



Contents lists available at ScienceDirect

# American Heart Journal Plus: Cardiology Research and Practice

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Short communication

## Prescription practices of antibiotic prophylaxis among patients at high risk of infective endocarditis

Eva Havers-Borgersen<sup>\*</sup>, Anna P. Englund, Jawad H. Butt, Lauge Østergaard, Lars Køber, Emil L. Fosbøl

Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark



### ARTICLE INFO

#### Keywords:

Infective endocarditis  
Antibiotic prophylaxis  
Epidemiology

### ABSTRACT

**Introduction:** Antibiotic prophylaxis is recommended for patients considered in high risk of infective endocarditis (i.e., patients with prior infective endocarditis, heart valve prosthesis, and certain congenital heart diseases).

**Methods:** This study investigated prescription patterns and prescription filling patterns of antibiotic prophylaxis in patients at high risk of infective endocarditis. Prescription and prescription filling were evaluated by examination of patients records and an unselected patient cohort using Danish nationwide registries, respectively.

**Results:** Approximately 50 % of the patients were prescribed relevant antibiotic prophylaxis but not all filled their prescription.

**Conclusion:** Compliance with guidelines by Danish clinicians is only approximately 50 % and not all the patients fill their prescription. Clearly, there is room for improvement – an improvement which has the potential to reduce the incidence of infective endocarditis.

### 1. Introduction

Infective endocarditis (IE) is associated with high morbidity and mortality [1]. Transient bacteremia due to poor oral hygiene, periodontal diseases, or invasive dental procedures is known to be associated with IE [2]. For many years, antibiotic prophylaxis (AP) was recommended for patients considered at moderate or high risk of IE undergoing dental procedures, but in 2007 the European Society of Cardiology and American Heart Association/American College of Cardiology recommended restriction of AP to those at high risk of IE. Currently, both the European and the Danish guidelines recommend AP in patients with: 1) prior IE, 2) heart valve prostheses, 3) certain CHD (i.e. untreated cyanotic CHD or CHD-patients with cardiac prostheses) [3]. AP is given prior to dental invasive procedures [3]. Recently, American guidelines further recommended AP for patients with prosthetic material (i.e. rings, chords, or clips) and cardiac transplant with valve regurgitation [4]. However, the effect of AP on the occurrence of IE has not been investigated in a randomized clinical trial, and due to the low incidence of IE, such studies are challenging to conduct. In 2008 the UK National Institute for Health and Care Excellence advised against the use of AP due to lack of benefit, risk of side effects, and high cost [3]. However, this conclusion has been challenged due to the low level of

evidence, and in 2016 the National Institute for Health and Care Excellence changed the wording so that AP is not recommended routinely [5]. A meta-analysis concluded that AP is effective in reducing bacteremia and that restriction of AP may be associated with a higher incidence of IE [6]. Also, a recently published study by Thornhill et al. found an association between invasive dental procedures and IE in those at high IE risk and also between AP use and reduced incidence of IE [7].

Plausibly, preventing bloodstream infections in patients with high risk of colonization of bacteria on cardiac material could prevent IE. Yet, uncertainty remains about the efficacy of AP on the incidence of IE and current guidelines are conflicting and poorly evidence based. These conflicting and low-strength recommendations may entail low compliance with guidelines among clinicians, and secondary affect the patients' compliance with the clinicians' recommendations. Therefore, this study sets out to validate the compliance with current European/Danish guidelines by investigating the AP prescription patterns and prescription filling patterns in patients at high-risk of IE. AP should be prescribed by the cardiologists when the patient is identified as a high-risk patient, thereafter, the patient should be encouraged to fill in the prescription prior to dental invasive procedures.

<sup>\*</sup> Corresponding author at: Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København Ø, Denmark.  
E-mail address: [eva.havers-borgersen@regionh.dk](mailto:eva.havers-borgersen@regionh.dk) (E. Havers-Borgersen).

## 2. Methods

Patients who were either 1) discharged after IE (n = 646), 2) discharged after prosthetic heart valve replacement (n = 3593), or 3) diagnosed with CHD (n = 4937) in the period from January 2015 to December 2021 at Rigshospitalet in Copenhagen, Denmark were identified from patient records. Approximately 100 patients were randomly selected from each of the three categories, and a total of 329 patients were included in the study. During the random selection process, we made sure that patients from every index year were included in the study population and that the randomly selected patients were similar to the groups they were selected from in terms of baseline characteristics (i.e., age, sex, and type of surgical procedure/CHD diagnosis).

