

Original Research

Prevalence and nature of off-label antibiotic prescribing for children in a tertiary setting: A descriptive study from Jordan

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ABSTRACT*

Objective: The aim of the present study was to evaluate the use of off-label antibiotics in neonatal intensive care units (NICUs) and paediatric wards in Jordan.

Methods: Data of patients admitted to the neonatal intensive care units and paediatric wards in King Abdullah University Hospital were collected over an 8-week survey between May and July 2012. Data collected in this study included patients' age, weight, medical history, diagnosis and the details of antibiotics prescribed to each patient.

Results: The study involved a total of 250 children (80 admitted to the NICU and 170 admitted to the wards). A total of 598 antibiotic prescriptions were issued for these patients (244 in NICUs and 354 in paediatric wards). The results of the present study show that off-label antibiotic prescribing to paediatric patients is very common. Off-label antibiotic prescribing to paediatric patients is related mostly to doses and indications, and rarely to age. The majority of admitted patients received at least one off-label antibiotic during their hospital stay.

Conclusion: This study reveals the high prevalence of off-label use of antibiotic among paediatric children in Jordan. There is a serious need for robust and continuous educational programs to improve the awareness of paediatricians of guidelines surrounding the use of antibiotics in paediatric patients. Furthermore, true collaboration between paediatricians and clinical

pharmacists towards safe and effective antibiotic prescribing in paediatric patients is crucial.

Keywords: Anti-Bacterial Agents; Off-Label Use; Drug Utilization; Child; Infant; Inpatients; Jordan

INTRODUCTION

Due to the relative lack of licensed products for the treatment of paediatrics¹, many of the prescriptions for hospitalised children, and a lesser proportion of prescriptions in primary care, involve use of medicines without a license for use in children (e.g. reformulated adult medicines) or outside of the license recommendations (off-label).² If a medicine does not have a licensed indication for use in children, the Patient Information Leaflet will contain no details regarding its use in this population.³ The off-label use of medicine in children is the use of licensed medicines outside their license in terms of recommended dose, recommended indication, recommended age and recommended route.

A number of high profile cases of dosing errors, some of which have caused fatalities, have been reported regarding the use of unlicensed and off-label medicines in children.⁴ Medication errors in children have three times the potential to cause harm when compared with similar errors in adults.⁵ Nonetheless such prescribing is essential if children are not to be denied therapeutic advances.⁶ Most clinicians believe that children should not be denied the benefit of such medicine use simply because pharmaceutical companies have not performed the necessary research to extend their product license to include children.⁷ Furthermore, in most of the cases the benefits of using unlicensed and off-label medications outweigh the risk of not using them.⁸

Antibiotics are the most commonly prescribed drugs to paediatrics.⁹ Use of antibiotics in an off-label manner in pediatric patients is very common due to various reasons including prescribing for younger age, prescribing off-label doses, and prescribing at an off-label frequency of drug administration.¹⁰ While some antibiotics have been labeled for the use in pediatric patients, many others such as fluoroquinolones, azithromycin, linezolid, or daptomycin are still being prescribed in an off-label manner.¹¹ This is of concern in the light of emerging multidrug-resistant pathogens.

The aim of the present study was to evaluate the use of off-label antibiotics in neonatal intensive care

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units (NICUs) and paediatric wards in Jordan via research conducted at King Abdulla University Hospital which is a tertiary health centre and the largest medical structure in the north of Jordan, serving approximately one million inhabitants.

METHODS

Antibiotic prescriptions were evaluated for all patients in the neonatal intensive care units (NICUs) and the paediatric medical and surgical wards in King Abdulla University Hospital, Irbid, Jordan.

All data obtained on patients presenting at different sites were collected by the same investigator during an 8-week survey between May and July 2012. Data included age, date of birth, weight, relevant medical history and diagnosis, together with details of all antibiotics prescribed (compound, route of administration, dose and indication for use). The study protocol was approved by the Research Committee at the School of Pharmacy and the Institutional Review Board and Deanship of Research at Jordan University of Science and Technology. Written informed consent was obtained from a parent or legal guardian, with children older than 8 years of age being asked to give personally their assent.

Off-label antibiotic use was determined based on drug related information found on the Drug Information Handbook (DIH) 2011 20th edition and on the package insert information. This reference is most commonly used by doctors and clinical pharmacists in Jordan. Off-label use was defined as the administration of an antibiotic in situations not covered by the product license or the summary of product characteristics, or at a different dose or frequency, or to different age groups, or by means of an alternative route. The age groups considered were those defined by European Medicine Agency: neonates (0–27 days), infants (28 days to 23 months), children (2–11 years) and adolescents (12–17 years). The prescriptions were then divided into three groups depending on whether the off-label use was related to the patient's age, the drug dose or the indication.

