Antimicrobial consumption in a tertiary children's hospital in Finland (2003–2013)

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ABSTRACT

Background Numbers of resistant pathogens are constantly increasing, and prudent use of antimicrobials is of paramount importance. In order to see whether any changes in the use of antimicrobials in recent years have occurred, we decided to monitor the consumption of these drugs at a single tertiary paediatric hospital.

Materials and methods This single-centre retrospective study investigated the consumption of antimicrobials in defined daily doses (DDDs according to the Anatomical Therapeutical Chemical /DDD index) in a 130-bed paediatric tertiary hospital. The data on the consumption of antimicrobials were collected from years 2003–2013 by using electronic surveillance records provided by the local pharmacy. The consumption was related to days of hospital care.

Results During 2003–2013, the use of penicillins, cephalosporins and carbapenems increased by 28%, 46% and 110%, respectively. The consumption of both aminoglycosides and vancomycin decreased by 61% and 41%, respectively. Amphotericin B use clearly decreased by 39% while the use of novel azoles and echinocandins increased.

Conclusions Increased use of carbapenems was the most significant finding of our study. The year-to-year consumption of antibacterials was in general relatively stable and new antibacterials were taken into use conservatively. In contrast to antibacterials, novel antifungals were rapidly adopted into use despite scarce evidence on their safety in children.

INTRODUCTION

Investigating and monitoring the consumption of antimicrobials in hospitals is necessary in order to encourage prudent use of these drugs. The use of broad spectrum antibacterials is a potential problem. It causes selection pressure and may lead to increasing numbers of resistant pathogens. In addition, such use of antibacterials most probably also causes difficult secondary infections.[1 2] Similarly, local knowledge on the use of antimicrobials is crucial and allows us to implement necessary measures to support appropriate use of antimicrobials.

When investigating the consumption of antimicrobials, defined daily doses (DDDs) can be used. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[3 4] Numerous studies have investigated the consumption of antimicrobials in hospitalised adult patients by using DDDs,[5–8] but such studies in paediatric patients are in large scale missing.

There are obvious obstacles when using DDDs in children. The most important being that the paediatric population is a very heterogeneous group with great variation in weight and age. Thus, comparing neonatal use with that of the adolescents is very challenging. The DDDs may, however, be used to describe paediatric consumption of individual antimicrobials over a certain period of time in a setting where no major changes in the hospital clientele took place.

We have studied the consumption of these drugs in the Children's Hospital, University of Helsinki, by using DDDs as parameters of antibiotic use. The overall age bands of our patients have stayed the same during the study period 2003–2013. The main purpose of this study was to explore whether any major changes in the use of antimicrobials during the recent years (2003–2013) could be found in a large tertiary paediatric hospital like ours. Since annual numbers of treated patients and corresponding days of hospital care vary, we related the consumption of antimicrobials (in DDDs) to the annual hospital days.

METHODS

Children's Hospital, University of Helsinki, is a tertiary hospital in Finland. It has active units of general paediatrics, paediatric surgery, oncology, transplantation and paediatric and neonatal intensive care units. The hospital has approximately 130 beds. Average annual number of patient days is approximately 30 000 days.

Our retrospective study investigated the consumption of antimicrobials in DDDs, according to the Anatomical Therapeutical Chemical (ATC)/DDD index defined by WHO.[9]

The antimicrobials included to this study were the following (according to ATC/DDD index defined by WHO 2010):

J anti-infectives for systemic use:

J01 antibacterials: J01A tetracyclines, J01B amphenicols, J01C beta-lactam antibacterials, penicillins, J01D other beta-lactam antibacterials, J01E sulfonamides and trimethoprim, J01F macrolides, lincosamides and streptogramins, J01G aminoglycoside antibacterials, J01M quinolone antibacterials, J01R combinations of antibacterials, J01X other antibacterials.

J02 antifungals: J02AA antibiotics, J02AC triazoles, J02AX other systemic antifungals.

