

IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAM IN THE PAEDIATRIC DEPARTMENT OF A TERTIARY HEALTH FACILITY IN NIGERIA.

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Abstract

Background: Antimicrobial resistance is a major issue limiting the successful treatment of infectious diseases. Development of antimicrobial resistance can be curbed by the adoption of antimicrobial stewardship programs which aims to optimize the use of antimicrobial agents and combat antimicrobial resistance. The study aimed to evaluate the impact of antimicrobial stewardship program implemented in the paediatric department of a tertiary healthcare facility.

Methods: This was a retrospective, cross-sectional study before and after the introduction of an antimicrobial stewardship program. A Global-point prevalence survey was conducted in 2017 to determine the baseline prescription practices. Based on the results, an antimicrobial stewardship program was developed. A second Global-point prevalence survey was conducted in 2018. The impact of the antimicrobial stewardship interventions was evaluated.

Results: An 8.1% reduction in antimicrobials prescribed, an 18% increase in targeted therapy and increased use of biomarkers in the institution of therapy were observed. There was an 8.2% reduction in parenteral therapy. Compliance with the antibiotic guideline was 67.8%. Utilization of the medical microbiology laboratory increased. An increase in the detection of multidrug-resistant organisms was observed. The majority of the antimicrobials prescribed were in the Access group of the AWaRe classification of antibiotics by WHO.

Conclusion: This study demonstrated an improvement in antimicrobial prescribing practices due to the implementation of an antimicrobial stewardship program. This study contributes to the growing body of evidence supporting the effectiveness of antimicrobial stewardship programs. Sustained practice of antimicrobial stewardship will improve antimicrobial prescription patterns thus controlling the development of antimicrobial resistance in healthcare facilities.

Keywords: Antimicrobial stewardship, paediatric, antimicrobial resistance, point prevalence, prescribing practice, Nigeria

BACKGROUND

Antimicrobial agents are the most common drugs prescribed in paediatrics (1,2). It has been estimated that 37-61% of infants and children on hospital admission receive antimicrobial agents (1,3-5). About 20-50% of these prescriptions are said to be either inappropriate or unnecessary (1,4,5). This inappropriate and excessive use of antimicrobial agents is a major contributor to the development of antimicrobial resistance (AMR) (1). Antimicrobial Resistance (AMR) is a significant public health challenge due to the spread of multidrug-resistant (MDR) microorganisms worldwide (3,6). Infections by MDR organisms are often difficult to treat, therapy involves the use of more expensive antimicrobial agents and a longer duration of treatment or hospitalized care (7,8). The emergence and global spread of antimicrobial resistance threatens effective treatment and control of many infections thereby putting the gains of the Millennium Development Goals at risk and endangering the achievement of the Sustainable Development Goals (8,9). In order to curb the rise in AMR, the World Health Organization (WHO) advocates that healthcare providers optimize the use of antimicrobial agents by adopting an antimicrobial stewardship program (ASP) (7). ASP are programs that involve coordinated interventions designed to measure and improve the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy and route of administration without compromising patient outcomes

hence promoting rational and appropriate antimicrobial use (1,7,10,11).

Following the implementation of an ASP, it is essential to evaluate its effectiveness to determine the gains and identify the areas with need for improvement. There is a dearth of published data on the impact of ASP in most sub-Saharan countries, Nigeria inclusive. The Global Point Prevalence Survey (G-PPS) is an accepted tool worldwide used in monitoring antimicrobial prescribing practices and multidrug resistance (6). Hence, the objective of this study was to determine the impact of the ASP on the prescription of antimicrobial agents as a means of controlling the development of AMR in the paediatric medical wards of a tertiary hospital in Nigeria using point prevalence surveys.

