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Original article

A Comparative Analysis of Antibiotic and Antiviral Drug Use in Pediatrics and Obstetrics-Gynecology over 12 years (2000-2001, 2005-2006 and 2012-2013) using Defined Daily Doses and Days of Therapy

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Abstract

Background: There are limited data published about antibiotics and antiviral consumption in terms of Defined Daily Doses (DDD) and Days Of Therapy (DOT) in Pediatrics and Obstetrics-Gynecology. Objectives: To characterize and quantify antimicrobial drug use as DDD/1000 patient-days per molecule, DOT/1000 patient-days per molecule, and mean dose (mg/kg/day) per molecule over a twelve-year period and explore the changes over time in Pediatrics and Obstetrics-Gynecology. Methods: Retrospective, cross-sectional, descriptive study, in a mother-child University Hospital Center, with 400 pediatric beds and 100 obstetric-gynecology beds. All inpatient (in Pediatrics and Obstetrics-Gynecology) who received one of the 51 authorized antibiotics or one of the 9 authorized antivirals on the institution's local formulary in 2000-2001, 2005-2006 and 2012-2013 were included. Prescriptions from the emergency room and outpatient clinics were excluded. Data were extracted from the patients' computerized medication profiles. We calculated DDD/1000 patient-days per molecule, DOT/1000 patient-days per molecule overall and for each molecule. The mean dose in mg/kg/day was calculated for each molecule for the ranges: ≤ 1.5 kg; > 1.5-5 kg; > 5-15 kg; > 15-30 kg; and > 30 kg. Results: Over 12 years: there was a 1.67-fold increase for antibiotics and a 3.77-fold increase for antivirals in the overall number of DDD/1000 patient-days. There was a 1.73-fold increase for antibiotics and a 2.57-fold increase for antivirals in the overall number of DOT/1000 patient-days. It reveals increases in dosage regimens for amoxicillin-clavulanic acid, gentamicin, piperacillin, piperacillin-tazobactam, and ticarcillin-clavulanic acid. Nevertheless, azithromycin and erythromycin dosage regimens decrease. The antivirals data reveals no predictable tendencies. Conclusion: This retrospective, cross-sectional, descriptive study reported the use of anti-infectious drugs at a mother-child hospitalover a 12-year time period. Both the overall numbers of DDD/1000 patient-days and the DOT/1000 patient-days increased. It should be monitored on a continuous basis by antimicrobial stewardship program in healthcare settings.

Introduction

There are many anti-infective drugs on the market and a growing use contributes to a significant number of drug-related problems including side-effects, medication errors, drug-drug interactions. Moreover, inappropriate use of antibiotics and antivirals may lead to the emergence of bacterial and viral resistance [1,2].

Several strategies have been implemented to improve antibiotic prescribing practices, including practice audits, retrospective/prospective drug utilization reviews, decentralized presence of pharmacists at the bedside and antimicrobial stewardship programs [3-6]. Infectious Diseases Society of America gives several recommendations about the role of an antimicrobial stewardship program like conducting prospective audits of antimicrobial use, organizing Formulary restriction and preauthorization requirements for specific agents, encouraging the multidisciplinary development of evidence based guidelines. It also identifies pediatric populations as a priority area in terms of antimicrobial surveillance [7]. Davey et al. have published a Cochrane systematic review on interventions to improve antibiotic prescribing practices for hospitals inpatients [8]. Their review showed that there are numerous interventions that can reduce antimicrobial resistance or hospital-acquired infections or improve clinical outcomes. Monitoring antimicrobials use and consumption is an important part of the antimicrobial stewardship program role [7].