Demographic Characteristics:	N (%)
Gender	
Male	152 (60.8)
Age	
0 – 27 days	82 (32.8)
28 days – 23 months	73 (29.2)
2 – 11 years	88 (35.2)
12 – 17 years	7 (2.8)
Units	
Wards	170 (68.0)
NICU	80 (32.0)
Care giver	
Parents	249 (99.6)
Caregiver	1 (0.4)
Presence of Chronic Illnesses	
Yes	65 (26.0)
No	185 (74.0)
Gestational Age (for NICU patients)	
Full term (\geq 37 weeks)	36 (59.1)
Preterm ($<$ 37 weeks)	25 (40.9)

Following data collection, drug information were coded and entered into a customized database in SPSS, version 17, for statistical analyses.

RESULTS

Study population

The study involved a total of 250 children admitted to King Abdulla University Hospital (80 admitted to the NICU and 170 admitted to the wards). A total of 568 antibiotic prescriptions were issued for these patients (244 in NICUs and 354 in paediatric wards, Table 1 show the demographic characteristics of the study patients.

Antibiotic prescribing in neonatal units

In the NICU settings, there were 132 episodes out of 244 prescriptions in which antibiotics were used in an off-label manner (54.1%). Regarding off-label prescription patterns, 104 episodes were used outside the registered dose. Ampicillin and gentamicin were the most frequent of such prescriptions and were prescribed because of proven or suspected sepsis. Table 2 shows the antibiotics used at an off-label dose in patients who were admitted to NICUs. In addition, approximately half the patients who administered off-label antibiotics in NICUs received these antibiotics in an inappropriate frequency.

Table 3 shows the antibiotics used for an off-label indication in patients admitted to the NICUs (n=74). The antibiotics most frequently prescribed for an off-label indication were ampicillin and imipenem. The most common indication was medical prophylaxis. More neonates with underlying chronic disease had off-label indications for the antibiotics received.

Antibiotic prescribing on paediatric wards

Of 354 prescriptions for antibiotics, 163 (46.0%) were for antibiotics used at off-label dose. The antibiotics most frequently used at off-label dose were Ceftriaxone (44/163, 27%) and Vancomycin (35/163, 21.5%) administered to children with lower

Antibiotic used at an off-label dose	N (%)
Antibiotic used at an off-label dose	104 (53.6)
Main molecule	
Ampicillin	33 (31.7)
Gentamicin	33 (31.7)
Meropenem	15 (14.5)
Vancomycin	16 (15.4)
Piperacillin/tazobactam	2(1.9)
Erythromycin	2 (1.9)
Fucidic acid	1 (1.0)
Others	2(1.9)
Main indications	
Higher than advised doses	42 (40.4)
Lower than advised doses	11 (10.6)
Incorrect frequency	51 (49.0)
Sepsis	39 (63.9)
Medical prophylaxis	22 (36.1)
Others	43 (41.3)
Patients with underlying chronic disease	22 (27.5)

		N (%)
Antibiotics used for an off-label indication		74 (38.1)
Main molecule		
	Ampicillin	27 (36.5)
	Imipenem	23 (31.1)
	Cefotaxime	17 (23.0)
	Gentamicin	3 (4.1)
	Amoxicillin/clavulanate	2 (2.7)
	Others	2 (2.7)
Main indications		
	Medical prophylaxis	41 (55.4)
	Sepsis	19 (25.7)
	Respiratory distress disease	10 (13.5)
	Others	4 (5.4)
Patients with underlying chronic disease		9 (12.2)

respiratory infections, sepsis, and meningitis. Table 4 shows the antibiotics used at an off-label dose administered to patients in paediatric wards.

Furthermore, 42 (11.9%) prescriptions were for antibiotics used at off-label indication. Cefotaxim (10/42, 23.8%) and Ceftriaxone (9/42, 21.4%) were most frequently used for off-label indications for treatment of children for surgical prophylaxis, sepsis, and meningitis. Table 5 shows the antibiotics used for off-label indications in patients admitted to paediatric wards in King Abdullah University Hospital.

