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Assessment of antibiotic prescriptions in pediatric care units in a regional university hospital

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Keywords: antibiotic stewardship, assessment of professional practices, pediatrics

ABSTRACT

Objectives. The main objective was to assess the relevance of antibiotic prescriptions in the pediatric wards of a regional university hospital in France. Secondary objectives were to assess adequacy of the dose, administration frequency, administration route, treatment duration, adaptation to bacteriological results, and treatment reevaluation.

Patients and methods. We assessed antibiotic prescriptions in pediatric settings. We included all patients under 18 years of age hospitalized in a pediatric ward who received a computerized prescription for antibiotic treatment between June 1st and June 30th, 2018; 163 clinical cases for 157 patients were analyzed. Patients hospitalized in neonatology, pediatric intensive care unit, and onco-hematology wards were excluded.

Results. The rate of relevance was 71%. The rates of adequacy for the other criteria were 60% for the dose, 99% for the administration frequency, 98% for the administration route, 72% for treatment duration, 98% for treatment adaptation to microbiological results, and 100% for treatment reevaluation. All criteria combined, the overall rate of adequacy was 28%.

Conclusions. Effort should be made regarding doses and treatment durations. Areas for improvement have been suggested to the wards: standardized prescription protocols, pediatric prescription guide, training of residents, setting up of the operational team in pediatric wards and a second clinical evaluation.

INTRODUCTION

Our regional university hospital set up an operational team made of an infectious disease specialist and a pharmacist in 2006 [1,2]. The team promotes the proper use of antibiotics and contributed to reducing antibiotic consumption in the hospital. Since 2017 an infectious disease specialist visits the hospital pharmacy on a daily basis to assess the relevance of “last resort” antibiotic prescriptions made to hospitalized patients, with the cooperation of a pharmacist. The infectious disease specialist also visits specific wards once a week or on demand, including pediatric wards. The lead infectious disease specialist also has a direct phone line; prescribers from any ward can thus contact him when seeking advice. As this strategy is not implemented in pediatric wards, we aimed to assess antibiotic prescriptions in such wards to assess the needs for such an operational team.

The main objective was to assess the relevance of antibiotic prescriptions in pediatric wards. Secondary objectives were to assess the adequacy of doses, administration frequency, administration route, treatment duration, treatment adaptation to microbiological results, and treatment reevaluation on Day 3 and Day 7.

MATERIAL AND METHODS

Material

Study site

We performed the study in a pediatric university hospital with 198 beds (excluding outpatient surgery and day hospitalization wards).

Inclusion criteria of patients

The analysis included all patients aged below 18 years hospitalized for more than 24 hours with a computerized prescription of antibiotics between June 1-30, 2018. We consulted the medical files of patients who received at least one administration of antibiotics.

Exclusion criteria of patients

Patients hospitalized in the neonatology, ICU, and onco-hematological wards were excluded from the study because these wards use prescription software other than the Pharma™ software. A total of 97 beds were analyzed: 50 in the medical ward and 47 in the surgical ward.

Software

All analyzed prescriptions were extracted from the Pharma™ 5.6.60419 software (Computer Engineering). Data required for the study was extracted from the DxCare™ 7.5.20p040 software (Medasys).

Statistical analyses were performed using the R software™ 3.6.0 (R Foundation).

Guidelines

We used the following guidelines: Guide for the pediatric prescription of antibiotics (2016) [3], 2016 antibioguide (AntibioLor) [4] – local and regional guidelines for the prescription of anti-infective agents – and guidelines from scientific societies or national agencies [5-13].

Evaluation of relevance

Our evaluation is based on the methodology for relevance reviews suggested by the French National Authority for Health (French acronym HAS) in November 2017 [14].

Method

Type of study

We performed an observational and retrospective relevance review of antibiotic prescription in pediatric wards.

Data collection

The list of patients and of all antibiotic prescriptions was extracted from the Pharma™ software, and the medical files of patients were consulted on the DxCare™ software.

Evaluation of relevance

We mainly used the Guide for pediatric antibiotic prescription to assess prescription relevance [3]. When a given clinical situation was not mentioned in the guide, the following guidelines were used in the following order: 2016 antibiotic guide [4] and guidelines from scientific societies or national agencies. We asked for the lead infectious disease specialist's advice for specific cases.

