

Off-label Use of Antimicrobial Agents at the University Hospital for Infectious Diseases, Zagreb, Croatia

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01 ABSTRACT

Background: Antimicrobial agents' (AMAs) off-label use can be associated with the prescriber's education. Little is known about the AMAs' off-label use by infectious disease (ID) specialists. We have conducted research at the University Hospital for Infectious Diseases (UHID), Zagreb, Croatia, a 230-bed tertiary center where ID specialists primarily prescribe AMAs.

Methods: A retrospective cross-sectional analysis was conducted on the day with the highest hospitalization number, January 17, 2019. Any use of AMA not complying with the SmPC was considered off-label and evaluated regarding modality (indication, dose, regimen, route of administration, and age) and justification by institutional or/and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines.

Results: The study included 155 patients, 63 (40.6%) adults and 92 (59.4%) children. 61 (96.8%) adult patients had at least one AMA. There were 134 AMA prescriptions in adults, 42 (31.3%) off-label. AMAs were most frequently prescribed off-label regarding regimen (21), dose (17), and indication (14). Institutional guidelines justified off-label prescriptions in 5 cases regarding dose, 4 regarding indication, and 2 regarding regimen. ESCMID guidelines justified off-label prescriptions in 5 cases regarding indication. The rest of the off-label was not supported by the existing guidelines. 60 (65.2%) pediatric patients had at least one AMA. There were 73 prescriptions, 31 (42.5%) off-label. AMAs were most frequently prescribed off-label regarding indication (19), dose (12), and age (2). Institutional guidelines justified 3 off-label cases regarding indication and 1 regarding dose. ESCMID guidelines justified no off-label in children. The lack of guidelines was the leading cause of off-label AMAs use in children.

Conclusion: One-third of AMAs are prescribed off-label regarding SmPC by ID specialists. However, institutional and international guidelines can justify part of this use.

02 INTRODUCTION

Drug use not complying with the Summary of Product Characteristics (SmPC) regarding indication, dose, dosing regimen, age, or route of administration is considered off-label. It is justified when it is the only option available, when there is scientific proof of safety and effectiveness, and when it is supported by the latest guidelines. Some research has shown that it is widespread, especially in patients rarely included in clinical trials (pediatric population, pregnant women, psychiatric patients).

AMAs are often prescribed off-label. Sometimes it is due to antimicrobial resistance (both the reason and the consequence), the lack of new AMAs, their unavailability, or price. But, it can also be associated with the prescriber's education.

The studies showed that the frequency of off-label drug prescribing differs among settings and populations. No studies investigated the frequency of off-label AMA's prescribing by ID specialists.

03 OBJECTIVES

- The primary aim was to determine the frequency of off-label prescribing of AMAs by ID specialists.
- A secondary aim was to determine the types of off-label prescribing and the compliance of off-label applied AMAs with institutional and ESCMID guidelines.

04 METHODS

A retrospective cross-sectional analysis was conducted on the day with the highest number of hospitalized patients in 2019, January 17.

Inclusion criteria:

- pediatric patients admitted to a daily outpatient department,
- hospitalized pediatric patients and
- adult patients hospitalized in three chosen hospital wards.

Exclusion criteria:

- patients on other wards and other outpatient departments.

The source of collected data was the patient's medical record in paper form. Any use of AMAs not compliant with the SmPC was considered off-label and evaluated regarding indication, dose, regimen, route of administration, age, and justification by institutional and ESCMID guidelines.