DISCUSSION

With the up-rise of off-label prescribing to children, health care professionals are increasingly put under a lot of pressures to ensure safe and effective medicine use.¹² Concerns regarding the safety and efficacy of off-label prescribing had always been raised by the public and by healthcare practitioners as well.¹³ In Jordan, such concerns have been mostly raised by paediatricians who specialize in infectious diseases, as the use of antibiotics in children has its own set of risks and efficacy concerns.⁹ In a previous study that explored the perceptions and attitudes of Jordanian paediatricians toward off-label prescribing, paediatricians who specialized in infectious diseases reported high familiarity levels with the term 'off-label prescribing' indicating that such use of medicines in children is prevalent, hence paediatricians will work to ensure a balance between the safety and efficacy of antibiotics prescribed for children and under the pressures of growing bacterial resistance to antibiotics which may lead them to increasingly rely on off-label prescribing.¹¹

Previous research carried out in various settings has indicated that the off-label prescribing is frequent in paediatrics, especially in neonates.¹ However, the latter have focused on all drugs prescribed to children and provided few details on the prescription pattern. To the best of our knowledge, this is the first study to evaluate off-label antibiotic prescribing in paediatric patients that sheds the light on the variables involved in prescription: the age of the patient, the total daily drug dose and its fractioning and the indication for

		N (%)
Antibiotics used at an off-label dose		163 (46.0)
Main molecule		
	Ceftriaxone	44 (26.9)
	Vancomycin	35 (21.4)
	Piperacillin/tazobactam	25 (15.3)
	Metronidazole	16 (9.8)
	Others	43 (26.3)
Age		
	0 – 27 days	21 (12.9)
	28 days – 23 months	50 (30.7)
	2 – 11 years	67 (41.1)
	12 – 17 years	25 (15.3)
	Median age (range), years	6.23 (0.02 – 16.70)
Main indications		
	Higher than advised doses	101 (61.9)
	Lower than advised doses	63 (38.6)
	Incorrect frequency	81 (47.3)
	Pneumonia	64 (39.3)
	Sepsis	42 (25.7)
	Cancer	26 (16.0)
	Meningitis	14 (8.6)
	Others	17 (10.4)
Patients with underlying chronic disease		30 (18.4)

treatment. Furthermore there is little knowledge of off-label paediatric prescribing, not only in Jordan but in the entire Middle East region.⁹ The present study comes to support the practice of paediatric medicine and pharmacy in developing countries and enhance the delivery of pediatric clinical pharmacy services.

The findings of the present study suggest that paediatric off-label antibiotic use is very common in Jordan. The majority of off-label use of antibiotics in paediatric patients is mostly related to doses and indications rather than age. The latter results are consistent with previous results of a study of off-label antibiotic use in children in three European countries (United Kingdom, Greece, and Italy) were the majority of off-label use of antibiotics in paediatrics was exclusively related to dose and indication.¹¹ Results of the present study are consistent as well with previous studies that

		N (%)
Antibiotics used at an off-label indication		42 (21.4)
Main molecule		
	Cefotaxim	10 (23.8)
	Ceftriaxone	9 (21.4)
	Metronidazole	8 (19.0)
	Meropenem	7 (16.7)
	Others	8 (19.0)
Age		
	0 – 27 days	4 (9.5)
	28 days – 23 months	10 (23.8)
	2 – 11 years	20 (47.6)
	12 – 17 years	8 (19.0)
	Median age (range), years	5.78 (0.01 – 15.30)
Main indications		
	Surgical Prophylaxis	12 (28.6)
	Sepsis	10 (23.8)
	Meningitis	3 (7.1)
	Others	7 (16.7)
Patients with underlying chronic disease		14 (33.3)

explored the views of paediatricians regarding off-label medicine prescribing as Jordanian paediatricians indicated that the most common reason given for off-label prescribing was prescribing for a different indication⁹ and Scottish and Northern Irish paediatricians reported that the most common pattern observed for off-label prescribing was prescribing at lower or higher than the recommended dose.^{7,10}