The antibiotic prescription was deemed relevant when the clinical situation required the prescription of an antibiotic treatment and when the prescribed molecules were those

mentioned in the guidelines for the first-line treatment. When the infectious disease specialist's advice was requested, the file was deemed relevant.

Additional assessment

We assessed six other criteria:

- weight-related dose taking into account the maximum dose. Results were assessed as the number of clinical cases and the number of prescription lines, making a distinction between under-dosing and overdosing;
- administration frequency;
- administration route;
- treatment duration documented in the patient's computerized file (DxCare™ software), taking into consideration the discharge letter if required;
- treatment adaptation based on microbiological results available in the patient's computerized file (DxCare™);
- treatment reevaluation on Day 3 and Day 7. We considered the situation as reevaluated when a computerized reevaluation using the Pharma™ software had been performed and when an hospitalization follow-up comment had been documented in the patient's file using the DxCare™ software.

The antibiotic treatment was considered adequate if the dose, administration frequency, administration route, and treatment duration complied with guidelines, but also if treatment was adapted to microbiological results and if it had been reevaluated on Day 3 and Day 7.

Definitions

The rate of relevance was defined as the number of prescriptions for which the antibiotic therapy indication complied with guidelines, divided by the total number of prescriptions.

The rate of adequacy was defined as the number of prescriptions for which the secondary objective (dose or administration frequency or administration route or treatment duration or treatment adaptation to microbiological results or reevaluation performed on Day 3 and Day 7) complied with guidelines, divided by the total number of prescriptions.

The overall rate of adequacy was defined as the number of prescriptions for which all criteria (indication, dose, administration frequency, administration route, treatment duration, adaptation to microbiological results, treatment reevaluation performed on Day 3 and Day 7) complied with guidelines, divided by the total number of prescriptions.

RESULTS

Patients and files

A total of 163 clinical cases were selected corresponding to 157 patients, *i.e.* 23% (n=163/718 admissions) of pediatric hospitalizations in the wards concerned. Ninety patients were hospitalized in the medical ward (55%) and 73 in the surgical ward (45%).

Ninety-three files related to boys and 70 to girls, *i.e.* a sex ratio of 1.3. Characteristics of the population and of the files by ward are presented in Table I.

These 163 clinical cases were associated with 352 prescription lines. The three most frequently prescribed antibiotics were amoxicillin-clavulanic acid (n=87/352; 25%),

cefotaxime (n=75/352; 21%), and amoxicillin (n=41/352; 12%). They accounted for 60% of the prescriptions.

Evaluation of relevance

All results are presented as percentages of clinical cases (n=163).

Of the 163 clinical cases, 115 were relevantly treated (71%).

The lead infectious disease specialist's advice was requested for 13 patients (n=13/163; 8%): four in the medical ward (n=4/90; 4%) and nine in the surgical ward (n=9/73; 12%). Surgeons thus tended to more frequently ask for the lead infectious disease specialist's advice ($p=0.08$). These clinical cases were considered relevantly treated.

The other 102 cases were considered relevant as they complied with guidelines.

Among the 48 irrelevantly treated cases (29%), 40 were hospitalized in the medical ward and eight in the surgical ward. They accounted for 44% of clinical cases in the medical ward (n=40/90) versus 11% in the surgical ward (n=8/73). A higher rate of irrelevant cases was thus observed in the medical than surgical ward ($p<0.0004$).

Reasons for irrelevance are detailed in Table II. Results were expressed as number and percentage of files irrelevantly treated. Of the 29% of irrelevant files: 15% were associated with a loss of chance because treatment was not the recommended antibiotic therapy or because the bacterium was resistant to the initial empirical antibiotic therapy; no impact on treatment effectiveness was observed in 10% of these files because the prescribed treatment was part of a potential alternative strategy, and 4% were useless

because the clinical situation did not require antibiotic prescription. The following cases were most frequently treated in an irrelevant way: pneumonia (n=9/48; 19%) mainly treated with josamycin instead of clarithromycin [3], acute pyelonephritis (n=11/48; 23%) sometimes treated with a third-generation cephalosporin (3GC) monotherapy and most often with an oral switch to cefixime instead of co-trimoxazole [3], and mother-to-fetus infections (n=5/48; 10%) where the prescribed aminoglycoside was amikacin while guidelines recommend gentamicin [8].