In order to monitor and benchmark antimicrobial drug use within the healthcare sector, the World Health Organization has recommended the use of defined daily doses (DDD) and days of therapy (DOT) per 1000 patient-days [9]. While the use of DDD is frequent in the adult population, the use of DOT/1000 patient-days is preferred in the pediatric population, given that there is not a single DDD per antibiotic applicable to children and because pediatric doses are usually adjusted according to weight. Other metrics as PDD and DU 75% or DU 90% have been studied in pedriatric population but are not considered in this study. Further studies are required to identify an optimal marker of drug use in pediatrics. For instance, Porta et al. have suggested a new algorithm to help evaluating and comparing the consumption of antibiotic in pediatric [10].

While some health agencies and hospitals have published quantitative profiles of their anti-infective use [12-29], few have reported on anti-infective use in the pediatric [23-29].

Methods

The objective of this retrospective, cross-sectional, descriptive study was to characterize antibiotic and antiviral drug use as DDD/1000 patient-days per molecule, the number of DOT/1000 patient-days per molecule, and the mean dose (mg/kg/day) per molecule over a twelve-year period.

The study was conducted at a 500-bed mother-child University Hospital Center (12 pediatric infectious disease beds, 62 pediatric NICU beds, 24 pediatric PICU beds, 42 pediatric hematology-oncology beds, 38 pediatric surgery beds, 222 pediatric beds, and 100 obstetrics-gynecology beds). The obstetrics-gynecology department is essentially occupied with women pre and post-partum.

The inclusion criteria are based on all inpatient prescriptions for one of the 51 authorized antibiotics and one of the nine authorized antivirals on the institution's local formulary: American Hospital Formulary Service class 8 :12.02 – aminoglycosides 8 :12.06 – cephalosporins , 8 :12.07 – miscellaneous β-lactams 8 :12.08 – chloramphenicol, 8 :12.12 – macrolides, 8 :12.16 – penicillins, 8 :12.18 – quinolones, 8 :12.24 tetracyclines, 8 :12.28 antibacterials, miscellaneous, 8 :16 – antituberculosis agents, class 8 :18.28 – Neuraminidase Inhibitors, 8 :18.32 – Nucleosides and Nucleotides, 8 :18.92 – Antivirals, Miscellaneous. Table I details drugs of each class.

Given that the cohort of children infected by HIV is specifically followed as outpatients, antiretroviral drugs were excluded for this study, as well as prescriptions from the emergency room and outpatient clinics were also excluded. Three fiscal years that ran from April 1st to March 31st of the following year were evaluated: 2000-2001, 2005-2006 and 2012-2013.

The data were extracted by members of the research team (AS, JG, DL) from the patients' computerized medication profiles (GesphaRx®, CGSI TI, Quebec, Canada) linked to patient admission, discharge and transfer data. The data were analyzed by members of the research team (CC, JG, DL, HR, JFB, PO). Data extraction was conducted using SQL (Structured Query Language) queries of raw data tables. The extracted data was copied to an Excel file in order to calculate DDD, DOT and mean dose in mg/kg/day. The mg/kg/day doses were arbitrarily broken down in weight ranges: ≤ 1.5 kg; > 1.5-5 kg; > 5-15 kg; > 15-30 kg; and > 30 kg. Data extraction was repeated for 7/51 (14%) of the antibiotics and for 2/9 (22%) of the antivirals by a second research assistant to confirm the reproducibility and quality of the data extraction.

Ethics approval was requested and granted for our study.

With respect to the main objective, the extracted data were coupled with patient admission, discharge and transfer data based on fiscal year in order to calculate the DDD and DOT per 1000 patient-days [11]. These parameters were calculated for each antibiotic, each antibiotic class, and overall, and for each antiviral and overall. The DDD used were extracted from World Health Organisation

We calculated the DDD/1000 patient-days ratios between the 2012-2013 and 2000-2001 fiscal years. No comparisons were done with 2005-2006 data, but data were reported to allow some trending. Ratios greater than 1.2 fold were identified as an increase and ratios smaller than 0.8 fold were identified as a decrease in antibiotic use. These values were arbitrarily identified to target the most important changes in practice. No statistical analysis was performed for comparisons of ratios between years considering these ratios represent absolute values (e.g. total applicable DDD or DOT divided by applicable patient-days).