J05 antivirals: J05AB nucleosides and nucleotides excluding reverse transcriptase inhibitors, J05AD phosphonic acid derivatives, J05AE protease inhibitors, J05AF nucleoside and nucleotide reverse transcriptase inhibitors, J05AG non-nucleoside reverse transcriptase inhibitors, J05AH neuraminidase inhibitors, J05AR antivirals for treatment of HIV infections.

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The data on the consumption of antimicrobials were collected from years 2003–2013 from electronic surveillance records provided by Helsinki University Central Hospital (HUCH) pharmacy. Analysis was quantitative. The data regarding the days of hospital care were collected from HUCH electronic records. During 2003–2013, the days of hospital care (HD) varied annually between 30 226 and 39 930.

Electronic surveillance records did not allow us to differentiate enteral and parenteral use from antimicrobials that are available in both parenteral and enteral formulations. We, therefore, included enteral consumption to our study from drugs that have got both enteral and parenteral formulations, such as sulfa trimethoprim, penicillins such as cloxacillin, fluoroquinolones, metronidazole, azoles and antivirals. Drugs with same ATC code, such as amphotericin deoxycholate and liposomal amphotericin, could not be separated, and the total DDD describes them both.

The change (in per cent) in the consumption of antibacterials was calculated by using linear function over the consumption of antimicrobials from 2003 to 2013. This approach was in use when the drug had been used throughout the whole surveillance period, 2003–2013. If the consumption of a drug started later than 2003, the change in percentage was calculated by the year the drug use was initiated, for example, the use of micafungin was initiated at 2010.

Electronic surveillance records did not allow the use of the individual ages of the children treated during the study period. Similarly, data on individual weights were not available. Hence, our study did not investigate the use of antimicrobials in children by using age-specific bands.

RESULTS

All antimicrobials

The overall consumption of systemic antimicrobials (according to ATC classes and in DDDs) during the study period 2003–2013 was relatively stable (18 843–23 057 DDD) (figure 1). The days of hospital care (HD) varied annually between 30 226 and 39 930. The mean annual use of the antimicrobials was 20 800 DDD, and the mean consumption per hospital days was 0.55 DDD/HD.

When the consumption of antimicrobials was calculated per patient-days, the most frequently used pharmaceuticals were antibacterials (mean annual use 15 100 DDD and 0.40 DDD/HD) covering approximately 72% of all use. The second most commonly used group of drugs were antifungals, 18% of all use (3700 DDD and 0.10 DDD/HD). Antivirals represented 10% (1900 DDD and 0.05 DDD/HD) of all antimicrobial consumption.

Overall consumption of systemic antimicrobials in DDDs according to ATC classes divided by the days of hospital care (HD)/year in the Children's Hospital during 2003–2013 is shown in figure 1.

Antibacterials

In 2003–2013, the most frequently used group of antibacterials were beta-lactams other than penicillins (J01D), including cephalosporins and carbapenems (annual consumption between 0.20 and 0.22 DDD/HD) (figure 2). The second most commonly used group of antibacterials were penicillins J01C (annual consumption between 0070 and 0105 DDD/HD).

Overall, when the early use (2003–2006) of penicillins, cephalosporins and carbapenems was compared with later use (2006–2013), a clear increase of 28%, 46% and 110% was recorded. On the opposite, the use of aminoglycosides and vancomycin has decreased during the same time periods by 61% and 41%, (figures 2–4), respectively.

