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RESEARCH ARTICLE

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# Evidence of support used for drug treatments in pediatric cardiology

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## Abstract

**Background and aims:** Clinical support systems are widely used in pediatric care. The aim of this study was to assess the support for drug treatments used at pediatric cardiac wards and intensive care units in Sweden.

**Methods:** Drug information, such as type of drug, indication, dose, and route of administration, for all in-hospital pediatric cardiac patients, was included in the study. Treatments were classified as either on-label (based on product information) or off-label. Support for off-label treatment was stratified by the use of clinical support systems (the national database on drugs, local, or other clinical experience guidelines).

**Results:** In all, 28 patients were included in the study. The total number of drug treatments was 233, encompassing 65 different drugs. Overall, 175 (75%) treatments were off-label. A majority of off-label drug treatments were supported by other sources of information shared by experts. A total of 7% of the drug treatments were used without support.

**Conclusion:** Off-label drug treatment is still common in Swedish pediatric cardiac care. However, the majority of treatments were supported by the experience shared in clinical support systems.

## Key Points

- Seventy-five percent of all prescriptions in pediatric cardiology care were off-label.
- A majority of patients received three or more drug treatments off-label.
- Use of clinical support systems and guidelines was common, but in 7% of all drug treatments, no support was found for the chosen treatment.

KEYWORDS
drugs, medical support systems, off-label, pediatric cardiology, pediatrics

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## 1 | INTRODUCTION

Children have the same right to licensed and safe medicines as adults. The Pediatric Regulation enacted in 2007 in the EU aimed to increase the number of safe medicines for children. The 10-year report showed that pediatric needs were still being neglected and drug development was driven rather by adult needs.[1] Drugs used in pediatrics are often prescribed outside what is suggested in the product information, "off-label." The prevalence of off-label prescription ranges from 16% to 60% in pediatrics and from 31% to 78% in pediatric cardiology.[2-5] At one pediatric intensive care unit, more than 90% of patients used at least one drug off-label.[6]

Off-label drug usage deviates from the licensed product information as regards either indication, age of patient, dosage, formulation, or route of administration. Off-label drug usage has been associated with an increased risk of adverse drug reaction, twofold to threefold that of on-label usage.[7] It may also lead to ineffective therapy due to underdosing, and is associated with a longer stay at a pediatric cardiac intensive care unit (pCICU), longer hospital stay, and higher mortality.[7-9]

Children differ from adults in body size and composition as well as in the maturation of organs and pharmacodynamic responses to a drug in terms of pharmacokinetics, that is, absorption, distribution, metabolism, and elimination of the substance.[10] All these factors make pediatric pharmacotherapy challenging.[10] Lack of clinical trials in