Results

Table I shows the antibiotic and antiviral drugs use for 2000-2001, 2005-2006 and 2012-2013. Regarding the antibiotics DDD, there was a 1.67-fold increase in the overall number of DDD/1000 patient-days, from 320 in 2000-2001 to 535 in 2012-2013.

Regarding the antivirals DDD, there was a 3.77-fold increase in the overall number of DDD/1000 patient-days, from 7.6 in 2000-2001 to 28.8 in 2012-2013.

Six antibiotics and no antiviral drug showed a decrease in their DDD/1000 patient-days from 2000-2001 to 2012-2013, whereas 24 antibiotics and three antiviral drugs showed an increase in their DDD/1000 patient-days from 2000-2001 to 2012-2013 (Table I). Ten antibiotics and two antivirals showed a non-significant variation in DDD/1000 patient-days. The ratio could not be calculated for 10 antibiotics and five antivirals because they were not used in both time periods.

Regarding the antibiotics DOT, there was a 1.73-fold increase in the total number of DOT/1000 patient-days, from 434 in 2000-2001 to 751 in 2012-2013. Five antibiotics showed a decrease in their DOT/1000 patient-days from 2000-2001 to 2012-2013, while 26 antibiotics showed an increase in their DOT/1000 patient-days from 2000-2001 to 2012-2013 (Table I). Regarding the antiviral drugs DOT, there was a 2.57-fold increase in the total number of DOT/1000 patient-days, from 21.5 in 2000-2001 to 55.4 in 2012-2013.

Figure 1 and Figure 2 presents the DDD/1000 patient-days and the DOT/1000 patient-days for the antibiotic classes and antivirals used for the 2000-2001 and the 2012-2013 fiscal years.

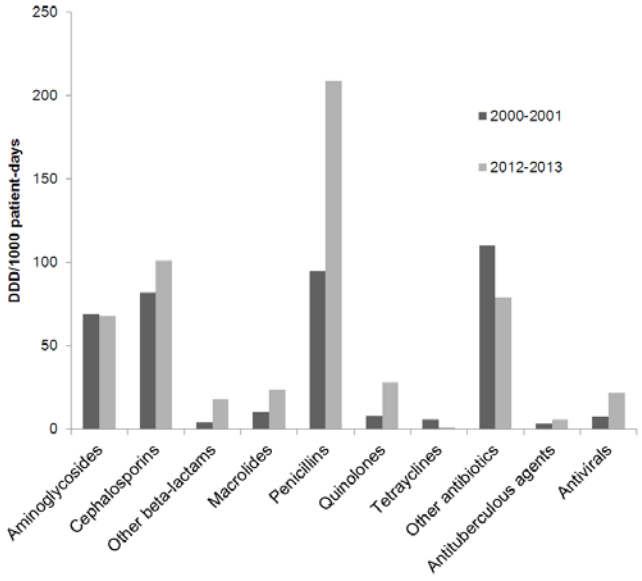

Fig 1. Relative share of the antibiotic classes and antivirals for the 2000-2001 and 2012-2013 fiscal years in defined daily doses per 1000 patient-days

Legend: DDD : Defined daily dose

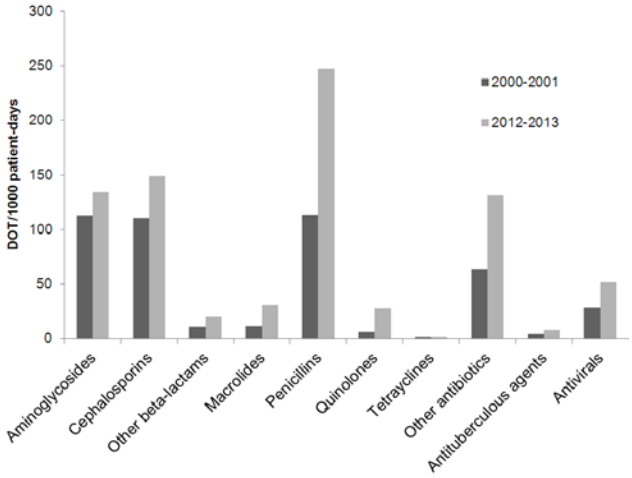

Fig 2. Relative share of the antibiotic classes and antivirals for the 2000-2001 and 2012-2013 fiscal years in days of therapy per 1000 patient-days

