptions are for respiratory tract infections, although respiratory tract infections are largely self-limiting and often viral.[3, 4] Hence, a large proportion of the prescribed antibiotics in primary care seem to be clinically unnecessary .[5]

The most common bacteriae associated with respiratory tract infections in primary care are *Streptococcus pneumoniae*, *Haemophilus influenzae* and group A streptococci.[6] In Norway, 92.5 % of *S. pneumoniae* found in blood and cerebrospinal fluid cultures are susceptible to benzylpenicillin, while 7.5 % are intermediately susceptible. 79.2 % of *H. influenzae*, isolated from blood and cerebrospinal fluid, are susceptible to benzylpenicillin, while 20.8 % are resistant. There is no resistance to benzylpenicillin in group A streptococci.[2] In many European countries, there is very little use of phenoxymethylpenicillin, while it is much higher in some North-European countries, including Norway.[7] However, the relative use of phenoxymethylpenicillin in Norway has decreased during recent years,[2] although Norwegian guidelines for primary care recommends phenoxymethylpenicillin as first line treatment for most respiratory tract infections when antibiotics are indicated.[8]

The reason behind the relative decrease of phenoxymethylpenicillin may be that general practitioners experience treatment failures. The aim of this study was to compare antibiotic treatment failure of narrow- and broad-spectrum antibiotics for respiratory tract infections in ambulatory care, evaluated as switch from one type of antibiotic to another.

Materials and methods

Ethics

As the data is anonymous, with no possibility of backwards identification, no ethical approval was required. The project was approved by the Norwegian Prescription Database, ref 15/2923. The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

Data source

Prescription data from June 1, 2013 to May 31, 2015 was extracted from the Norwegian Prescription Database. The Norwegian Prescription Database contains information on all prescription drugs, dispensed at Norwegian pharmacies to patients in ambulatory care, i.e. general practice, out-of-hours services and specialist services.[9] Variables included in the study were personal identity number (encrypted), age, gender, prescriber´s specialty, ATC codes, trade names, number of defined daily doses per prescription and dispensing date.

Inclusion criteria

We included antibiotics mainly used to treat respiratory tract infections in Norway: doxycycline (ATC code J01AA02), amoxicillin (J01CA04), phenoxymethylpenicillin (J01CE02) and macrolides (J01FA – erythromycin, spiramycin, clarithromycin, azithromycin). If two or more of these antibiotics were dispensed to the same person on the same day, the prescriptions were excluded.

Antibiotic switch

An antibiotic switch was defined as dispensing of an antibiotic of a different group within 28 days after the index date. The index date was defined as the date of the first dispensing of a respiratory tract infection antibiotic.

Statistical analysis

The statistical analysis was conducted with IBM SPSS Statistics 22. We calculated the prevalence of antibiotic switch within 10 days from the index date and adjusted odds ratios (ORs) with phenoxymethylpenicillin as reference (Table 1). In addition, we calculated the total switch rate and adjusted OR for each antibiotic on all 28 days after the index date (Figure 1). The ORs were adjusted for age group, gender and prescribers´ specialty.

Results

29 697 (1.6 %) dispensings were excluded from the dataset, as they were dispensed to the same persons on the same day. The dataset consisted of 1 860 036 dispensings to 1 162 043 patients, corresponding to 22 % of the Norwegian population. The material constitutes 45.6 % of the total number of antibiotic dispensings for antibiotics in ATC group J01 (41.2 % of the total number of defined daily doses) in Norway during the study period. 103 076 (5.5 %) of dispensings were followed by an antibiotic switch within 28 days. Of the total number of respiratory tract infection antibiotics dispensed, 40.9 % were phenoxymethylpenicillin, 15.3 % amoxicillin, 26.1 % macrolides and 17.7 % doxycycline.