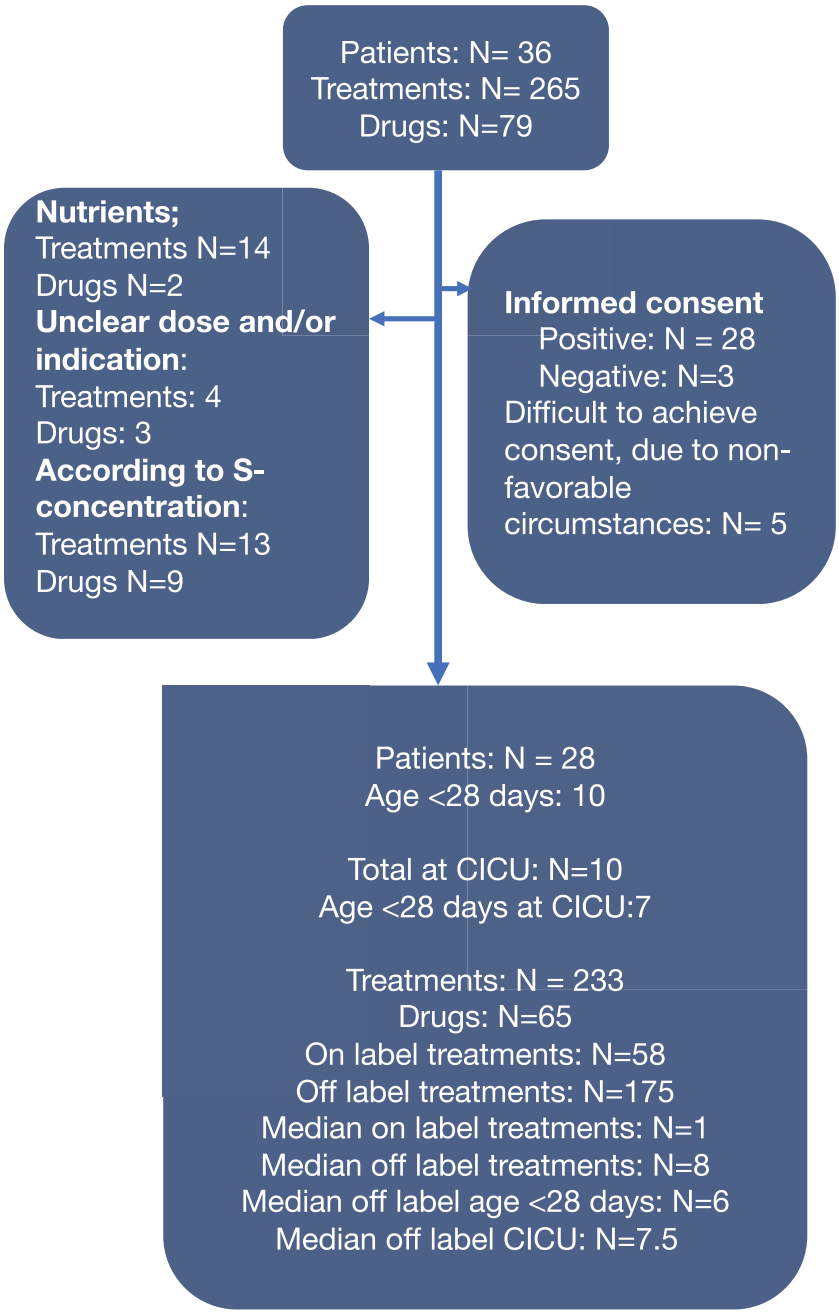


**FIGURE 1** Study population, treatments and drug

the summary of product characteristics (SmPC) is the most frequent cause for prescription in children being categorized as off-label.[1,11]

Due to the lack of licensed medicines, drug prescriptions in pediatrics often depend on experience-based knowledge and high quality academic trials and research. Such prescriptions are referred to as "on-evidence." Information regarding on-evidence treatment in pediatric clinical practice can be found in sources such as local, national, or international guidelines and in clinical decision support systems, which are often online databases describing experiences of a drug with regard to indications, dosages, formulations, and routes of administration. An example is the frequently used Swedish national database www.ePed.se. Local, national, and international guidelines are often limited to shared information on the treatment of a specific disease, while ePed.se is an evidence-based source of information shared by experts (doctors and pharmacists) and taken from peer-reviewed published studies on drugs used in pediatrics. Information on indications, dosages, formulations, and routes of administration is offered in this database, locally adapted for each pediatric clinic in Sweden.[12-15]

We hypothesized that off-label use of drugs in pediatric cardiology would still be common, but that evidence shared and clinical decision support systems might support the off-label use of specific drugs. The aim of this study was to identify support used for drug treatments at cardiac wards and pCICUs in Swedish pediatric cardiac centers.

## 2 | PATIENTS AND METHODS

All in-hospital cardiac patients at the pCICUs and pediatric cardiac wards of the three pediatric cardiac centers in Stockholm, Lund, and Gothenburg were included in the study. Information on each child's medical history, demographics, and medical treatment during one random treatment day was retrieved between February and March 2019. All demographic and drug information was retrieved from the medical records of each patient.

Demographic data included age, bodyweight, height, and type of cardiac malformation. Type of cardiac disease was stratified as follows: left-to-right shunts, left-sided lesions, right-sided lesions, complex congenital malformations, other types of cardiac malformations, and arrhythmias. Complex congenital malformations included anomalous left coronary from the pulmonary artery and hypoplastic left chamber syndrome.

Information on drugs, the stated indication for each drug, dosage, formulation, and route of administration was retrieved for each patient. Fluids, supplements, and drugs for which the dosage was determined based on serum concentration were excluded. The number of treatments using each type of drug was summed up and is referred to as drug treatment.

