Evidence of support used for drug treatments in pediatric cardiology

Julia Back1 | Håkan Wåhlander2 | Katarina Hanseus3 | Gunnar Bergman4 | Estelle Naumburg1

1Institution of Clinical Science, Paediatrics, Umeå University, Umeå, Sweden
2Department of Cardiology, Paediatric Heart Centre, Queen Silvia’s Children’s Hospital, Institution of Clinical Sciences, Department of Paediatrics, University of Gothenburg, Gothenburg, Sweden
3Department of Cardiology, Paediatric Heart Centre, Skåne University Hospital Lund and Lund University, Lund, Sweden
4Department of Women’s and Children’s Health, Karolinska Institute, Stockholm, Sweden

Correspondence
Estelle Naumburg, Institution of Clinical Science, Paediatrics, Umeå University, Umeå 901 87, Sweden.
Email: estelle.naumburg@umu.se

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
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

---

**Study population, treatments and drug**

- **Patients**: N = 28
  - Age <28 days: 10
- **Total at CICU**: N = 10
  - Age <28 days at CICU: 7
- **Treatments**: N = 233
  - On label treatments: N = 58
  - Off label treatments: N = 175
  - Median on label treatments: N = 1
  - Median off label treatments: N = 8
  - Median off label age <28 days: N = 6
  - Median off label CICU: N = 7.5

---

**Informed consent**

- Positive: N = 28
- Negative: N = 3
- Difficult to achieve consent, due to non-favorable circumstances: N = 5

---

**Nutrients**

- Treatments: N = 14
- Drugs: N = 2

**Unclear dose and/or indication**

- Treatments: 4
- Drugs: 3

**According to S-concentration**

- Treatments: N = 13
- Drugs: N = 9

---

**Patients**: N = 36

- Treatments: N = 265
- Drugs: N = 79
the summary of product characteristics (SmPC) is the most frequent cause for prescription in children being categorized as off-label. 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.

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.
| Patient’s indication for treatment | Type of drug (generic name) | Number of treatments | Number of on label treatment | Total number of on label treatment | Total number of off-label treatment | Off-label by high dose | Off-label by low dose | Off-label by indication | Off-label by type of formulation | Off-label by age | No information on treatment for children |
|-----------------------------------|-----------------------------|----------------------|-----------------------------|-----------------------------------|-----------------------------------|------------------------|------------------------|------------------------|-----------------------------------|----------------|----------------------------------|
| **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                      | 1                      |                                   |               |                                  |
|                                  | Naloxone                    | 7                    | 7                           | 7                                 |                                    |                        |                        |                        |                                   |               |                                  |
|                                  | Sedative                    | 4                    | 4                           | 4                                 |                                    |                        |                        |                        | 4                                 |               |                                  |
|                                  | Choral 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                           |                                    |                                    |                        |                        |                        | 1                                 |               |                                  |
|                                  | Macrogol + potassium chloride| 3                   | 1                           | 2                                 | 2                                 |                         |                        |                        |                                   |               |                                  |
|                                  | Oral naloxone hydrochloride | 4                    | 4                           |                                    |                                    |                        |                        |                        | 4                                 |               |                                  |
|                                  | Sorbitol laxative           | 1                    | 1                           |                                    |                                    |                        |                        |                        | 1                                 |               |                                  |
| 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<sup>a</sup> | Off-label by low dose<sup>a</sup> | Off-label by indication<sup>a</sup> | Off-label by type of formulation<sup>a</sup> | Off-label by age<sup>a</sup> | No information on treatment for children<sup>a</sup> |
|-----------------------------------|-----------------------------|----------------------|-----------------------------------|-----------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Infections                        | Amphotericin B              | 1                    | 1                                 | 2                                 | 2                              |                                |                                |                                |                                |                                |
|                                  | Sulfamethoxazole             | 2                    | 2                                 |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Trimethoprim                 |                      |                                    |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Benzyl-penicillin            | 1                    | 1                                 | 1                                 |                                |                                |                                |                                |                                |                                |
|                                  | Cefotaxime                   | 4                    | 2                                 | 2                                 |                                |                                |                                |                                |                                |                                |
|                                  | Cefuroxime                   | 2                    | 2                                 |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Daptomycin                   | 1                    | 1                                 |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Fluconazole                  | 1                    | 1                                 |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Flucloroxacin                | 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                                 |                                    |                                |                                |                                |                                |                                | 1                                |
|                                  | Phenobarbitol                | 5                    | 5                                 |                                    |                                | 1                              | 4                              |                                |                                |                                |
|                                  | Racekadoril                  | 1                    | 1                                 |                                    |                                |                                |                                |                                |                                |                                |
|                                  | Melatonin                    | 2                    | 2                                 |                                    |                                |                                |                                |                                |                                | 2                                |
|                                  | Sodium nitroprusside         | 1                    | 1                                 |                                    |                                |                                |                                |                                |                                | 1                                |
|                                  | Octreotide                   | 1                    | 1                                 |                                    |                                |                                |                                |                                |                                | 1                                |
|                                  | Ondansetron                  | 3                    | 3                                 |                                    |                                |                                |                                |                                |                                |                                |