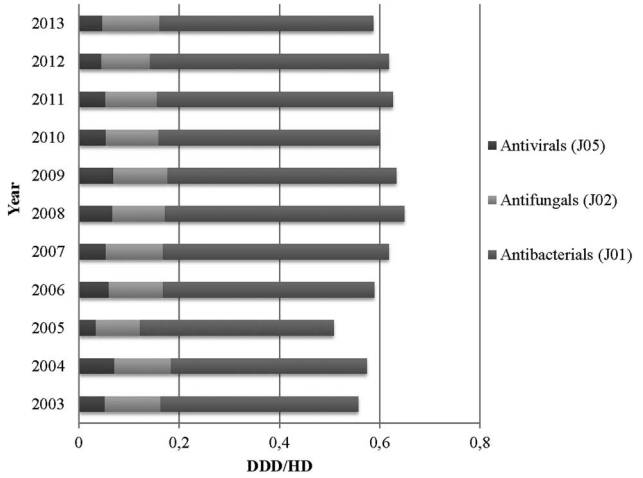

Figure 1 Overall consumption of antimicrobials in the Children's Hospital during 2003–2013 according to Anatomical Therapeutical Chemical classification and in defined daily doses (DDDs) divided by the annual days of hospital care (HD).

When special emphasis on drugs used against *Pseudomonas* infections was paid, the consumption of the antibacterials, such as carbapenems, piperacillin-tazobactam (PIP-TAZ) and ceftazidime, increased constantly during 2003–2013 by 110%, 500% and 47%, respectively (figure 4). During the study period, the total number of invasive *pseudomonas* infections did, however, not increase. We were also unable to see any major differences in the drug resistance pattern of the isolates.

Beta-lactam antibacterials (penicillins, cephalosporins and carbapenems)

The use of different beta-lactams is shown in figure 2. Cefuroxime was the single most frequently used antibacterial

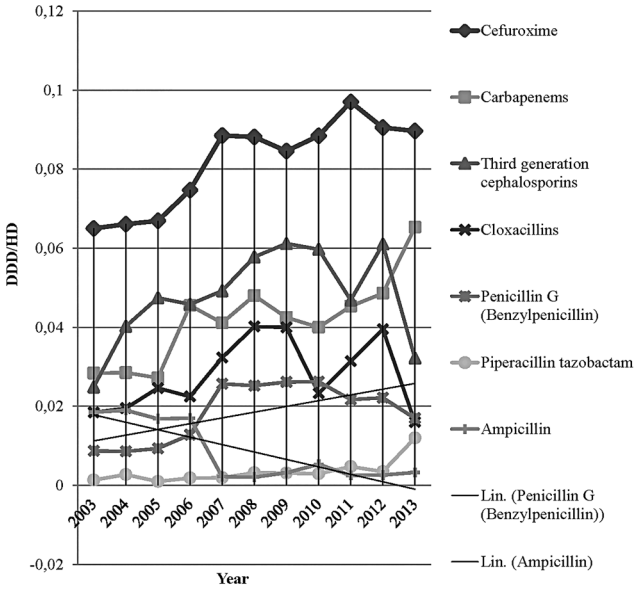

Figure 2 The use of beta-lactam antibacterials in the Children's Hospital during 2003–2013 according to Anatomical Therapeutical Chemical classification, penicillins (J01C), cephalosporins (J01DC, J01DD) and carbapenems (J01DH) in defined daily doses (DDDs) divided by the days of hospital care (HD)/year.

agent and its use grew steadily during 2003–2013. A clear change in consumption of ampicillin was seen at 2006–2007 compared with previous years. At the same time, the use of penicillin G was increased. Overall, during 2003–2013 the use of ampicillin decreased by 94% and the use of penicillin G increased by 100%. This shift from ampicillin to penicillin G took place due to changes in therapy recommendations given at 2006.

Non-beta-lactam antibacterials

Overall, the use of non–beta-lactams did not change significantly during 2003–2013 (figure 3). The consumption of both aminoglycosides and vancomycin decreased by 61% and 41%, respectively, whereas the use of fluoroquinolones remained mainly the same. Linezolid, a relatively novel antibacterial, was increasingly used over study period.