Each drug treatment was categorized in a structured manner based on the evidence in support of its use: (a) on-label (the drug was used in accordance with SmPC and as approved by the competent authorities for use in Sweden), or (b) off-label (departure from the

**TABLE 1** Demographic data of patients included in the study

| | CICU | Cardiac ward | Total |
|---|---|---|---|
| *Number of patients* | 10 | 18 | 28 |
| Stockholm | 1 | 3 | 4 |
| Gothenburg | 4 | 9 | 13 |
| Lund | 5 | 6 | 11 |
| *Median age (months)* | 0.68 (0.1-71.1) | 12.5 (0.7-176.3) | 5 (0.1-176.3) |
| *Gender (M/F)* | 8/2 | 8/10 | 16/12 |
| *Median weight (kg)* | 3.9 (3.2-20.5) | 5.9 (2.8-44.8) | 4.4 (2.8–44.8) |
| *Cardiac malformation* | | | |
| Left to right shunts | 2 | 7 | 9 |
| Left sided lesions | 3 | 2 | 5 |
| Right sided lesions | 5 | 2 | 7 |
| Complex heart malformations | 0 | 2 | 2 |
| Arrhythmias | 0 | 2 | 2 |
| Other | 0 | 3 | 3 |
| *Median number of treatments/patient* | 8 (3-19) | 8 (1-15) | 8 (1-19) |
| *Number of off-label treatments/patient* | | | |
| One (%) | 1 (10%) | 3 (17%) | 4 (14%) |
| Two (%) | 2 (20%) | 1 (6%) | 3 (11%) |
| Three or more (%) | 7 (70%) | 14 (78%) | 21 (75%) |
| *Median number of off-label treatments/patient* | | | |
| | 8 (1-15) | 6 (1-15) | 6 (1-15) |

Abbreviations: CICU, paediatric cardiac intensive care unit; M, male; F, female.

**TABLE 2** Number of drug-treatments by patient´s indication, on- or off-label and off-label cause

| Patient's indication for treatment | Type of drug (generic name) | Number of treatments | Total number of on label treatment | Total number of off-label treatment | Off-label by high dose[a] | Off-label by low dose[a] | Off-label by indication[a] | Off-label by type of formulation[a] | Off-label by age[a] | No information on treatment for children[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Heart failure | Furosemide (i.v) | 27 | 6 | 21 | 21 | | | | | |
| | Furosemide (oral) | 8 | 8 | | | | | | | |
| | Captopril | 5 | | 5 | | | | 5 | | |
| | Metolazone | 2 | | 2 | | | | | | 2 |
| | hANP | 1 | | 1 | | | | 1 | | |
| | Spironolactone | 12 | | 12 | | | | 3 | | 9 |
| | Noradrenaline | 2 | | 2 | | | | | | 2 |
| | Nitro-glycerine | 1 | | 1 | | | | | | 1 |
| Pain/ Abstinence/ antidote | Ibuprofen | 1 | 1 | 0 | | | | | | |
| | Ketobemidone | 4 | | 4 | | | | 4 | | |
| | Clonidine | 15 | | 15 | | | 15 | | | |
| | Morphine | 12 | | 12 | | | | | | 12 |
| | Oxycodone | 10 | | 10 | | | | | | 10 |
| | Paracetamol | 17 | 11 | 6 | 4 | 1 | | 1 | | |
| | Naloxone | 7 | | 7 | | | 7 | | | |
| Sedative | Dexmedetomidine | 4 | | 4 | | | | | | 4 |
| | Chloral hydrate | 4 | | 4 | | | | 4 | | |
| | Midazolam | 6 | 1 | 5 | | | | 2 | 3 | |
| | Propofol | 2 | 2 | | | | | | | |
| | Lorazepam | 1 | | 1 | | | | | | 1 |
| Laxative | Macrogol | 1 | 1 | | | | | | | |
| | Docusate sorbitol | 2 | | 2 | | | | | | 2 |
| | Lactulose | 1 | 1 | | | | | | | |
| | Macrogol + potassium chloride | 3 | 1 | 2 | | | | | 2 | |
| | Oral naloxone hydrochloride | 4 | | 4 | | | 4 | | | |
| | Sorbitol laxative | 1 | 1 | | | | | | | |