05 RESULTS

TABLE 1. Baseline demographics for 155 patients included in analysis

Adults (n=63)		Children (n=92) n=43 wards, n=49 daily outpatient department	
male gender (%)	36 (57.1)	male gender (%)	44 (47.8)
age, median yrs (IQR)	62.5 (44-73)	age (%)	
		0-27 days	5 (5.4)
		28 days-23 months	45 (48.9)
		2-11 years	32 (34.8)
		12-17 years	9 (9.8)
		unknown	1 (1.1)
patients on AMA (%)	61 (96.8)	patients on AMA (%)	60 (65.2)
ICD-10*, median (IQR)	10 (6-13)	ICD-10*, median (IQR)	2 (1-4)
additional drugs in therapy*, median (IQR)	4 (3-7)	additional drugs in therapy*, median (IQR)	0 (0-2)
AMA prescriptions (n)	134	AMA prescriptions (n)	73

ICD-10 - International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
 *only patients on AMA

FIGURE 1. Frequency of off-label AMAs prescriptions in adults

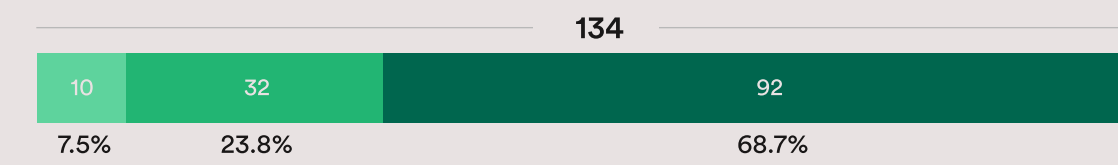


FIGURE 2. Frequency of off-label AMAs prescriptions in children

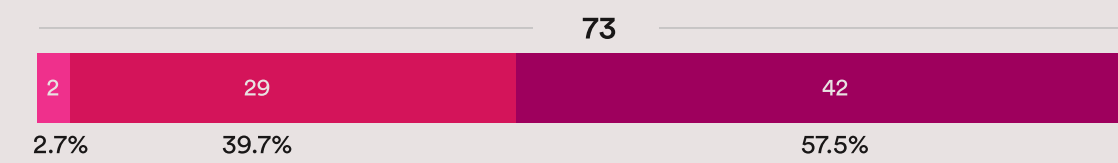


FIGURE 3. Antimicrobial treatment type, cases (n)

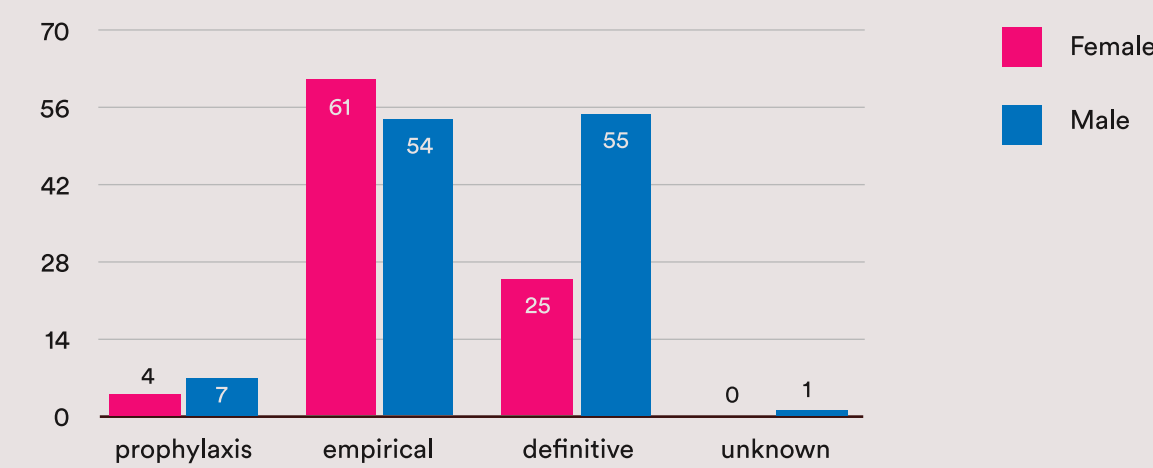


FIGURE 4. Off-label treatment modalities, cases (n)