Legend: DOT : days of therapy

Table I Defined daily doses per 1000 patient-days and days of therapy per 1000 patient-days profile

Drugs	2000-2001		2005-2006		2012-2013		Ratios	
	DDD*	DOT†	DDD*	DOT†	DDD*	DOT†	DDD* 2012-2013 / DDD* 2000-2001	DOT† 2012-2013 / DOT† 2000-2001
Antibiotics								
Amikacin	1	1	1	2	1	1	1	1
Amoxicillin	9	11	23	26	38	41	4.22	3.72
Amoxicillin-Clavulanic Acid	4	4	11	11	16	14	4	3.5
Ampicillin	40	43	51	71	92	93	2.3	2.16
Azithromycin	1	0.5	4	3	11	10	11	22
Aztreonam	0.1	0.1	1	0.4	0.3	0.1	3	1
Chloramphenicol	0.01	0.03	NA	NA	NA	NA	NA	NA
Cefaclor	0.1	0.1	0.01	0.03	0.1	0.03	1	0.3
Cefadroxil	NA	NA	0.02	0.02	0.02	0.03	NA	NA
Cefazolin	22	32	28	42	31	46	1.41	1.44
Cefixime	0.1	0.2	1	1	2	3	20	15
Cefotaxime	7	12	10	17	31	46	4.43	3.83
Cefoxitin	3	8	2	5	3	7	1	0.88
Cefprozil	2	6	2	5	1	2	0.5	0.33
Ceftazidime	17	14	13	14	19	20	1.12	1.43
Ceftriaxone	8	11	10	16	6	12	0.78	1.09
Cefuroxime	20	31	9	13	1	1	0.05	0.03
Cephalexin	3	4	5	8	7	12	2.33	3
Ciprofloxacin	8	6	14	12	22	21	2.75	3.5
Clarithromycin	7	8	13	14	8	11	1.14	1.38
Clindamycin	22	29	4	6	22	30	1	1.03
Cloxacillin	20	11	25	19	25	18	1.25	1.64
Colisthimethate	1	2	1	1	4	5	4	2.5

Drugs	2000-2001		2005-2006		2012-2013		Ratios	
	DDD*	DOT†	DDD*	DOT†	DDD*	DOT†	DDD* 2012-2013 / DDD* 2000-2001	DOT† 2012-2013 / DOT† 2000-2001
Dapsone	0.05	0.1	0.2	0.3	0.01	0.02	0.2	0.2
Doxycyline	6	2	2	3	1	2	0.17	1
Erythromycin	2	3	5	10	5	10	2.5	3.33
Ethambutol	0.1	0.2	0.1	0.3	1	2	10	10
Gatifloxacin	NA	NA	0.04	0.04	NA	NA	NA	NA
Gentamicin	27	60	30	85	29	80	1.1	1.33
Imipenem	0.01	0.03	1	1	1	1	100	33.33
Isoniazide	1	1	1	1	3	2	3	2
Levofloxacin	0.2	0.3	0.5	0.5	6	7	30	23.33
Linezolid	NA	NA	0.1	0.05	1	2	NA	NA
Meropenem	4	3	13	13	17	19	4.25	6.33
Metronidazole	6	12	13	22	14	26	2.33	2.17
Nitrofurantoin	1	1	2	3	1	2	1	2
Paromomycin	NA	NA	NA	NA	NA	NA	NA	NA
Pentamidine	4	4	2	2	4	5	1	1.25
Piperacillin	10	21	4	12	1	2	0.1	0.01
Piperacillin-Tazobactam	9	17	10	20	25	54	2.78	3.18
Pyrazinamide	0.2	1	0.1	0.2	0.4	1	2	1
Quinupristine/dalfopristine	NA	NA	0.5	1	NA	NA	NA	NA
Rifabutin	0.1	0.04	NA	NA	NA	NA	NA	NA
Rifampicin	2	2	2	4	2	3	1	1.5
Streptomycin	0.04	0.2	0.1	0.2	NA	NA	NA	NA
Sulfadiazine	NA	NA	NA	NA	NA	NA	NA	NA
Sulfasalazine	0.2	0.4	0.3	0.4	0.4	0.3	2	0.75
Ticarcillin-Clavulanic Acid	3	6	29	53	12	25	4	4.17