**TABLE 2** (Continued)

| Patient's indication for treatment | Type of drug (generic name) | Number of treatments | Total number of on label treatment | Total number of off-label treatment | Off-label by high dose[a] | Off-label by low dose[a] | Off-label by indication[a] | Off-label by type of formulation[a] | Off-label by age[a] | No information on treatment for children[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Infections | Amphotericin B | 1 | 1 | | | | | | | |
| | Sulfamethoxazole Trimethoprim | 2 | | 2 | | 2 | | | | |
| | Benzyl-penicillin | 1 | | 1 | 1 | | | | | |
| | Cefotaxime | 4 | 2 | 2 | | 2 | | | | |
| | Cefuroxime | 2 | | 2 | | | | 2 | | |
| | Daptomycin | 1 | 1 | | | | | | | |
| | Fluconazole | 1 | 1 | | | | | | | |
| | Flucloxacillin | 1 | 1 | | | | | | | |
| | Meropenem | 1 | 1 | | | | | | | |
| | Anidulafungin | 1 | | 1 | | | | | | 1 |
| | Piperacillin-tazobactam | 1 | | 1 | | | | | | 1 |
| | Rifampicin | 1 | 1 | | | | | | | |
| | Nystatin | 1 | 1 | | | | | | | |
| | Valganciclovir | 1 | 1 | | | | | | | |
| | Palivizumab | 3 | 2 | 1 | 1 | | | | | |
| Haemostasis | Acetylsalicylic acid | 4 | | 4 | | | | | 4 | |
| | Dalteparin | 8 | | 8 | | | | | | 8 |
| | Antithrombin III | 1 | 1 | | | | | | | |
| Anti-arrhythmic | Diltiazem | 1 | 1 | | | | | | | |
| | Flecainide | 1 | | 1 | | | | | 1 | |
| | Propranolol | 2 | | 2 | | | | 2 | | |
| Antacids | Esomeprazole | 11 | 2 | 9 | | 1 | | 5 | 3 | |
| | Lansoprazole | 1 | | 1 | | | | | | 1 |
| Other | Amitriptyline | 1 | | 1 | | | | | | 1 |
| | Budesonide | 1 | 1 | | | | | | | |
| | Phenobarbital | 5 | | 5 | | 1 | | 4 | | |
| | Racekadotril | 1 | 1 | | | | | | | |
| | Melatonin | 2 | | 2 | | | | | | 2 |
| | Sodium nitroprusside | 1 | | 1 | | | | 1 | | |
| | Octreotide | 1 | | 1 | | | | 1 | | |
| | Ondansetron | 3 | 3 | | | | | | | |

(Continues)

**TABLE 2** (Continued)

| Patient's indication for treatment | Type of drug (generic name) | Number of treatments | Total number of on label treatment | Total number of off-label treatment | Off-label by high dose[a] | Off-label by low dose[a] | Off-label by indication[a] | Off-label by type of formulation[a] | Off-label by age[a] | No information on treatment for children[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sildenafil | 1 | 1 | | | | | | | |
| | Caffeine | 1 | 1 | | | | | | | |
| | Alprostadil | 2 | 1 | 1 | 1 | | | | | |
| | Clemastin | 1 | | 1 | | | | | | 2 |
| | Ursodiol | 1 | 1 | | | | | | | |
| | Mycofenolatemophetil | 2 | | 2 | | | | | | 2 |
| | Prednisone | 2 | | 2 | | | | | | 2 |
| | Salbutamol | 4 | | 4 | | | | | 5 | |
| Total | | 233 | 58 | 175 | 28 | 6 | 26 | 35 | 18 | 49 |

[a]According to product information Summary of Product Characteristics (SmPC).

SmPC). The reason for off-label treatment was determined based on chosen dosage, age, indication, or formulation. In case of difficulties in stratification of a treatment as regards the cause of off-label treatment, it was categorized to "unknown."

Support for each off-label treatment was assessed in a structured manner and stratified as follows: (a) support in the national clinical support system ePed.se,[13] (b) support in local guidelines (drug use departing from product information and ePed.se, but in accordance with local guidelines), (c) support in other national or international guidelines (drug use not supported by product information, ePed.se or local guidelines), or (d) no support (drug use not supported by product information, ePed.se, local, national or international guidelines). Sources for published guidelines were local guidelines at each center, other Swedish guidelines provided by the government and the pediatric society, the Swedish drug information database janusinfo.se, and international sources such as drugs.com, MedScape.com, BNF.org, uptodate.com or published studies.[14,15]

All data are presented as median (range) or percentage (%) depending on their type and distribution.

## 3 | ETHICS

The study was approved by the Swedish Ethical Review Authority (Dnr: 2019-00258). Informed consent was obtained from the parents of all study participants.