Anti-*pseudomonas* antibacterials

In general, *pseudomonas* species have been rare causes of invasive infections at our hospital. Nevertheless, the use of anti-*pseudomonas* drugs has grown. During 2003–2013, the use of aminoglycosides has decreased by 61%, whereas the use of PIP-TAZ, ceftazidime and carbapenems increased by 500%, 47% and 110% (figure 4), respectively.

The resistance of *Pseudomonas aeruginosa* towards different antibacterials has somewhat increased over time. The antibiotic sensitivity of 435 *P. aeruginosa* strains isolated from the blood or superficial samples taken during 2003–2013 were analysed (data not shown). Some year-to-year variation in resistance was seen. Overall, the resistance towards different antibacterials seemed to increase. For example, resistance towards PIP-TAZ reached its peak in 2011 when almost 40% of the isolates were resistant to the drug. Resistance towards meropenem and ciprofloxacin has likewise grown rapidly; in the year 2012, approximately 50% of the isolates were resistant to these drugs.

Antifungals

The overall consumption of all antifungals was somewhat decreased during the study period. During 2003–2013, the use of amphotericin and fluconazole decreased by 39% and 23% (figure 5). On the contrary, during 2003–2013 the use of voriconazole, posaconazole, caspofungin and micafungin increased by 34%, 295%, 134% and 67% (from the year 2010 to 2013), respectively.

Antivirals

The consumption of frequently used antivirals, such as valganciclovir, aciclovir and valaciclovir, increased by 29%, 28% and 153%, whereas the use of ganciclovir decreased by 68% during 2003–2013 (figure 6).

DISCUSSION

Summary of key findings

Measuring the consumption of antimicrobials is recommended by the WHO.[10] Monitoring of antibiotic use is also a prerequisite of local control of these pharmaceuticals. According to Cochrane review, interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcome.[11]

Consumption of antibacterials in Finnish hospitals in adults and children has been relatively moderate compared with other European countries.[12] The most often used group of antibacterials are beta-lactams. This use is rationale since they are well tolerated and efficient against several pathogens causing community-acquired paediatric infections such as pneumococci, meningococci and streptococci. In a recent study of 21 European paediatric hospitals, the most commonly used antimicrobials were ceftriaxone, ampicillin, cefuroxime and oral amoxicillin.[13] The profile of antibiotic use in our hospital was very similar: beta-lactams were the most often used antibacterials.

During 2003–2013, there was a clear rise in the consumption of penicillins. During 2003–2013, three major changes over the use of penicillins can be seen. The reduction in the use of ampicillin was obviously due to the change in guidelines of neonatal infections: penicillin G replaced ampicillin. This change was introduced because of the very low frequency of listeria infections, and therefore, the recommendation of empiric therapy of

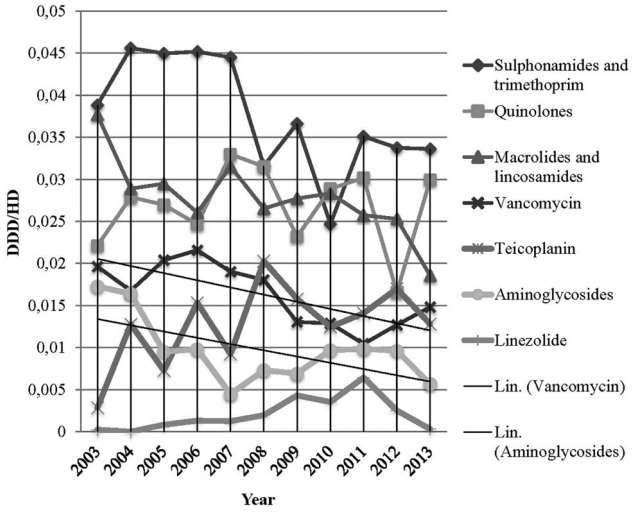

Figure 3 The consumption of different non-beta-lactams in defined daily doses (DDDs) according to Anatomical Therapeutical Chemical classes divided by the days of hospital care (HD)/year in the Children's Hospital during 2003–2013.