(Continues)
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 81-19 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 2 (Continued)

| Patient’s indication for treatment | Type of drug (generic name) | Number of treatments | Total number of off-label treatment | Total number of on-label treatment | Total number of high dose | Total number of low dose | Total number of by indication | Total number of by age | Total number of by formulation | Total number of by type of formulation |
|----------------------------------|----------------------------|----------------------|------------------------------------|-----------------------------------|--------------------------|-------------------------|---------------------------|--------------------------|-------------------------------|---------------------------------------|
|                                  | Sildenafil                 | 1                    | 1                                  | 1                                 | 2                        | 2                       | 2                         | 2                        | 2                             | 2                                     |
|                                  | Caffeine                   | 1                    | 1                                  | 1                                 | 1                        | 1                       | 1                         | 1                        | 1                             | 1                                     |
|                                  | Alprostadil                | 1                    | 2                                  | 1                                 | 1                        | 1                       | 1                         | 1                        | 1                             | 1                                     |
|                                  | Clemastin                  | 1                    | 1                                  | 1                                 | 1                        | 1                       | 1                         | 1                        | 1                             | 1                                     |
|                                  | Ursodiol                   | 1                    | 1                                  | 1                                 | 1                        | 1                       | 1                         | 1                        | 1                             | 1                                     |
|                                  | Methylprednisolone         | 2                    | 2                                  | 2                                 | 2                        | 2                       | 2                         | 2                        | 2                             | 2                                     |
|                                  | Mycofenolate Mephitil      | 2                    | 2                                  | 2                                 | 2                        | 2                       | 2                         | 2                        | 2                             | 2                                     |
|                                  | Prednisone                 | 2                    | 2                                  | 2                                 | 2                        | 2                       | 2                         | 2                        | 2                             | 2                                     |
|                                  | Salbutamol                 | 4                    | 4                                  | 4                                 | 4                        | 4                       | 4                         | 4                        | 4                             | 4                                     |
|                                  | Total                      | 233                  | 58                                 | 175                               | 28                       | 6                       | 6                         | 26                       | 18                            | 35                                     |
## 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                                                                     |                                                 |                                                 |                               |                                                                          |
|                                  | Spironolactone                 | 12                   | 12                                   | 12                                                                    |                                                 |                                                 |                               |                                                                          |
|                                  | hANP                           | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Nitro-glycerine                | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Noradrenaline                  | 2                    | 2                                    | 1                                                                     |                                                 |                                                 |                               |                                                                          |
| Pain/Abstinence                   | Ibuprofen                      | 1                    | 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                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
| Sedative                          | Dexametomidine                 | 4                    | 4                                    | 4                                                                     |                                                 |                                                 |                               |                                                                          |
|                                  | Chloral hydrate                | 4                    | 4                                    | 4                                                                     |                                                 |                                                 |                               |                                                                          |
|                                  | Midazolam                      | 6                    | 5                                    | 4                                                                     |                                                 |                                                 |                               | 1                           |
|                                  | Lorazepam                      | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               | 1                           |
|                                  | Propofol                       | 2                    | 2                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
| Laxation                          | Makrogol                       | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Docusate sorbitol              | 2                    | 2                                    | 1                                                                     | 1                                               |                                                 |                               |                                                                          |
|                                  | Lactulose                      | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Macrogol + potassium chloride  | 3                    | 2                                    |                                                                        | 1                                               |                                                 |                               | 1                           |
|                                  | Oral naloxone hydrochloride    | 4                    | 4                                    | 3                                                                     |                                                 |                                                 |                               | 1                           |
|                                  | Sorbitol laxative              | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
| Infections                        | Sulfamethoxazole               | 2                    | 2                                    |                                                                        | 1                                               | 1                                              |                               |                                                                          |
|                                  | Trimethoprim                   |                      |                                       |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Benzyl-penicillin              | 1                    | 1                                    | 1                                                                     |                                                 |                                                 |                               |                                                                          |
|                                  | Cefotaxime                     | 4                    | 2                                    | 1                                                                     | 1                                               |                                                 |                               |                                                                          |
|                                  | Cefuroxime                     | 2                    | 2                                    | 1                                                                     |                                                 |                                                 |                               | 1                           |
|                                  | Fluconazole                    | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Flucloxacinillin               | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Meronym                        | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Piperacillin-tazobactan        | 1                    | 1                                    | 1                                                                     |                                                 |                                                 |                               |                                                                          |
|                                  | Amphotericin B                 | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Nystatin                       | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |
|                                  | Rifampicin                     | 1                    | 1                                    |                                                                        |                                                 |                                                 |                               |                                                                          |