## 4 | RESULTS

A total of 36 patients were treated for cardiac conditions at the three centers during the study period. For three patients, consent was not given for inclusion in the study, and the parents of five patients could not be reached to obtain informed consent. In three of these cases, the parents were absent while their child was in the operating theatre or catheter lab and in two cases we were unable to reach the parents. In all, 28 patients were included in the study population: 10 patients treated at the pCICUs and 18 treated at the pediatric cardiac wards (Figure 1).

The median age of the patients was 5 months (0.1-176.3 months) and their median bodyweight was 4.4 kg (2.8-44.8 kg; Table 1). There were 10 neonatal patients (under 28 days of age) in the study. Two patients had had heart transplants. Most of the patients were male: N = 16 (57%). The most common types of the cardiac lesion were left-to-right shunts and right-sided lesions (Table 1). A majority, 21 patients (75%), received three or more drug treatments off-label (Table 1).

In all, 233 drug treatments and 65 different drugs were used in these 28 patients. The median number of treatments was 8[1-19] per patient (Table 1). In total, 58 (25%) drug treatments were on-label and 175 (75%) drug treatments were off-label, in which 159 (68%) were supported by guidelines or other clinical decision support systems (Table 2). For 13 drug treatments, there was missing information on

**TABLE 3** Off-label treatments, stratified by indication and level of support

| Patient's indication for treatment | Type of drug (generic name) | Number of treatments | Total number of off-label treatments | Off-label treatment, supported by shared clinical support system (ePed.se) | Off-label, treatment supported by local guidelines | Off-label treatment, supported by national and international guidelines | Off-label treatment, no support | Undecidable type of support due to unclear indication, dose or formulation |
|---|---|---|---|---|---|---|---|---|
| Heart failure | Furosemide (i.v) | 27 | 21 | 21 | | | | |
| | Furosemide (oral) | 8 | 0 | | | | | |
| | Captopril | 5 | 5 | 4 | | | | 1 |
| | Metolazone | 2 | 2 | 0 | | | | 2 |
| | Spironolactone | 12 | 12 | 12 | | | | |
| | hANP | 1 | 1 | | | 1 | | |
| | Nitro-glycerine | 1 | 1 | | | 1 | | |
| | Noradrenaline | 2 | 2 | 1 | | | 1 | |
| Pain/ Abstinence | Ibuprofen | 1 | | | | | | |
| | Ketobemidone | 4 | 4 | 3 | 1 | | | |
| | Clonidine | 15 | 15 | 11 | | 2 | 2 | |
| | Morphine | 12 | 12 | 3 | 5 | 1 | 3 | |
| | Oxycodone | 10 | 10 | 6 | 2 | | | 2 |
| | Paracetamol | 17 | 6 | 5 | | | | 1 |
| | Naloxone | 7 | 7 | 7 | | | | |
| Sedative | Dexmedetomidine | 4 | 4 | 4 | | | | |
| | Chloral hydrate | 4 | 4 | 4 | | | | |
| | Midazolam | 6 | 5 | 4 | | | | 1 |
| | Lorazepam | 1 | 1 | | | 1 | | |
| | Propofol | 2 | | | | | | |
| Laxation | Makrogol | 1 | | | | | | |
| | Docusate sorbitol | 2 | 2 | 1 | | | 1 | |
| | Lactulose | 1 | | | | | | |
| | Macrogol + potassium chloride | 3 | 2 | | | 1 | | 1 |
| | Oral naloxone hydrochloride | 4 | 4 | | 3 | | 1 | |
| | Sorbitol laxative | 1 | | | | | | |
| Infections | Sulfamethoxazole Trimethoprim | 2 | 2 | | | | 1 | 1 |
| | Benzyl-penicillin | 1 | 1 | 1 | | | | |
| | Cefotaxime | 4 | 2 | 1 | 1 | | | |
| | Cefuroxime | 2 | 2 | 1 | | 1 | | |
| | Fluconazole | 1 | | | | | | |
| | Flucloxacillin | 1 | | | | | | |
| | Meronym | 1 | | | | | | |
| | Piperacillin-tazobactam | 1 | 1 | 1 | | | | |
| | Amphotericin B | 1 | | | | | | |
| | Nystatin | 1 | | | | | | |
| | Rifampicin | 1 | | | | | | |

(Continues)