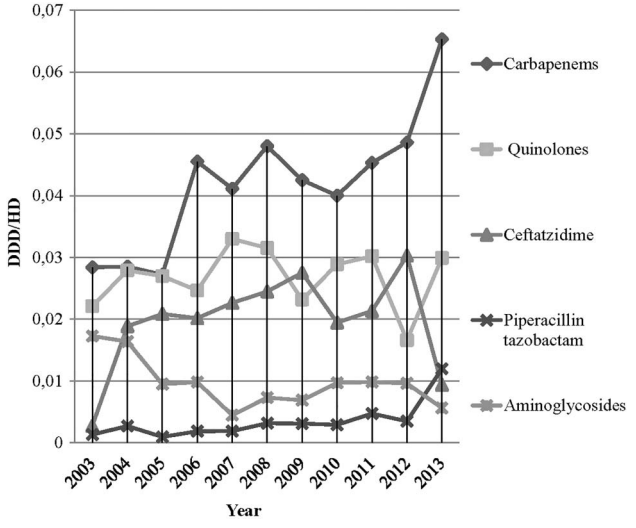

Figure 4 The use of anti-*Pseudomonas* antibiotics in defined daily doses (DDDs) according to Anatomical Therapeutical Chemical classes divided by the days of hospital care (HD)/year in the Children's Hospital during 2003–2013.

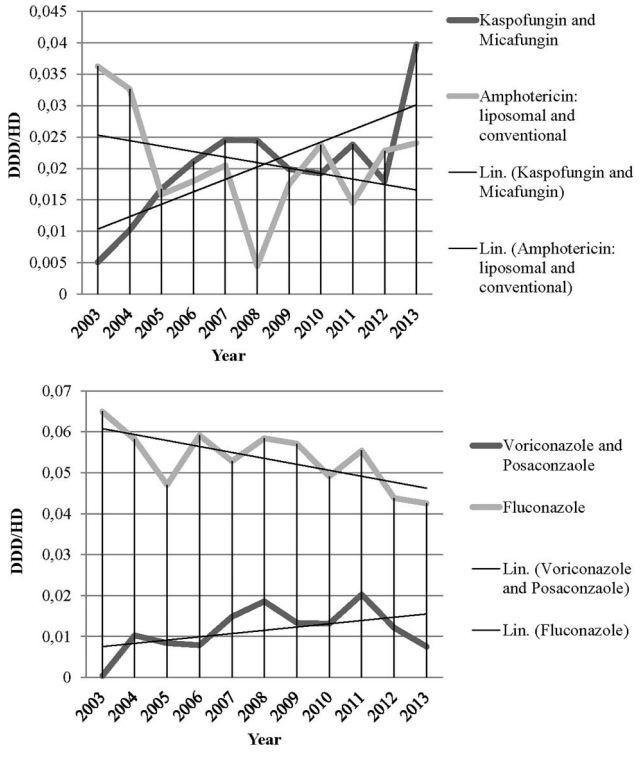

Figure 5 The use of antifungals in defined daily doses (DDDs) according to Anatomical Therapeutical Chemical classes divided by the days of hospital care (HD)/year in the Children's Hospital during 2003–2013.

early neonatal sepsis was changed from ampicillin (+an aminoglycoside) to penicillin G (+an aminoglycoside). Later on, we likewise saw a clear reduction in the consumption of penicillin G at 2011–2012. The reduced consumption of penicillin G took place at the same time pneumococcal conjugate vaccine was introduced to the national immunisation programme at 2010. We noticed a reduction of approximately 80% in the numbers of invasive pneumococcal infections during the years 2011–2013 compared with the pre-immunisation era (data not shown).