Drugs	2000-2001		2005-2006		2012-2013		Ratios	
	DDD*	DOT†	DDD*	DOT†	DDD*	DOT†	DDD* 2012-2013 / DDD* 2000-2001	DOT† 2012-2013 / DOT† 2000-2001
Tobramycin	41	51	68	76	38	53	0.93	1.04
Trimethoprim	NA	NA	0.2	1	0.004	0.03	NA	NA
Vancomycin	8	15	25	47	33	61	4.13	4.07
Antivirals								
Acyclovir IV	3.7	16	4.4	21.3	3	22	0.81	1.38
Acyclovir PO	0.1	0.5	0.1	0.8	0.5	5	5	10
Cidofovir	NA	NA	1	0.2	7	1	NA	NA
Famciclovir	1.4	1	4	3.9	13	15	9.28	15
Foscarnet	NA	NA	1.4	3.0	0.3	1	NA	NA
Ganciclovir	2.3	4	1.7	4	2	5	0.87	1.25
Oseltamivir	NA	NA	0.1	0.1	1	2	NA	NA
Ribavirin	0.03	0.04	1.2	3.7	0.1	0.4	3.33	10
Valacyclovir	NA	NA	0.1	0.4	1	3	NA	NA
Valgancyclovir	NA	NA	0.2	0.3	0.4	1	NA	NA

DDD per 1000 patient-days; †DOT per 1000 patient-days

Legend: DDD : defined daily dose; DOT : days of therapy; NA : Not Applicable (no antibiotic use in this period)

Table II presents the mean dose in mg/kg/day per antibiotic or antiviral for the 2000-2001 and 2012-2013 fiscal years for five weight ranges (≤ 1.5 kg; > 1.5-5 kg; > 5-15 kg; > 15-30 kg; and > 30 kg). For antibiotics, a comparison of these data reveals the following increases in dosage regimens for the majority of weight ranges for amoxicillin-clavulanic acid, gentamicin, piperacillin, and ticarcillin-clavulanic acid. Nevertheless, two decreases are seen in dosage regimens for the majority of weight range for azithromycin and erythromycin. The comparison of the antivirals data reveals no predictable tendencies and variations may only be related to case mix.

Discussion

This descriptive study showed an increase in antibiotic and antiviral drugs in a Canadian mother-child university hospital center over a twelve-year period. While the ratios describe the amount of antibiotics and antivirals used and the current trends within a hospital, they cannot be used alone to assess the nature and the relevance of drug use.

The increase of use observed in our study may be related to numerous factors: a possible increase in the complexity of patients (e.g. more hematology-oncology patients, patients receiving immunosuppressive and/or immunomodulation for chronic diseases and bone marrow transplants with use of vancomycin, meropenem and piperacillin/tazobactam and antivirals), protocol and guidelines changes (e.g. use of ticarcilline/clavulanic acid for febrile neutropenia in early 2000; emphasis on ampicillin for community acquired pneumonia in 2007; zoster prophylaxis in 2007 and afterwards all of our hematopoietic stem cell transplanted who had a history of varicella received a prophylactic treatment with famciclovir), changes in recommended dose regimens and the availability of new products (e.g. oseltamivir is specifically used for the treatment and the prophylaxis of influenza A virus and is available since 2008; the 2010 pandemic flu participated largely of the increase consumption of this product, despite the absence of strong data of efficacy and safety in children and toddlers). The increase of penicillin consumption can be mainly explained notably by a higher use of this therapeutic class for community-acquired pneumonia following repeated intervention.