Evaluation of doses

The dosing regimen of antibiotic treatments was adequate in 97 clinical cases (60%). Of the 66 (40%) with an inadequate dosing regimen: 32 were medical ward cases (n=32/90; 36%) and 34 were surgical ward cases (n=34/73; 47%), thus reflecting a slightly better prescription trend in the medical ward ($p=0.199$).

Reasons for dose inadequacy are detailed by ward in Table III.

A total of 91 prescription lines were associated with an inadequate dose (n=91/352; 26%). The same number of prescription mistakes was observed in the medical (n=45/197; 23%) and surgical (n=46/155; 30%) wards ($p=0.29$).

Clinical cases with inadequate doses are detailed in Table IV.

Evaluation of administration frequency

Administration frequency was adequate in 162 clinical cases (99%). The sole inadequate administration frequency was observed in a patient treated for Lyme neuroborreliosis with amoxicillin twice a day instead of three times a day (medical ward) (n=1/90; 1%).

Evaluation of the administration route

The administration route was adequate in 159 cases (98%). The oral route was used instead of the parenteral route in four patients (2%): one in the medical ward (n=1/90; 1%) and three in the surgical ward (n=3/73; 4%).

Evaluation of treatment duration

Treatment duration was not documented in the discharge letter for two cases (1%). Statistics by ward are presented in Table V. No difference was observed between the medical and the surgical wards (31% *versus* 25%; $p=0.39$).

Clinical cases most often treated with an inadequate treatment duration were cases of common pneumonia (9-12 days instead of 7 days), atypical pneumonia (7-8 days instead of 14 days), acute pyelonephritis (11-21 days instead of 10 days), peritonitis (6-15 days instead of 3-7 days for a localized or generalized presentation, respectively), inflammatory appendicitis (3 days instead of a single day), and surgical “antibiotic prophylaxis” for fractures (2-7 days instead of a unique dose).

Evaluation of treatment adaptation based on microbiological results

One-hundred and fourteen cases did not require treatment adaptation to microbiological results (70%), 46 cases benefited from treatment adaptation (28%) but no treatment adaptation was made for three cases (2%), all in the medical ward (n=3/90; 3%). The treatment suggested for the first patient was useless. For the two other, the targeted bacterium was resistant to the prescribed antibiotic.

Evaluation of treatment reevaluation on Day 3 and Day 7

All clinical cases underwent computerized reevaluation (100%). However, these results had to be cautiously interpreted because computerized reevaluation of antibiotic prescriptions was “compulsory” in our facility on Day 3 and Day 7. The prescription software was configured so as to make the physician validate the prescription line to continue treatment. Upon validation of the physician, the treatment line was considered reevaluated.

Evaluation (all criteria)

Considering all criteria, the overall rate of adequacy reached 28% (n=45/163; all wards included). This rate was 21% in the medical ward (n=19/90) and 36% in the surgical ward (n=26/73); we thus observed a better prescription trends in the surgical ward ($p=0.052$).

DISCUSSION

The rate of relevance was 71%. The adequacy rates of other criteria were 60% for the dose (74% for prescription lines), 99% for the administration frequency, 98% for the administration route, 72% for treatment duration, 98% for treatment adaptation to microbiological results, and 100% for treatment reevaluation. When taking into consideration all criteria, the overall rate of adequacy was 28%.