In the NICU prompt treatment of suspected or proven sepsis consisted of prescribing a combination of ampicillin and an aminoglycoside (amikacin or gentamicin).¹⁴ The latter regimen abides with current published guidelines in terms of the drugs of choice to treat neonatal sepsis; however the prescribed doses varied with the age of the patient and the severity of each case increasing the prevalence of antibiotic prescribed at off-label dose.¹⁵ Lower doses of antibiotics were prescribed to younger neonates to avoid adverse drug reactions while higher doses were prescribed in severe cases or when the antibiotics were not effective putting patients under the risk of adverse events. Though ampicillin and an aminoglycoside are indicated in the case of neonatal sepsis, pathogen resistance to those molecules has been on the rise, especially in late onset sepsis and nosocomial infections.¹⁶ A fact which is leading doctors to prescribe alternative treatment regimens, instead of increasing the dose of administered antibiotics. A better choice of treatment may be the prescription of a carbapenem, a class of beta-lactam antibiotics with a broad spectrum of antibacterial activity and are considered of the antibiotics of last resort for many bacterial infections.¹⁷ For instance, published research indicated that meropenem has been successfully used in the treatment of sepsis in children older than three months of age and regardless of the fact that it has not been registered for neonates and infants younger than three months of age it is yet prescribed to this age group which may justify the use of off-label imipenem (a carbapenem) in children younger than three months of age in the present study.¹⁸ Imipenem has been also prescribed for medical prophylaxis in children admitted to the NICU which is considered an off-label use of a carbapenem.

It is important to note that the most appropriate approach in treating suspected or proven sepsis in neonates is by using narrow spectrum antibiotics, treating for infection and not colonization, and limiting the duration of therapy. However, antibiotics approved for use in neonates have been licensed for long and bacterial resistance towards those agents is being suspected leading neonatologists to prescribe alternative off-label antibiotics.¹⁹

In paediatric wards Ceftriaxone was the most antibiotic prescribed in an off-label manner at an off-label dose, mostly above than the recommended dose and for the treatment of meningitis. Current guidelines state that the treatment of meningitis depends on patients' age, most likely organisms within age group, and patient's weight with higher doses being prescribed for complicated cases.²⁰ In

the present study, paediatricians exceeded the maximum recommended dose and treated all cases of meningitis as complicated infections. This pattern of off-label prescribing has been previously found in the literature where paediatricians tend to prescribe higher than the recommended dose to ensure efficacy regardless of safety concerns. Emerging resistance towards cephalosporins may be a good reason to justify the prescription of higher doses that also may fail in treating paediatric infections which highlights the need for comprehensive prescribing and dosing guidelines for antibiotics prescribed for paediatrics.²¹ However, studies indicate that paediatricians knowingly prescribe in an off-label manner, especially when dealing with infectious diseases.^{7,9} A better approach towards the treatment of resistant infections in paediatrics may be the prescription of off-label quinolones as this group of antibiotics, which is not licensed for using during the first 18 years of life, can be administered to paediatric patients with good results and without any significant adverse events.²² However, the prescription of off-label quinolones should be limited to cases caused by pathogens resistant to all of the other licensed drugs as quinolones may rapidly select for antimicrobial resistance in the case of widespread and uncontrolled administration.²³

In consistence with previous studies, aminoglycosides were prescribed in doses lower than recommended for pediatric patients admitted to the paediatric wards. The risk of toxicity in children when prescribing aminoglycosides may lead paediatricians to prescribe lower doses of antibiotics which may raise the chances of treatment failure and increase the resistance of pathogens to this class of antibiotics.²³ However, the use of antibiotics at lower doses for paediatric patients may be due to clinicians translating the findings of post marketing surveillance. For example, aminoglycosides have been licensed by recommending dividing the dose into two or three administrations based on the patients' age and renal function. Trials have shown equivalent or superior clinical outcomes from once-daily dosing of the total daily dose, with a reduced lower risk of toxicity.²³

The outcomes of the current study shed the light on the high prevalence of off-label use of antibiotics in children in Jordan, a situation that calls for further research and studies to explore and find solutions for such medicine used in children. Healthcare and academic institution should give priority to paediatric medical research especially on the proper use of antibiotics as it is now a global necessity to find solutions for the up rise of antimicrobial resistance all over the world.

CONCLUSIONS

This study confirms that the off-label use of antibiotics in paediatric population is prevalent among paediatric patients in Jordan and that the majority of off-label prescription cannot be justified on the basis of optimizing anti-infective therapy. Studies on medicines not labeled for use in paediatrics are very important in order to assess

how antibiotics should be administered to different age groups of paediatrics, to guarantee optimal treatment outcomes, and to minimize the risk of adverse events. Finally, clinical pharmacy programs should be incorporated comprehensively on pediatric ward and neonatal intensive care units (NICUs) to collaborate with fellow paediatricians towards the optimal treatment and prevention of different neonatal and paediatric infections.

CONFLICT OF INTEREST

None declared.

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