There are few studies in the pediatric literature that allow a comparison to our local data [23-29]. Zhang et al. noted an overall decrease in the use of 56 antibiotics in five Chinese pediatric hospitals from 2002 to 2006 with the DDD/1000 patient-days going from 682 in 2002 to 584 in 2003 and 658 in 2004 to 656 in 2005 and 499 in 2006, respectively [23]. In similar time periods, these values were higher than those in our study and their observed decrease was related to education and guidelines about antibiotic use. In a study conducted by Porta et al. for the Pediatrics and Neonatology units of four European hospitals (two in the UK, one in Italy and one in Greece) from February to May 2009, that focused on 47 antibiotics, the authors noted a lower DDD/1000 patient-days ratio than in our study, i.e., 230 (UK1), 159 (UK2), 252 (Italy) and 158 (Greece)[10]. These lower values data compared to our hospital are not surprising given the absence of oncology and solid organ transplantation patients in these studies.

Wang et al. reported an increase in antibiotic use in a pediatric hospital in China from 2000 to 2004 [27]. Total antibiotic use went from 378 DDD/1000 patient-days in 2000 to 420 DDD/1000 patient-days in 2004, a 1.11-fold increase.

In a study conducted in a 120-bed facility in USA, Levy and al. have calculated annually DOT/1000 patient-days for 48 antimicrobials between February 2007 and December 2010. The trends of antimicrobials use are relatively similar to ours. Indeed, the authors noticed a significant increase in the use of vancomycin and broad spectrum agents as beta lactam/beta lactamase inhibitors combinations and third- or fourth-generation cephalosporins and a decrease for gentamicine and rifampicine which is coherent with our data. The rates of use of metronidazole remained stable whereas they decrease in the Levy study. Finally Levy and al. observed a decrease for ampicillin rates while in our study they increase all over the time [28]. These results reveal that it can be difficult to compare antibiotic use in DDD/1000 patient-days and DOT/1000 patient-days among institutions, especially when these data do not take into account the types of patients treated, the profile of the antibiotics available in each country, treatment guidelines in effect, and the prevalence of various infection types and antibiotic resistance. However, data on antibiotic use can be very useful when monitoring use within an institution over time. In a recent study, Gerber and al. assessed a substantial variability among children hospitals in the United States treating -four selected diagnoses (pneumonia, cystic fibrosis, appendectomy, skin and soft tissue infections).They examined, for each diagnosis, the proportion of patients treated by Infectious Diseases Society of America and the Pediatric Infectious Diseases Society guideline-recommended therapies [29].

Table II Profile of the mean dose in mg/kg/day per molecule for the 2000-2001 and 2010-2011 fiscal years for five weight ranges