Patients with prior IE were identified using the following ICD-10 codes: I33 (acute and sub-acute endocarditis), I38 (endocarditis, valve unspecified), or I398 (endocarditis unspecified). Patients with IE were excluded if they were discharged with lifelong antibiotics or died during admission.

Patients undergoing heart valve replacement were identified using the following NCSP-codes: KFKD (mitral valve replacement), KFMD (aortic valve replacement), KFJF (pulmonary valve replacement), and KFGE (tricuspid valve replacement). Patients were excluded if they had IE prior to surgery, had a CHD diagnosis, were discharged with lifelong antibiotics, or died during admission.

CHD-patients were identified using the following ICD-10 codes: DQ20-26 (except DQ265-266, non-specific for CHD) and 10 patients from each selected category of CHDs (i.e., transposition of the arteries, malformation of the arteries, tetralogy of Fallot, ventricular septal defect, atrial septal defect, atrioventricular septal defect, malformation of the aortic valve, malformation of the tricuspid valve, malformation of the pulmonary valve, and malformation of the mitral valve) were included. Patients were excluded if the diagnosis of CHD was not correct.

The patient records were examined by two medical reviewers and the following data were collected: age/birth year, sex, diagnosis, surgery, and prescription of AP.

In order to examine prescription filling patterns, we also identified an unselected cohort of patients with prior IE, undergoing heart valve replacement, or diagnosed with CHD from Rigshospitalet after January 1994 using the Danish National Patient Registry and data on prescription fills (amoxicillin 2 g or clarithromycin 500 mg for those with penicillin allergy confer Danish guidelines) within 2 years after discharge/diagnosis were obtained from the Danish National Prescription Registry. AP is recommended prior to dental invasive procedures. Patients were excluded if they died within 2 years after discharge/diagnosis. The Danish state subsidizes dental visits if the visit takes place within every 12–24 months (less if active disease in the teeth, gingiva, or oral cavity).

The primary outcome of interest was prescription of AP. For patients discharged from the hospital (i.e., after IE or heart valve replacement), AP was defined as a prescription of relevant antibiotics within three months after discharge. Concerning CHD-patients, AP was defined as compliance with guidelines (i.e., antibiotics to those with cyanotic CHD, non-complete correction, or 6 months after complete correction prescribed within reasonable time after diagnosis/surgery depending on the exact indication, and no antibiotics if no indication). The secondary outcome of interest was AP prescription filling within two years after discharge/diagnosis. The proportion of patients prescribed relevant AP was examined, and patients with and without relevant prescriptions were compared. Further, the proportion of patients with filled prescriptions was examined.

## 3. Results

In total, 150 patients with prior IE were randomly selected and after exclusion criteria were applied, 132 patients (77 % men, median age 67

years [IQR 14–88 years]) were included. Moreover, 100 patients undergoing valve replacement (75 % men, median age 72 years [IQR 35–93 years]) were randomly selected and none of these were excluded. Finally, 100 CHD-patients were randomly selected, 3 of these were excluded, thus 97 patients with CHD (41 % men, born in 1948–2019, 79 % undergoing surgery) were included. All the randomly selected patients were similar to the groups they were selected from.

Among patients with IE, 63 (48 %) were prescribed AP within three months after discharge, and no appreciable difference with respect to age or sex was found when compared with those who were not prescribed AP (75 % men, median age 67 years [IQR 54–75 years] and 70 % men, median age 67 years [IQR 53–74 years], respectively). Among patients undergoing heart valve replacement, 56 (56 %) were prescribed AP within three months after discharge, and these were older compared with those who were not prescribed AP (76 % men, median age 76 years [IQR 68–80 years] and 77 % men, median age 65 years [IQR 61–73 years], respectively). Notably, prescription of AP was most common to those undergoing transcatheter aortic valve replacement (n = 43, 98 %). Among patients with CHD, 56 (57 %) were prescribed AP as recommended by guidelines and no significant difference in sex or age compared with those who were not prescribed AP were found (40 % men, median birth year 1992 [IQR 1983–1997] and 43 % men, median birth year 1992 [IQR 1984–1997], respectively). However, patients with CHD who received AP more often had malformations of the heart valves (n = 29 (53 %) versus n = 8 (19 %)) and underwent surgery less often (n = 38 (69 %) versus n = 18 (43 %)) than those who did not receive AP.