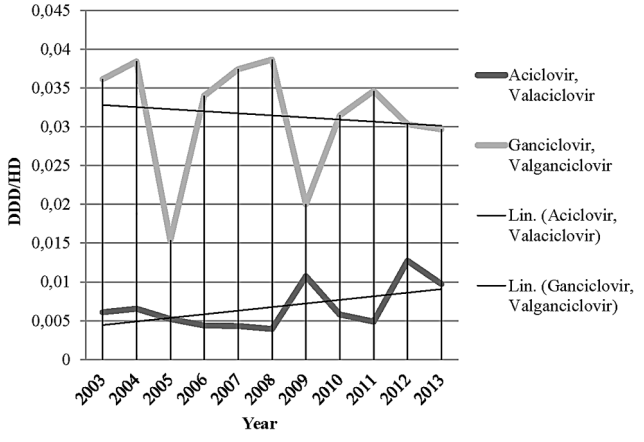

Figure 6 The use of antivirals in defined daily doses (DDDs) according to Anatomical Therapeutical Chemical classes divided by the days of hospital care (HD)/year in the Children's Hospital during 2003–2013.

A third significant change was seen in the use of PIP-TAZ in the year 2012. This increase was due to new recommendations in the empiric treatment of sepsis of neutropenic patients. PIP-TAZ monotherapy replaced the previously used combination of ceftazime+cloxacillin in the treatment of neutropenic sepsis.

Increased use of carbapenems was the most prominent finding of our study. This change has been reported from other European countries and hospitals in adults and children as well.[13 14] One reason for this is that oncologists have become more concerned of *pseudomonas* and other multiresistant gram-negative bacteria. Hence, guidelines were updated, and previous empiric therapy with a combination of cephalosporins and aminoglycosides was replaced by either carbapenems or PIP-TAZ. The same practice has taken place in other Scandinavian countries.[15] On the other hand, the use of other anti-*pseudomonas* drugs (aminoglycosides, ceftatzidime, fluoroquinolones) did not increase significantly during 2003–2013.

The increased use of carbapenems should, however, be carefully evaluated. The overuse may induce an increase in numbers of carbapenem-resistant bacteria.[16] Other disadvantages associated with the use of the carbapenems may include increased number of fungal infections, disturbances of the normal flora resulting in alterations in the microbiome.

The use of vancomycin has decreased during 2003–2013. One reason for this might be extensive training given to prescribers on appropriate use of vancomycin in order to reduce inappropriate use.[17] Empiric misuse of vancomycin in staphylococcal infections is relatively common, despite methicillin-resistant Staphylococcus aureus (MRSA) infections being very rare at our hospital. Other reason for decline in the consumption in vancomycin is increased consumption in teicoplanin. These two, however, cannot be compared by using DDDs. Teicoplanin is more often prescribed for older children with malignancies, whereas vancomycin is more often used in neonatal units.

The overall consumption of antifungals was somewhat decreased during the study period. Novel antifungals were rapidly adapted into use despite lack of data on safety and efficacy.[18] The most frequently used antifungal was fluconazole followed by caspofungin and amphotericin B. However, the use of amphotericin B and fluconazole decreased over the years, whereas the use of novel azoles (voriconazole and posaconazole) and echinocandins (caspofungin and micafungin) increased. Reduced use of amphotericin B (including both conventional AMB and liposomal AMB) was most probably due to the replacement of these drugs by less toxic azoles and echinocandins.

Regarding the use of antivirals, the total consumption of valganciclovir was the greatest followed by cidofovir and zanamavir. The use of aciclovir, valaciclovir and valganciclovir has increased, whereas the use of ganciclovir has decreased. The use of oseltamivir peaked in 2009. In Europe, the use of antivirals varies greatly and is largely determined by the use of HIV/AIDS drugs.[19] In our study, we excluded the HIV antimicrobials from this study since the consumption is very low and the prevalence of HIV is very low in Finland.[20]