**TABLE 3** (Continued)

| Patient's indication for treatment | Type of drug (generic name) | Number of treatments | Total number of off-label treatments | Off-label treatment, supported by shared clinical support system (ePed.se) | Off-label, treatment supported by local guidelines | Off-label treatment, supported by national and international guidelines | Off-label treatment, no support | Undecidable type of support due to unclear indication, dose or formulation |
|---|---|---|---|---|---|---|---|---|
| | Daptomycin | 1 | | | | | | |
| | Palivizumab | 3 | 1 | | | | 1 | |
| | Valganciclovir | 1 | | | | | | |
| | Anidulafungin | 1 | 1 | | | | 1 | |
| Haemostasis | Acetylsalicylic acid | 4 | 4 | 1 | 1 | 1 | 1 | |
| | Antithrombin III | 1 | | | | | | |
| | Dalteparin | 8 | 8 | | 4 | 4 | | |
| Antacids | Esomeprazole | 11 | 9 | 9 | | | | |
| | Lansoprazole | 1 | 1 | 1 | | | | |
| Anti-Arrhythmias | Diltiazem | 1 | | | | | | |
| | Flecainide | 1 | 1 | | | 1 | | |
| | Propranolol | 2 | 2 | | | | 2 | |
| Other | Amitriptyline | 1 | 1 | | | | | 1 |
| | Budesonide | 1 | | | | | | |
| | Phenobarbital | 5 | 5 | 3 | | 1 | | 1 |
| | Racekadotril | 1 | | | | | | |
| | Melatonin | 2 | 2 | | 1 | | | 1 |
| | Sodium nitroprusside | 1 | 1 | | | 1 | | |
| | Octreotide | 1 | 1 | 1 | | | | |
| | Ondansetron | 3 | | | | | | |
| | Sildenafil | 1 | | | | | | |
| | Caffeine | 1 | | | | | | |
| | Alprostadil | 2 | 1 | | | | 1 | |
| | Clemastin | 1 | 1 | | 1 | | | |
| | Ursodiol | 1 | | | | | | |
| | Mycofenolatemophetil | 2 | 2 | | 1 | | 1 | |
| | Prednisone | 2 | 2 | | | 2 | | |
| | Salbutamol | 4 | 4 | 1 | | 2 | | 1 |
| Total | | 233 | 175 | 106 | 19 | 20 | 16 | 13 |

dosage or indication for use (Table 2). No information on pediatric use in the product information was the most common cause for treatment being categorized as off-label (N = 49), followed by inaccurate use of formulation (N = 35; Table 2).

The most common source of support for off-label use was the national clinical support system (www.ePed.se; Table 3). This was especially common in heart failure treatment. In prescriptions of drug treatments for pain relief or abstinence, or antidotes, all source types were used (Table 3). For 16 (7%) drug treatments, there was no support (Table 3).

## 5 | DISCUSSION

The use of off-label treatment in pediatric cardiac care is common in Sweden and every patient in this study was on at least one off-label drug treatment. In total, 175 (75%) drug treatments were off-label, but most of the prescriptions were based on information regarding the chosen drug from other clinical decision support sources. For 16 drug treatments (7%), there was no evidence.

The common use of off-label drug treatments in our study is in line with results from other studies on drugs used in cardiac pediatric

patients (31%-78%).[5,6,16] Use of off-label drugs at the pCICUs in our study was increased or similar to that seen in other studies from pCICUs or general pediatric intensive care units.[6,17,18] Analgesics and cardiovascular drugs were the most commonly used drugs in our study, which is in line with other studies.[6,16]

Neonates with cardiac diseases are more often exposed to off-label drug treatment than older children, especially at pCICUs.[6] Our study included children of all ages. Ten of the patients in our study were under the age of 28 days (neonates). The median number of off-label drug treatments was six among neonates and eight in older patients. This may explain the lower number of off-label drug treatments used at the pCICUs in our study.