The rate of prescription relevance in our study (71%) was relatively similar to those reported in the literature: 82% and 63% in the pediatric intensive care unit [15,16], 85% in the pediatric emergency department of a Parisian hospital but with 31% of “questionable” cases [17], 67% in the medical wards of Lille University Hospital when evaluating three classes of antibiotics [18], and 70% in a Congolese study [19]. A higher rate of relevance was

observed in the surgical ward (89% versus 56%; $p < 0.0004$). This could partly be explained by surgeons more frequently requesting the infectious disease specialist's advice (12% versus 4%; $p = 0.08$). The importance of the infectious disease specialist's advice has already been demonstrated, mainly by Byl *et al.* who reported that 54% of empirical antibiotic treatments prescribed by non-specialist physicians were adequate versus 78% of prescriptions made by infectious disease specialists ($p < 0.0001$) [20]. Of all cases of irrelevant prescriptions, 35% did not have any impact on treatment effectiveness: although the antibiotic was not recommended for the first-line treatment, it could still be prescribed as an alternative. Several explanations were possible. This could depend on the presence of protocols implemented within the facility or within the ward. This was the case for the treatment of mother-to-fetus infections for which the suggested aminoglycoside was amikacin and not gentamicin, as recommended by the French Society of Neonatology [8]. The prescriber's experience in terms of patients' predictable compliance was also important: the taste of oral drugs is important for treatment compliance of children [21]. It was sometimes less detrimental to prescribe a good tasting second-line antibiotic than the bitter tasting first-line antibiotic that children would not want to swallow, thus risking clinical failure or even selection of resistance [22, 23]. Finally, this could also be due to unfamiliarity with latest guidelines because of the lack of continuing education. Urinary tract infections (UTI) were sometimes treated with a 3GC monotherapy, without any aminoglycoside. Yet, it has been demonstrated that UTIs caused by extended-spectrum beta-lactamase Enterobacteriaceae (ESBLE) were on the rise in the pediatric population (increased prevalence from 2.4% to 5.1% between 2007 and 2012 in France) [24]. Literature data revealed that children with UTI should be prescribed an effective treatment as soon as possible to prevent kidney sequelae [25], except for those with a catheter as indicated in another study of adults and children

[26]. Nevertheless, we did not identify any ESBL in our study. Poey *et al.* and Madhy *et al.* recommended amikacin monotherapy for the treatment of febrile UTIs because of the associated lower ecological impact [24,27]. The literature review by Goodlet *et al.* also reported similar microbiological success rates between a single dose treatment with an aminoglycoside and the comparator for lower UTIs [28]. However, studies assessed in the present study were old and results needed to be confirmed for pyelonephritis.

As for the dose, 74% of prescription lines were associated with an adequate dose, *i.e.* 26% of lines with dosing regimen mistakes. This result is similar to the 23% reported in a pediatric ICU [16], but far higher than the 6% reported in the Congolese study [19]. The most incriminated antibiotic was amoxicillin-clavulanic acid. It was also the most prescribed drug and its dosing regimen highly varied by indication, hence the increased risk of mistakes. The proper use of this antibiotic is therefore highly important, especially as it leads to resistance [29]. These mistakes could be mainly due to poor knowledge of the dosing regimen required for a given disease; the prescriber rather referred to the usual dosing of the antibiotic. Training should be offered to prescribers and pharmacists, and specific standardized protocols should be implemented for each indication in the computerized prescription software.

Administration frequencies were adequately respected (99% of adequacy). This rate is similar to those found in the literature [16, 18].

Analysis of the administration route revealed that pediatricians tended to favor the oral versus parenteral route. This was the main reason behind the 2% of inadequate prescriptions, in line with literature data [16]. Several reasons are possible: injections are more painful than swallowing tablets; vein integrity of children is often poor and maintaining

a venous line for a prolonged time may be difficult and associated with an increased risk of complications such as infectious complications. Injectable drugs were also more expensive than oral drugs. When the drug had excellent bioavailability, oral administration did not lower effectiveness and was favored.

Problems related to treatment duration accounted for 28% of inadequate prescriptions, with a tendency to excessive treatment durations rather than excessively short durations. This percentage is higher than those reported in the literature: 12% [16] and 16% [19]. No difference was observed between wards (31% *versus* 25%; $p=0.39$). The most frequent clinical situations associated with inadequate treatment durations were pneumonia, peritonitis, inflammatory appendicitis, acute pyelonephritis, and surgical antibiotic prophylaxis for fracture. Treatment durations are often reevaluated by scientific societies, with a shortening tendency for equivalent effectiveness [30, 31]. Poor knowledge of such changes could explain these results. Shortening objectives of treatment duration aim at limiting adverse effects, reducing the impact on the commensal flora and on the selection pressure of antibiotics. They also aim at increasing patient's compliance, while maintaining effectiveness and reducing costs [31]. Reminders are thus sent to new interns at the beginning of each semester. A specific form adapted by the French Infectious Diseases Society [32] from Wintenberger *et al.* [33] is handed out to them.