	Mean dose in mg/kg/day, for each range of weight									
Drugs	**≤ 1.5kg**		>1.5-5 kg		>5-15 kg		>15-30 kg		> 30 kg	
	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013
Antibiotics										
Amikacin	NA	NA	NA	NA	19	NA	27	31	25	30
Amoxicillin	21	23	32	38	50	75	47	68	32	33
Amoxicillin-Clavulanic Acid	NA	NA	54	58	46	76	41	70	27	41
Ampicillin	110	113	123	150	158	190	132	180	93	135
Azithromycin	NA	NA	NA	16	7	9	12	9	11	9
Cefazolin	48	65	94	96	87	93	86	95	60	70
Cefixime	NA	NA	8	8	8	9	9	9	7	7
Cefotaxime	108	139	186	202	183	195	183	197	126	150
Cefoxitin	NA	NA	66	76	65	70	75	81	64	86
Cefprozil	NA	NA	28	28	29	28	28	29	19	20
Ceftazidime	NA	127	167	129	151	155	169	145	144	137
Ceftriaxone	NA	50	79	68	82	64	80	65	47	38
Cefuroxime	94	NA	138	101	142	147	138	147	95	150
Cephalexin	NA	NA	50	65	56	72	64	49	50	43
Ciprofloxacin	NA	NA	30	27	27	26	28	26	22	18
Clarithromycin	NA	NA	15	18	15	15	15	15	15	15
Clindamycin	13	NA	32	25	35	35	33	35	33	34
Cloxacillin	NA	101	159	144	170	192	160	182	106	152
Erythromycin	NA	NA	21	NA	17	33	35	17	44	15
Gentamicin	3	4	4	5	5	7	5	7	4	5
Isoniazide	NA	NA	10	NA	13	14	10	14	6	9
Levofloxacin	NA	NA	NA	NA	NA	19	NA	14	8	12
Linezolid	NA	NA	NA	NA	NA	29	NA	35	NA	25

Mean dose in mg/kg/day, for each range of weight										
Drugs	**≤ 1.5kg**		>1.5-5 kg		>5-15 kg		>15-30 kg		> 30 kg	
	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013	2000-2001	2012-2013
Meropenem	NA	90	70	89	61	85	69	87	65	80
Metronidazole	10	6	19	16	24	29	29	28	26	27
Piperacillin	NA	222	219	243	256	280	268	332	247	326
Piperacillin-Tazobactam	221	NA	226	210	274	241	275	316	233	315
Pyrazinamide	NA	NA	30	NA	31	33	26	32	33	22
Rifampicine	18	19	11	14	21	18	18	14	11	9
Ticarcillin-Clavulanic Acid	NA	NA	271	260	231	290	237	294	230	264
Tobramycin	NA	4	8	5	7	7	8	7	6	6
Vancomycin	24	33	39	36	46	54	46	51	32	39
Antivirals										
Acyclovir IV	NA	40	47	58	39	36	39	25	27.0	19
Acyclovir PO	NA	NA	35	53	75	60	52	61	33	18
Cidofovir	NA	NA	NA	NA	NA	5	NA	3	NA	3
Famciclovir	NA	NA	NA	NA	NA	20	19	22	20	17
Foscarnet	NA	NA	NA	NA	NA	163	NA	NA	NA	160
Ganciclovir	NA	NA	10	12	10	12	9	9	7.2	8
Oseltamivir	NA	NA	NA	7	NA	5	NA	4	NA	2
Ribavirin	NA	NA	NA	NA	NA	156	NA	NA	15	39
Valacyclovir	NA	NA	NA	NA	NA	15	NA	142	NA	30
Valgancyclovir	NA	NA	NA	31	NA	23	NA	20	NA	19

Legend: NA : Not Applicable

In our literature search, we did not identify reports of the global use of antiviral drug per hospital using DDD /1000 patient-days and DOT/1000 patient-days. The European Centre for Disease Prevention and Control (ECDC) is using ratios of DDD and DOT per 1000 inhabitant-days (e.g. population-based ratio rather than hospital based-ratio) to describe antiviral consumption among European adult population [30]. Calculated ratios are much lower, as their basis is the whole population.

The literature recognizes the limitations of using DDD/1000 patient-days in pediatrics [1]. In fact, the defined daily dose does not take into account the range of doses per patient weight. Using DOT/1000 patient-days appears to be more appropriate. Fortin et al. have conducted a systematic review of available measures of antimicrobial use applicable to paediatrics [31]. They concluded that the measure of antimicrobial use that best predicts antimicrobial resistance prevalence and rates, for surveillance purposes, has still not been identified; additional evidence on this topic is a necessity. In our case, a provincial directives mandate the reporting of both DDD and DOT. While we recognize the necessity to use and monitor DOT in pediatrics, we do believe it is appropriate to report both as raw data for further exploration and comparisons in the literature with other centers.