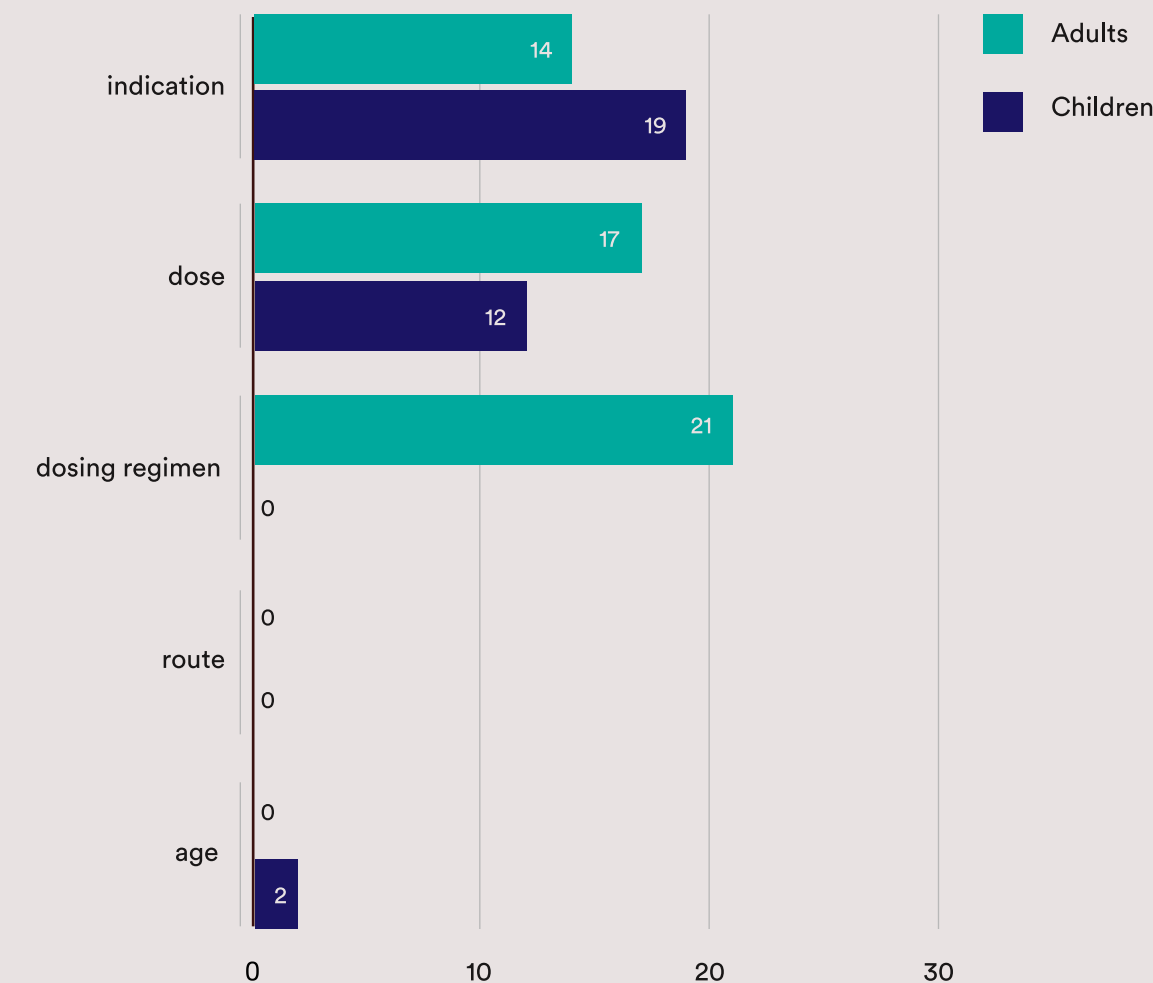
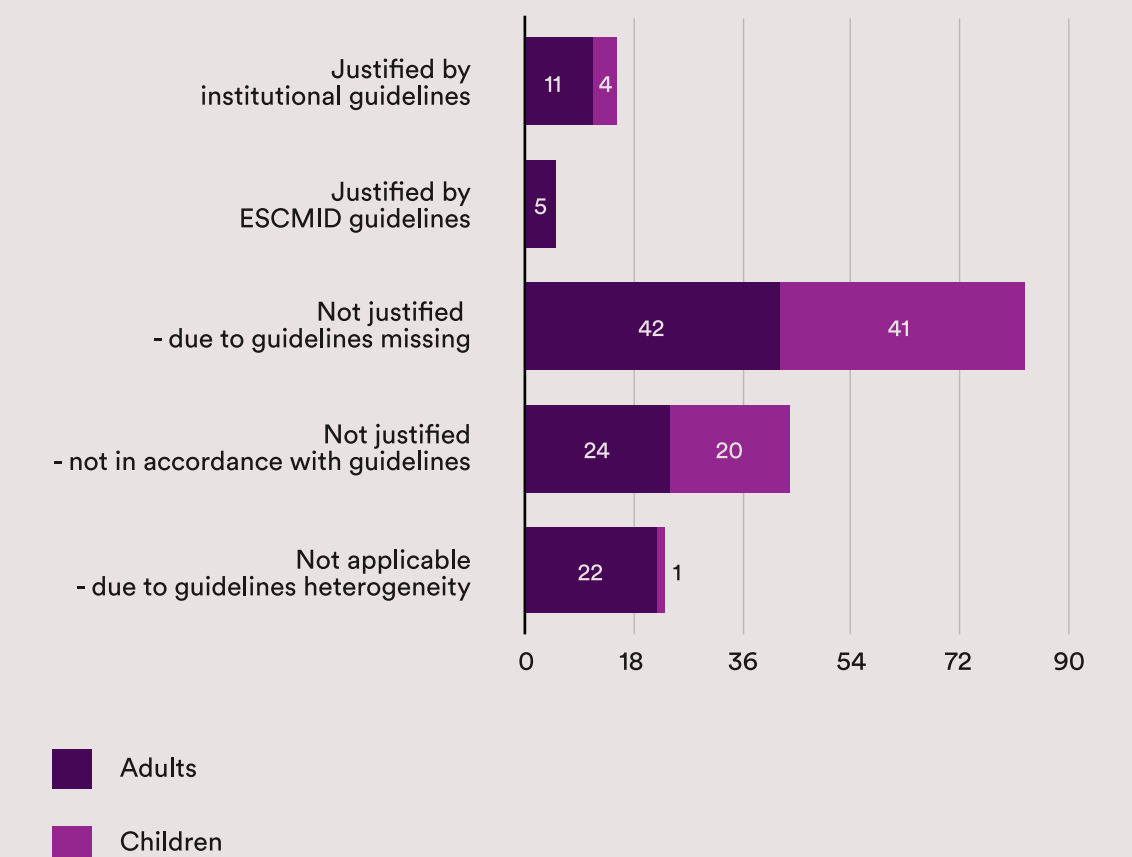


TABLE 2. The most frequently off-label prescribed AMAs

Adults	off-label type (n)					cases (n)
	indication	dose	regimen	route	age	
oseltamivir	1	6	9	0	0	16
cefuroxime axetil	4	0	0	0	0	4
piperacillin/tazobactam	0	2	3	0	0	5
meropenem	1	1	2	0	0	4
vancomycin	1	2	2	0	0	5
cases (n, %)	7	11	16	0	0	34 (65.4%)

Children	off-label type (n)					cases (n)
	indication	dose	regimen	route	age	
ceftriaxone	6	2	0	0	0	8
oseltamivir	3	4	0	0	0	7
azithromycin	3	1	0	0	0	4
vancomycin	1	1	0	0	0	2
meropenem	0	1	0	0	1	2
ertapenem	1	0	0	0	1	2
cases (n, %)	14	9	0	0	2	25 (75.8%)

FIGURE 5. Off-label justification by guidelines, cases (n)



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