Although we performed the study during the month of June to avoid the winter epidemic period, it has several limitations. There is a recruitment bias as we excluded several wards: the neonatology ward and the ICU as they used paper prescriptions. We therefore could not retrospectively assess prescriptions. There was also no guidelines for pediatric febrile neutropenia; yet, they accounted for a great number of reasons for anti-infective

prescription in onco-hematology wards. It would be interesting to perform a study in these wards. Only one person took care of the analysis (a pharmacy intern trained to antibiotic prescription validation) with the help of an infectious disease specialist when needed, although not on a systematic basis. Such analysis was only based on general guidelines, which did not take into account potential ward specificities. The studied period was also limited (one month). Data was collected from computerized software, which could lead to questioning the reliability and integrity of data copied by healthcare professionals. One may also question our decision to consider as immediately relevant prescriptions made on the basis of the infectious disease specialist's advice. However, we could not question such advice while data provided at that time was not available (clinical examination, additional information given orally, etc.).

Although numerous guidelines are available on the proper use of antibiotics, measures should be taken at the facility level [34]. Computerized protocols for antibiotic prescriptions based on the chosen indication have thus been suggested as well as specific standardized protocols for each indication. A "pediatrics" tablet could be added to the current Antibio guide (paper version and Smartphone application) so that physicians can always have it on hand. Training provided by senior physicians should also be offered to medical and pharmacy interns. Such training could take the form of key messages and pretend clinical cases via a computer software. It could also be interesting to set up an operational team made of an infectious disease specialist and a pharmacist, which would be dedicated to pediatric wards. This team could analyze last resort antibiotic prescriptions upon initiation, and a systematic reevaluation could be performed at least once a week similarly to what is being implemented since 2006 for adults at the University Hospital of Nancy [1,2]. Findings from the present study were presented to the Neonatology Pole to set

up an action plan. The main problems will also be communicated to wards concerned to suggest rooms for improvement, mainly for treatment duration for pneumonia and urinary tract infections in general pediatric wards, and appendicitis and peritonitis in pediatric gastroenterological surgery.

CONCLUSION

Antibiotic misuse is a major public health challenge considering its economic and ecological implications. This type of study contributes to identifying problems and to suggesting interventions to promote the proper use of antibiotics.

Our study revealed a satisfactory rate of relevant antibiotic prescriptions in pediatric settings, but effort should be made to comply with recommended doses and treatment durations. Solutions have been suggested to the various wards concerned. A second evaluation could contribute to evaluating the impact of the present study following implementation of the suggested solutions.

Disclosure of interest

The authors declare no conflict of interest.

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J.W performed the study and wrote the article, S.M, C.S, and B.D supervised the study, A.C contributed to analyzing the files.

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Tableau I. Caractéristiques de la population et des dossiers

Table I. Characteristics of the population and records

	Medicine	Surgery	Total
Patients			
Number (% total)	90 (55%)	73 (45%)	163 (100%)
Sex ratio	1	1.9	1.3
Mean age (years)	4.7 ± 4.7	7.4 ± 4.7	5.9 ± 4.9
[min ; max]	[0.04 ; 17]	[0.03 ; 16]	[0.03 ; 17]
Median age (years)	3	7	5
Records			
Number of clinical cases	90	73	163
Prescription lines (total percentage)	207 (59%)	145 (41%)	352 (100%)

Tableau II. Motifs de non-pertinence (n = 48 cas cliniques)

Table II. Reasons for irrelevance (n=48 clinical cases)