METHOD

This was a longitudinal study of 2 point prevalence surveys conducted in the paediatric medical wards of the University College Hospital, Ibadan, Nigeria, a 1,445-bedded tertiary hospital with an average in-patient admission of about 3,500 per month. The first point prevalence survey was conducted in December 2017 to determine the baseline prescription practices while the second survey was conducted in December 2018. Each paediatric medical ward included in the survey was appraised only once on a single day in order to calculate correctly the denominator (total number of admitted patients). The survey included all in-patients in the paediatric medical wards receiving antimicrobials on the day

of the survey, who had been admitted at least 24 hours before the survey and were still on admission at 8 am on the day of the survey. The paediatric emergency ward as well as patients on topical antimicrobial agents and those admitted after 8 am on the day of the survey were excluded from the survey.

Data collected included the patients' biodata, diagnosis, prescribed antimicrobial agent/s and indications for treatment along with other quality indicators such as documentation of the reason for antimicrobial use, compliance with local guidelines, documentation of a stop/review date, and empirical or targeted treatment. In the case of targeted treatment, the choice of antimicrobial agent based on available microbiological data and treatment of multidrug resistance organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, third-generation cephalosporin-resistant *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae* among others. Based on the results obtained, education of prescribers on the rational use of antibiotics was carried out and an ASP was commenced with the constitution of an Antimicrobial Stewardship (AMS) committee. The ASP included the development of an antibiotic policy and guidelines, institution of antimicrobial formulary restriction as well as prior authorization of the carbapenems. A second point prevalence survey was conducted in December 2018 using the same parameters described above to evaluate the impact of the ASP.

Ethical approval was obtained from the Joint Ethical Committee of the University College Hospital, Ibadan. Each patient was given a unique not identifiable survey number which was automatically generated by a computer program. Informed consent was not needed as there was no direct interaction with the patients. Data collected was entered into a web-based application designed by the University of Antwerp, Belgium [www.global-pps.be] for validation, analysis and reporting.

RESULTS

A total of 142 in-patients were surveyed in both years, 70 in the year 2017 and 72 in the year 2018 (Table I). Their ages ranged from 1 day to 12 years. Following the intervention, there was an 8.1 % (91.4-83.3%) reduction in the antimicrobial agents prescribed. A total of 119 and 112 antimicrobial agents were prescribed in the pre-intervention and post-intervention survey respectively. More than 1 antimicrobial agent was prescribed for the majority (71.4% and 63.9%) of the patients in both surveys; however, there was a 7.5% reduction in the use of multiple antimicrobial agents. Antibacterial agents accounted for the largest proportion of antimicrobial agents prescribed. There was an 8.2% decrease in the use of parenteral antimicrobial agents. The main indication for the prescription of antimicrobial agent was community-acquired infection in both years. Antimicrobial agents were mainly prescribed for medical prophylaxis on account of presumed sepsis in the neonatal intensive care unit. There was an 18% (96.6-78.6%) reduction in the use of empirical antimicrobial agents. A 3.7% increase (1.7-5.4%) was observed in the use of biomarkers as an indicator of an infective process before the commencement of antimicrobial therapy. There was 67.8% adherence to the local antibiotic guideline. However,

there was a further decline (4.1%) in the documentation of stop/review date of antimicrobial agents. There was an 18% (3.4-21.4%) increase in the use of microbiological data in the choice of antimicrobial agent. There was an increase in the detection of microorganisms with MDR organisms accounting for 58.3% of the organisms detected (Table II). In the post-intervention survey, 8 (7.1%) of the prescriptions were for the treatment of methicillin-resistant *Staphylococcus aureus* and 2 (1.8%) of the prescriptions were for the treatment of MDR *Enterobacteriaceae*. Broad-spectrum antibacterial agents were most commonly prescribed in both years. The majority, 60.5% and 55.5% of antibiotics prescribed in the pre-intervention and post-intervention surveys respectively were in the Access group of antibiotics of the AWARe classification of antibiotics by WHO (Figure 1). Watch group of antibiotics accounted for 36.3% and 25.9% in the pre-intervention and post-intervention surveys respectively. None of the antimicrobials prescribed were in the Reserve group of antibiotics. Aminoglycosides (gentamicin and amikacin) were the most commonly prescribed antimicrobial agents; however, a 7.5% (36.1-28.6%) decrease in its prescription was observed in the post-intervention survey. There was also a reduction in the prescription of the cephalosporins (ceftriaxone and ceftazidime) and metronidazole with an increase in the prescription of penicillins with enzyme inhibitors combinations such as amoxicillin-clavulanate and ampicillin-sulbactam; quinolones (levofloxacin), lincosamide (clindamycin) and antifungal agents (fluconazole) in the post-intervention survey.