(Continues)
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 care.
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. 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. 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 mis-handling and to harmonize drug therapy among children. 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. 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. 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. Further, adverse drug reactions may be difficult to interpret among children at very young ages. 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. 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.
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

Estelle Naumburg https://orcid.org/0000-0001-6090-494X

REFERENCES

1. EMA. 10-year Report to the European Commission General report on the experience acquired as a result of the application of the Paediatric Regulation; 2016. https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf
2. Kimland E, Odling V, Bottiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals—a nationwide study. Acta Paediatrica. 2012;101:772-778.
3. Conroy S, Choonara I, Impicciatore P. Survey of unlicensed and off label drug use in paediatric wards in European countries. European network for drug investigation in children. BMJ. 2000;320(7227):79-82.
4. Palmaro A, Bissuel R, Renaud N, et al. Off-label prescribing in paediatric outpatients. Pediatrics. 2015;135(1):49-58.
5. Pasquale SK, Hall M, Slonim AD, Jenkins KJ, Marino BS, Cohen MS, Shah SS. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. Circ Cardiovasc Qual Outcomes. 2008;12(2):74-83.
6. Maltz LAK, Spaeder D, Wessel MC. Off-label drug use in a single-center pediatric cardiac intensive care unit. World J Pediatr Congen Heart Surg. 2013;4(3):262-266. https://doi.org/10.1177/2151035113481042
7. Bellis JR, Kirkham J, Thiesen S, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. BMC Med. 2013;11(238). https://doi.org/10.1186/1741-7015-11-238.
8. Czaja AS, Reiter PD, Schultz ML, Valuck RJ. Patterns of off-label prescribing in the pediatric intensive care unit and prioritizing future research. J Pediatr Pharmacol Ther. 2015;20(3):186-196.
9. EMA. Evidence of harm from off-label or unlicensed medicines in children EMEA; 2004. https://www.ema.europa.eu/en/documents/other/evidence-harm-label-unlicensed-medicines-children_en.pdf
10. Yaffe S, Aranda J. Neonatal and Pediatric Pharmacology. 3rd ed. Lippincott Williams & Wilkins; 2005.
11. Nordenmalm S, Tomasi P. More medicines for children: impact of the EU paediatric regulation. Arch Dis Child. 2018;103:557-564. https://doi.org/10.1136/archdischild-2017-313309
12. Pediatrics AAo. AAP makes recommendations on use of off-label drugs for children. American Academy of Pediatrics; 2014 https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Makes-Recommendations-On-Use-of-Off-Label-Drugs-For-Children.aspx
13. ePed.se. Stockholms länslansding, ePed.se.
14. Working Group on Management of Congenital Heart Diseases, Saxena A, Juneja R, Ramakrishnan S. Drug therapy of cardiac diseases in children. Indian Pediatr. 2009;46(4):310-338.