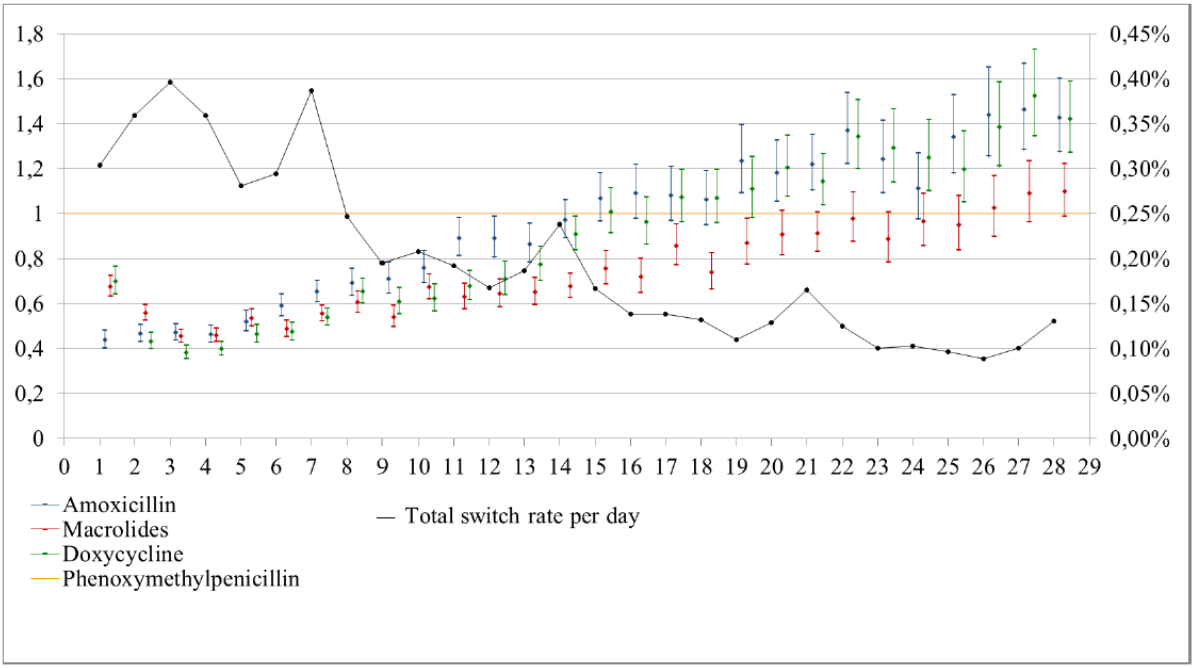
Within ten days after the index date, initially dispensed phenoxymethylpenicillin was associated with a higher switch rate compared to the other antibiotics (Table 1). In this period, the total switch rate was 3 %. The OR for antibiotic switch was higher in women, children 0-6 years and adults > 44 years. Among children 0-6 years, 4.7 % of dispensed phenoxymethylpenicillin was followed by a switch, compared to 2.0 % for the other antibiotics combined.

Table 1: Logistic regression analysis showing independent factors associated with antibiotic switch from the specified antibiotic to any of the other antibiotics within 10 days after initial dispensing. Total initial dispensings from the Norwegian prescription database, June 2013 - May 2015. The odds ratios (ORs) for each variable are adjusted for the other variables.

	Total initial dispensings	Antibiotic switches (%) within 10 days	OR (95% CI)
Initially dispensed antibiotic			
Phenoxymethylpenicillin	760882	31325 (4,1 %)	1 (reference)
Amoxicillin	284261	6977 (2,5 %)	0,55 (0,53-0,56)
Macrolides	484812	10787 (2,2 %)	0,53 (0,52-0,55)
Doxycycline	330081	7289 (2,2 %)	0,49 (0,48-0,51)
Patient gender			
Male	812955	22854 (2,8 %)	1 (reference)
Female	1047081	33524 (3,2 %)	1,17 (1,15-1,19)
Patient age group			
< 6	199210	6636 (3,3 %)	1 (reference)
6-12	93621	1924 (2,1 %)	0,57 (0,54-0,60)
13-18	97262	2288 (2,4 %)	0,69 (0,66-0,72)
19-44	634948	17566 (2,8 %)	0,86 (0,84-0,89)
45-64	458363	14871 (3,2 %)	1,09 (1,05-1,12)
65-79	273812	9414 (3,4 %)	1,19 (1,15-1,23)
80+	102820	3679 (3,6 %)	1,18 (1,14-1,23)
Prescriber speciality			
Not specialist	1349644	42925 (3,2 %)	1 (reference)
GP specialist	266070	8200 (3,1 %)	0,99 (0,97-1,01)
Specialist (other than GP)	244322	5253 (2,2 %)	0,73 (0,71-0,76)

The switch rate of amoxicillin and doxycycline was lower than that of phenoxymethylpenicillin the first 13 days (adjusted OR significantly < 1; Figure 1). After 14 days, their switch rate was as high as, or higher, than that of phenoxymethylpenicillin (OR ≈ 1 or > 1). The switch rate of macrolides was lower than that of phenoxymethylpenicillin the first 21 days. The total number of antibiotic switches peaked on days 3, 7, 14 and 21. The difference between phenoxymethylpenicillin and the other antibiotics was largest on day 3.