Lack of pediatric indication in the product information was the fourth most common reason for the drug to be classified to be used off-label use in our study, while this has often been found to be the main cause behind off-label drug use in other studies.[3,7,17] Most off-label drug treatments in our study were supported by the national clinical support system (www.ePed.se). A clinical support system, as well as other local, national, and international guidelines shared by experts, is a valuable source of information for doctors when choosing a treatment. The main aim of a clinical support system with information shared by experts, such as ePed.se, is to minimize the risk of mishandling and to harmonize drug therapy among children.[13] ePed is a database describing experiences of drug use and providing clinical trial evidence if available. It is implemented at all pediatric units in Sweden and locally adapted to each clinic. Similar databases or handbooks exist in other countries.[14,15,19-23] Our study indicated that the use of clinical support systems and local, national, and international guidelines was common in pediatric cardiology care, and that the use of off-label treatment without any shared evidence was rare. Our study encompassed many drugs (N = 65) and treatments (N = 233); it may be that a harmonization to a national protocol for drugs used in pediatric cardiac care, based on databases like ePed.se or sources in other countries, could be beneficial. However, the use of unlicensed and insufficiently studied medicines, even with a basis in shared experience, increases the risks of unexpected adverse drug reactions and underdosing causing ineffective drug therapy.[7,11,24] Extrapolation of drug efficacy from clinical trials in adults to the pediatric population may minimize the exposure of children to clinical trials, but medical product safety in children must be increased through pediatric clinical trials in children of different ages, since neonates, children, and adolescents differ in several aspects. Children of all ages are susceptible to drug-induced growth and development disorders as well as delayed adverse drug reactions which are not found in adults.[7] Further, adverse drug reactions may be difficult to interpret among children at very young ages.[25-27] The limited data available on pediatric medicines, resulting from a lack of studies on pharmacokinetics and dosages, must be increased through pediatric trials, taking the maturation, growth, and development of the pediatric population into account.[28,29] Safe and effective pharmacotherapy is based on three pillars—the right dosage, efficacy, and safety—in accordance with the principles of evidence-based medicine. None of these pillars seems to be fully addressed by any of the support tools. Further, sharing of medical expertise cannot meet this need; the long follow-up required on adverse drug reactions is not addressed and studies on this are necessary.

The national approach of this study, including all of Sweden's operating and catheter intervention centers for pediatric cardiology, is a strength. Patients in our study were referred from all over the country for interventions or surgery and were often hospitalized after heart surgery. Thus, it is likely that drugs used in this study are related to the care of more severely ill patients, with other medical needs, for example, regarding pain relief and sedation, than the average cardiac patient. This can, in turn, introduce selection bias and limit comparisons to other studies including cardiac outpatients. As this was a cross-sectional study performed during one single day at each center, there was a range in time to and after surgery among the patients, and the risk of selection bias due to patient selection was small. Furthermore, retrieval of data was performed on regular weekdays, avoiding holiday periods, making the sample likely to be representative of the pediatric cardiology in-patient population in Sweden. We believe that the risk of selection bias by retrieval, age, gender, heart condition, or severity of the condition, was minimized.

Information on drug treatment was retrieved solely from medical records. For some drugs, there was no information on medical indications for a chosen drug. If no indication could be identified, the treatment was labeled "unknown," rather than off-label. This limits the study, as the number of included drugs and treatments decreased, but increased validity as only drugs with clear indications were included. A medical student (J.B.) was responsible for the retrieval of data well as the stratification of drugs in our study, which could have introduced a risk of misclassification. However, we believe this risk to be small, as this student was trained and supervised by a pediatric cardiologist (EN). Concentrating the study to a single day made the patient sample small, which is a limitation of the study.

Off-label drug use in pediatric cardiac care remains common. However, drug treatments are often based on information from clinical support systems and other sources of information from experts. There is a need for studies with larger pediatric populations as well as longitudinal studies to assess adverse drug reactions and pharmacovigilance.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## AUTHOR CONTRIBUTIONS

Conceptualization: Estelle Naumburg
Formal Analysis: Julia Back
Methodology: Estelle Naumburg
Supervision: Estelle Naumburg
Writing – review and editing: Julia Back, Håkan Wåhlander, Katarina Hanseus, Gunnar Bergman, Estelle Naumburg

Writing – original draft: Julia Back and Estelle Naumburg

Medical Students Julia Back, Umeå University, had responsibility for protocol development, patient enrolment, outcome assessment, preliminary data analysis. Dr Håkan Wåhlander, Dr Katarina Hanseus, and Dr Gunnar Bergman participated in the analytical framework for the study and contributed to the writing of the manuscript. Dr Estelle Naumburg had primary responsibility for study, protocol development, patient enrolment, outcome assessment, preliminary data analysis, and writing the manuscript.

All authors have read and approved the final version of the manuscript.

Medical student Julia Back and Dr Naumburg had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

## TRANSPARENCY STATEMENT

Dr Naumburg affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

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