In total, 45 % of patients with prior IE, 49 % of patients undergoing valve replacement, and 37 % of patients with CHD filled an AP prescription within 24 months after admission/diagnosis. Fig. 1 depicts the proportion of prescription and prescription filling of AP.

## 4. Discussion

In this study, we examined prescription and prescription filling of AP in patients at high risk of IE in Denmark. The study yielded the following major findings: First, prescription of guideline-recommended AP ranged from 48 % to 57 % with the lowest compliance among patients with prior IE. Second, the proportion of high-risk patients filling AB prescriptions ranged from 37 % to 49 %.

Few prior studies have investigated compliance with guidelines and found similar low prescription rates [7–9] including a recently published study by Thornhill et al. who found that AP were prescribed to cover 32.6 % of high-risk patients during invasive dental procedures [7]. The present study also suggests that there is indeed room for improvement in the daily clinical work.

This study is limited by the fact that patients could be prescribed AP

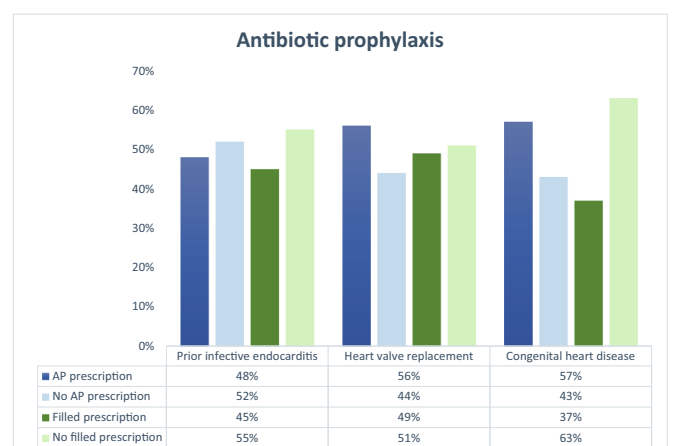


Fig. 1. Percent of patients in high risk of infective endocarditis who are prescribed antibiotic prophylaxis (AP) and those filling a prescription.

from their GP or dentist, which we cannot capture in our database looking at prescriptions. Nonetheless, the expertise within the field of prescription of AP to these patients lies with the cardiologists and we would expect that the majority of patients would (and should) receive the prescription from the specialists. When looking at prescription filling any doctor could have made the prescription, thus, we capture all prescriptions. Filling of the prescription however depends on the patient undergoing invasive dental procedure, which we do not have access to data on. The Danish state subsidizes dentist visits if they take place within every 24 months, which increases the change of patients visiting the dentist within 2 years after discharge/diagnosis. Further, we do not make sure that patients who filled in their prescription also ingest the drug, but prior studies on the concordance between prescription filling and drug ingestion are reassuring [10].

Because of high morbidity and mortality [1] prevention of IE is of great importance. Improving compliance with guidelines and informing patients better in order to improve patient compliance could hypothetically reduce the incidence of IE, and this could be an indirect measure of the efficacy of AP.

In brief, increased awareness on the current guidelines could improve compliance among clinicians and hopefully also among patients.

## 5. Conclusion

European and Danish guidelines recommend AP for patients with; 1) prior IE, 2) heart valve prosthesis, 3) certain CHD. Notably, compliance with guidelines by Danish clinicians is only approximately 50 %. Further the proportion of high-risk patients filling an AP prescription is only approximately 40 %. Clearly, there is room for improvement – an improvement which has the potential to reduce the incidence of IE and increase quality of life among patients at high risk of IE.

## Ethics

In Denmark, registry-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study is approved by the data responsible institute (the Capital Region of Denmark [approval number: P-2019-523]) in accordance with the General Data Protection Regulation. We received approval to review the medical charts on the patient sample.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## Funding

None.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

None.

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