Figure 1: Total switch rate (right Y-axis) and adjusted odds ratios for switch, with phenoxymethylpenicillin as reference (left Y-axis), on day 1-28 after initial dispensing. Adjusted for patient gender and age group and prescriber's speciality. Vertical lines indicate 95 % confidence intervals.



Discussion

We found a total antibiotic switch rate of 5.5 % in the 28 days after first dispensing. In the first two weeks after the index date, the switch rate was higher when phenoxymethylpenicillin was initially dispensed.

Antibiotic treatment failure may be due to antibiotic resistance, faulty diagnosis (e.g. viral infections) and non-compliance.[10] Due to the not negligible penicillin resistance levels in *H. influenzae*[2] and the natural penicillin resistance in atypical bacteria, it is not surprising that the switch rate was highest for phenoxymethylpenicillin. In addition, when the prescriber chooses to prescribe an antibiotic other than phenoxymethylpenicillin, this may be due to a reliable etiological diagnosis, e.g. after PCR or culture, or to treatment failure after first line treatment, including the large proportion of respiratory tract infections in which antibiotics have no effect. A first line empirical treatment is bound to have a higher switch rate than second line treatments.

The antibiotic switch rate was high among the youngest patients, especially for phenoxymethylpenicillin. This may partly be explained by palatability, as phenoxymethylpenicillin has a sharp taste.[11] We can assume that this will lead to switch shortly

after the index date, and may partly explain the difference between phenoxymethylpenicillin and the other antibiotics on day 3.

We chose a 28 days period in order to be able to explore the development of switches after index date, and to avoid missing any switches. This definition of failure was also used in a similar study. [12] However, by using such a long period, both relapses and new infections will be included as switches. After day 14 the switch rate seem to level out. This indicates that a two week limit may distinguish between prescriptions attributable to the index infection, and prescriptions attributable to a new infection.

Most pharmacies are closed on Sundays. This may partly explain the peaks each seventh day, as all other days may be Sundays.

A similar study from the United Kingdom followed patients with certain specified diagnoses for 30 days.[12] Antibiotic switch was one of several components of treatment failure, present in 94 % of failures. Switches to all classes of antibiotics were included. In 2012, the treatment failure rate was 12.6% in upper respiratory tract infections and 21.0% in lower respiratory tract infections. Phenoxymethylpenicillin had the lowest failure rate (9.4 %) in upper respiratory tract infections. Due to differences between the studies, the numbers are not directly comparable. However, the level of antibiotic switches seems to be lower in our study. There is a widespread use of antibiotics for respiratory tract infections in primary care, although most of these conditions are self-limiting.[4] Up to 50 % of antibiotics prescribed for respiratory tract infections may be unnecessary.[5] Hence, many of the antibiotics in both studies may not have had a therapeutic effect. National differences in switch rates may be explained by differences in prescription rates and in the public's beliefs about antibiotics.

The antibiotic consumption in Norway is decreasing,[2] in accordance with the target of The National Strategy against Antibiotic Resistance to reduce antibiotic use by 30 % until 2020.[13] Whether a changed prescription practice in ambulatory care will affect the rate of treatment failures should be examined in future studies.

Strengths and weaknesses

Of antibiotics prescribed by general practitioners, only 92 % are dispensed.[14] We used the Norwegian Prescription database, a nationwide database that includes all antibiotics dispensed to out-patients in Norway. This method yields a more valid estimation of consumed antibiotics than databases based on prescriptions issued by general practitioners. Moreover, the data includes the whole population in Norway.

Our study has some limitations. As the Norwegian Prescription Database does not contain information on the diagnoses for the prescription, we do not know whether the initial antibiotic was for a respiratory tract infection, and whether a new antibiotic was prescribed for the same diagnosis as the initial antibiotic. The selected respiratory tract infection antibiotics constitute 97.5 % of antibiotics issued for respiratory tract infections in Norwegian primary care.[15] Furthermore, we have no information on serious consequences of treatment failure, i.e. hospitalization or death. However, these are rare events, constituting less than 1% of antibiotic treatment failures in a British study.[12] In addition, we do not know what caused the antibiotic switch. A switch might have several causes, e.g. treatment failure, side effects and unpleasant taste. Hence, we believe that our study results do not underestimate true treatment failure rates.

Conclusion

The antibiotic switch rate in ambulatory care is higher when the initially dispensed antibiotic is narrow-spectrum penicillin, compared to more broad-spectrum antibiotics. However, the switch rate is still low, and may partly be explained by other factors than treatment failure. Thus, our study supports the recommendation of phenoxymethylpenicillin as first choice when treatment is indicated for respiratory tract infections.

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Disclosure of interest

The authors report no conflicts of interest.

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