15. Daubeney PEF. Pediatric heart disease: a practical guide. Wiley Online Library. 2012. https://onlinelibrary.wiley.com/doi/book/10.1002/9781444360981
16. Bajcetic M, Jelasavc M, Mitrovic J, et al. Off label and unlicensed drugs use in paediatric cardiology. Eur J Clin Pharmacol. 2005;61(10):775-779.
17. Garcia-Lopez I, Fuentes-Rios JE, Manrique-Rodriguez S. Off-label and unlicensed drug use: results from a pilot study in a pediatric intensive care unit. An Pediatr. 2017;86(1):28-36. https://doi.org/10.1016/j.anpedi.2016.01.026
18. Jobanputra N, Save SU, Bavdekar SB. Off-label and unlicensed drug use in children admitted to pediatric intensive care units (PICU). Int J Risk Saf Med. 2015;27(3):113-121. https://doi.org/10.3233/JRS-150653
19. Nasjonalt kompetansenettverk for legemidler til barn. https://www.legemidlertilbarn.no/Sider/default.aspx
20. Taketomo CK. Pediatric & Neonatal Dosage Handbook; 25th ed 2018.
21. National Institute for Health and Care Excellence. British national formulary for children. https://www.nice.org.uk/bnf-uk-only
22. Group JCSW. Guidelines for drug therapy in pediatric patients with cardiovascular diseases (JCS 2012). Digest Version Circ J. 2014;78(2):507-533. https://doi.org/10.1253/circj-66-0083
23. van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M. Dutch Paediatric pharmacotherapy expertise network N. Developing a paediatric drug formulary for The Netherlands. Arch Dis Child. 2017;102(4):357-361.
24. Phan H, Leder M, Fishley M, Moeller M, Nahata M. Off-label and unlicensed medication use and associated adverse drug events in a pediatric emergency department. Pediatr Emerg Care. 2010;26(6):424-430. https://doi.org/10.1097/PEC.0b013e3181e057e1
25. Kidon MI, See Y. Adverse drug reactions in Singaporean children. Singapore Med J. 2004;45(12):574-577.
26. Stewart D, Helms P, McCaig D, Bond C, McLay J. Monitoring adverse drug reactions in children using community pharmacies: a pilot study. Br J Clin Pharmacol. 2005;59(6):677-683. https://doi.org/10.1111/j.1365-2125.2005.02424.x
27. Wallerstedt SM, Brunlof G, Sundstrom A. Rates of spontaneous reports of adverse drug reactions for drugs reported in children: a cross-sectional study with data from the Swedish adverse drug reaction database and the Swedish Prescribed Drug Register. Drug Saf. 2011;34(8):669-682. https://doi.org/10.2165/11591730-000000000-00000
28. Schirm E, Tobi H, van Puijenbroek EP, Monster-Simons MH, de Jong-van den Berg LT. Reported adverse drug reactions and their
determinants in Dutch children outside the hospital. *Pharmacoepidemiol Drug Saf.* 2004;13(3):159-165. https://doi.org/10.1002/pds.843

29. Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. *J Clin Epidemiol.* 2000;53(10):1076-1080. https://doi.org/10.1016/s0895-4356(00)00190-6

**How to cite this article:** Back J, Wåhlander H, Hanseus K, Bergman G, Naumburg E. Evidence of support used for drug treatments in pediatric cardiology. *Health Sci Rep.* 2021;4:e288. https://doi.org/10.1002/hsr2.288