	17
Antibiotics that should only be prescribed as alternatives	(35%)
Pneumonia	9 (19%)
Acute pyelonephritis	5 (10%)
Angiocholitis	1 (2%)
Acute otitis media	1 (2%)
Sinusitis	1 (2%)
	12
The chosen antibiotic was not recommended	(25%)
Mother-to-fetus infection	5 (10%)
Fever in patients with sickle cell disease	1 (2%)
Fracture with osteosynthesis	1 (2%)
Closed fracture with osteosynthesis	1 (2%)
Lyme neuroborreliosis	1 (2%)
Acute pyelonephritis	1 (2%)
Acute rheumatic fever	1 (2%)
Urine sterilization for JJ stent	1 (2%)
Useless antibiotic therapy	6 (13%)
Tonsillectomy	2 (4%)
Appendectomy after acute presentation	2 (4%)

Celioscopy + exeresis	1 (2%)
Isolated fever in a female patient with cardiac disease	1 (2%)
Monotherapy instead of a two-drug combination + antibiotics that should only be prescribed as alternatives*	6 (13%)
Acute pyelonephritis	6 (13%)
Two-drug combination instead of a three-drug combination	2 (4%)
Mother-to-fetus infection	2 (4%)
Monotherapy instead of a two-drug combination	2 (4%)
Mother-to-fetus infection	1 (2%)
Acute pyelonephritis	1 (2%)
Chosen antibiotic not recommended + no treatment adaptation to microbiological results	1 (2%)
Acute pyelonephritis	1 (2%)
Two-drug combination instead of monotherapy + no treatment adaptation to microbiological results	1 (2%)
Exacerbation of cystic fibrosis	1 (2%)
No treatment adaptation to microbiological results	1 (2%)
Pneumonia	1 (2%)
Total	48 (100%)

Tableau III. Causes de non-conformité de dose par service

Table III. Reasons for inadequate doses by ward

	Medicine	Surgery	Total
	n	n	n (%)
Overdosing	16	12	28 (17%)
Under-dosing	7	18	25 (15%)
Under-dosing followed by overdosing after modification	3	2	5 (3%)
Overdosing followed by under-dosing after modification	2	2	4 (2%)
No loading dose	1	0	1 (1%)
Overdosing without any loading dose	3	0	3 (2%)
Total of inadequate prescriptions	32	34	66 (40%)
Total of clinical cases	90	73	163 (100%)

Tableau IV. Principaux cas cliniques avec dose inadaptée

Table IV. Main clinical cases with inadequate doses

Clinical cases Type, n ¹ (%) ²	Prescriptio	Antibiotics	Prescribed
	n lines n ¹ (%) ²		dose/recommen ded dose in mg/kg (standard deviation in %) ³
Open fracture, 6/7 (86%)	9/11 (82%)	amoxicillin-clavulanic acid	67/50 (+35%)
Implant infection, 3/4 (75%)	9/21 (43%)	amoxicillin-clavulanic acid	130/90 (+44%)
		cefotaxime	80/50 (+60%)
		ceftriaxone	43/50 (-14%)
		clindamycin	33/40 (-18%)
		rifampicin	10/20 (-50%)
Dental avulsion, 6/14 (43%)	6/14 (43%)	amoxicillin	39.75/50 (-22%)
			62.5/50 (+25%)
Mother-to-fetus infection, 5/8 (63%)	9/26 (35%)	amoxicillin	167/100 (+67%)
		cefotaxime	231/200 (+16%)

Peritonitis 3/3 (100%)	3/8 (38%)	amoxicillin-clavulanic acid	117/150 (-22%)
Pertussis, 2/2 (100%)	2/2 (100%)	azithromycin	10.3/20 (-49%)

¹Number; ²Frequency; ³Prescribed dose compared with the recommended dose in the guidelines with, in between brackets, the calculated deviation between the prescribed and the recommended dose. A percentage preceded by the “-” sign indicates under-dosing while a percentage preceded by the “+” sign indicates overdosing.

Tableau V. Causes de non-conformité de durée de traitement par service

Table V. Reasons for inadequate treatment duration by ward

	Medicine	Surgery	Total
Adequate treatment duration	62 (69%)	55 (75%)	117 (72%)
Inadequate treatment duration	28 (31%)	18 (25%)	46 (28%)
Excessively short treatment duration	7 (8%)	4 (5%)	11 (7%)
Excessively long treatment duration	21 (23%)	14 (20%)	35 (21%)
<i>Total</i>	<i>90</i>	<i>73</i>	<i>163</i>