With respect to the data in mg/kg per weight range, it is possible to identify changes in practice that are specific for a given weight group for a particular antibiotic or antiviral. The emergence of resistance to pneumococci was associated to prescriptions of higher doses of amoxicillin and amoxillin/clavulanic acid for otitis media especially in the range > 5-15 kg and > 15-30 kg. A higher dose of cefazolin for osteomyelitis and a higher starting dose of gentamycin and vancomycin in neonatology could also be explain the increase of doses per mg/kg/day for these antibiotics.

In Quebec, there is a close monitoring of antibiotic and antiviral use particularly with decentralized pharmacist presence in programs of care. A 2011 governmental directive has forced the implementation of antimicrobial stewardship program throughout the province to improve anti infectious drugs use and to generate standardized data to monitor drug use and requires period collection and analysis of DDD and DOT/1000 patient-days is in place. The 12 years-period is a sufficient time period to allow the identification of emerging prescribing changes; however, further studies are required to evaluate the impact of new protocols and the impact of biological markers (e.g. procalcitonin, viral load).

The antimicrobial stewardship program in our hospital is co-chaired by an infectious disease pediatrician and a clinical pharmacist working within the infectious diseases unit. It includes a pediatrician from the department of microbiology and three pharmacists from obstetrics-gynecolgy, neonatology and intensive care units patients care units. The antimicrobial stewardship program seems to have an influence on antibiotics and antivirals prescribing practices through the diffusion of guidelines (e.g. guidelines with restricted indications and prescribers for some antivirals, pre-printed orders) produced by the program but we need more data to evaluate the impact of the use of DDD and DOT as an effective mean to optimize drug use. It appears that such statistics can help to identify practice change but consumption data are probably sufficient enough to point out these new trends and suggest corrective relevant measures. A multicentric study conducted by Hersh and al. over almost 9 years from January 2004 to October 2012 in USA showed that antimicrobial stewardship programs have a statistically significant impact in reducing antibiotic use in freestanding children's hospitals in particular for antibiotics which are routinely monitored. Antibiotic use was evaluated with DOT/1000 patient-days [32]

This study has limitations. The extracted data came from a historic database for inpatients. A combined analysis of inpatient and outpatient data can be more relevant especially when we consider some indications (e.g. urinary tract infections, bone infections), especially if resistance patterns are taken into account. However, this approach would rely on a different denominator. Besides, combining data from paediatric and obstetric/gynecology populations is not optimal even though this follows a requirement from the regulatory authority as a stand alone facility. Analysis per clientele (e.g. pediatrics, ob-gyn, etc.) would better profile the current use. Also, DOT should be preferred in pediatrics; we did keep both DDD and DOT as they are also included in the reporting framework required by the regulatory authority. In terms of dose calculations in mg/kg/day, each patient's weight varied over time. For our ratios, the maximum weight per admission was used to calculate an average mg/kg/day dose per patient. This measure may have underestimated the mg/kg/day value in the case of very lengthy hospitalizations. The indications for use were not captured in the dataset available which does influence prescribed doses. No statistical analysis have been tested to prove significance, it was an arbitrary decision. Finally, no analyses of use by patient type were conducted. We also did not take account of the hospital changes and the impact of the antimicrobial stewardship program over these 12 years to explain the antibiotic consumption evolution. As there is very limited inpatient Canadian data about the use of antibiotics and antivirals in children, we believe such profile constitutes a good basis for further benchmarking in the country.

Conclusion

This retrospective, cross-sectional, descriptive study reported the use of antibiotic and antiviral drugs at a mother-child UHC over a 12-year time period. Both the overall numbers of DDD/1000 patient-days and the DOT/1000 patient-days increased over time. Antibiotic and antiviral consumption should be monitored on a continuous basis by antimicrobial stewardship program in healthcare settings. DDD and DOT ratios can be used. Such monitoring may contribute to support antimicrobial stewardship programs and initiatives.

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