DDDs and measuring the consumption of drugs in paediatrics

Whether or not the DDDs represent actual use of antimicrobials in paediatrics, that is, prescription daily doses (PDDs), has been widely discussed. The PDDs of a drug will give the amount of the drug that actually has been prescribed. DDDs represent the daily use of a drug for its main indication with its average dose. If the drug is used for other purposes besides its main indication

or with another dose, it is not equivalent with the DDDs. One study suggests that there is a strong correlation between the DDDs and PDDs.[21] Others have, however, concluded that there are differences between the two.[22–24]

Despite these difficulties, many studies investigating the consumption of antimicrobials in DDDs in children[25–28] have been published. A review regarding ways of measuring antimicrobial consumption concluded that up to date there are no ideal ways of measuring the consumption of antimicrobials in children.[29] Fortin *et al* concluded that the most frequently used method of measuring antimicrobial consumption in paediatrics was the use of DDDs, which was applied by 42% of studies. Currently, the WHO does not, however, recommend the use of DDDs as measurement in children, but in practice this approach is commonly used since more accurate methods are not available.[30] Thus, there are no generally accepted DDDs for children, although some studies have suggested possible DDDs for different ages of children.[31 32]

At the moment, there is an obvious need for the development of novel means of measuring antimicrobial use in paediatric patients. One possible way of producing such data would be based on the weight of individual patients. The study by Porta *et al*[31] (European ARPEC project) suggested age-appropriate DDDs for antibiotics especially for neonates. On the other hand, some studies suggest that adult DDDs in paediatrics may be equal with PDDs or higher.[13 14]

In our study, we used DDDs for measuring antimicrobial consumption. Although the DDDs are definitely not ideal for measuring consumption of antimicrobials in children, our study was able to describe how the consumption of different antimicrobials has changed during 2003–2013 in tertiary children's hospital. We feel that this method allows us to compare temporal trends in a single hospital during the study period.

Strengths and limitations

The strength of this study is the large material covering the consumption of all antimicrobials used in the Children's Hospital during the past 11 years. This long surveillance period gives a good insight into the consumption of antimicrobials in a tertiary care hospital in a country with relatively low number of resistant bacteria such as MRSA and extended spectrum beta-lactamase.

Our study cannot be directly compared with other hospitals with different patient profiles. Similarly, the consumption cannot necessarily be compared with countries where multiresistant bacteria are more frequent. Likewise, guidelines of antimicrobial use can differ from country to country. In addition, choice and dosing of an antimicrobial for a certain infection can vary. In addition, in children, the quantification of consumption by using DDDs is not as precise as that of the adults. Therefore, consumption of different antimicrobials cannot be compared since the DDDs vary greatly between different drugs. Likewise, if the use of one antimicrobial is reduced at neonatal ward, it will most likely not be seen in DDD figures, but if the same use of the drug is reduced at a ward that takes care of adolescent patients mostly, it will be seen in decreased DDDs.

Finally, to further estimate the consumption and rational use of antimicrobials, more data, such as prescription data, indications and the ages of the children, are needed to evaluate the trends in the use of different antimicrobials.

CONCLUSION

Our most significant finding was the increased use of carbapenems. The consumption of antimicrobials needs to be carefully monitored in order to preserve broad spectrum antimicrobials for actual need and to avoid the development of drug resistance. More care and effort should be taken to appropriate prescribing antimicrobial in paediatric hospitals in order to further investigate antimicrobial policy and guidelines of antimicrobial usage.

What this paper adds

What is already known on this subject

- Monitoring the consumption of antimicrobials is a prerequisite for prudent use of antimicrobials.
- Consumption of antimicrobials can be measured by using defined daily doses.
- There are no optimal ways of measuring consumption of antimicrobials in paediatric hospitals.
- Methods to improve the paediatric use of antimicrobials should be improved.

What this study adds

- The quantity of antimicrobial consumption was relatively stable during the study period.
- The quality of antibacterials used has changed—particularly the use of carbapenems has increased.
- The use of conventional antifungals such as amphotericin B was decreased and that of the novel azoles and echinocandins has increased.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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