DISCUSSION

Assessing the impact of ASP is essential to evaluate the program as well as identify areas for improvement. It is also important in feedback and planning of future interventions. This study demonstrated the impact of ASP on the pattern of antimicrobial prescription in a paediatric department of a tertiary hospital in Nigeria. It showed an improvement in antibiotic prescribing pattern in this hospital as there was a reduction in the total number of prescribed antimicrobial agents, 8.1 % (91.4-83.3%). This rate is still high compared to that in Europe and America, 31- 61% but it is within the observed range in Africa (12-19). A study in Lagos, Nigeria also reported improvement in the prescribing practice with significantly lower rates of prescription of antimicrobial agents (51.1%) following the implementation of antimicrobial stewardship (20). The rate of antibiotic prescription observed in the pre-intervention survey was very high (91.4%). This might be attributable to the absence of an antibiotic policy, absence of antibiotic guidelines and poor utilisation of the medical microbiology laboratory. There was also a reduction in the use of combination antimicrobial therapy. However, the use of combination antimicrobial therapy is still higher than reports from other studies (13,14). The frequent use of combination therapy might be due to the desire of the prescribing physicians to provide antimicrobial coverage against all possible microorganisms implicated during the prescription of empirical therapy. Some studies have reported that the use of combination antimicrobial therapy provides potential synergy and a broader spectrum of antimicrobial activity but there is insufficient evidence to support its routine use in the treatment of infections (21). Furthermore, the frequent use of combination therapy is associated with several demerits such as an increase in drug-drug interactions, adverse drug

effects experienced, development of antimicrobial resistance and increased cost of healthcare (22). Thereby, underscoring the need for targeted therapy and by extension improved utilisation of the medical microbiology laboratory.

Majority of the antimicrobial agents prescribed were broad-spectrum in both surveys possibly due to an inadequate understanding of the spectrum of activity of the antimicrobial agents among the prescribers. The use of broad-spectrum antimicrobial agents might also be attributed to failure to utilize the available diagnostic tools. The use of broad-spectrum antimicrobial agents unfortunately contributes to the development of AMR (7). There was an improvement in the use of oral antimicrobial agents; this will reduce the risk of HAI and the possible need for more potent and expensive drugs in its treatment. However, the rate of prescription of parenteral antimicrobial agents can be further improved as it is still high and contrary to the practice advocated in AMS. This is similar to observations in other studies whereby the rate of prescription of parenteral antimicrobials ranged from 89.9 – 97.6% (15,16). Community-acquired infections accounted for the majority of the indications for antimicrobial use. However, treatment of healthcare-associated infections (HAI) increased in the post-intervention survey. This emphasises the importance of inclusion of infection prevention and control, a key component to a successful ASP (23).

The use of targeted therapy was very low although there was an improvement. Targeted therapy is essential in ensuring the right antimicrobial agent is used; hence, decreasing the occurrence of selective pressure and development of AMR as well as the cost of healthcare (9,24). This is similar to the rate observed in another study in Nigeria (18). Other studies in Nigeria also reported that empiric therapy accounted for 93.8 - 96.6% of prescriptions (16,17). A study in Nigeria reported that only 15.9% of prescribers utilised the medical microbiology laboratory when treating suspected infections or infectious diseases (25). The reasons obtained for suboptimal use of the laboratory included perceptions that clinical diagnosis is sufficient, long turn-around time in obtaining laboratory reports and poor access to the laboratory. There was an improvement in the use of biomarkers albeit low. This is similar to the report in another Nigerian study (18). The use of biomarkers such as procalcitonin and C-reactive protein is relatively new and expensive in this hospital and most parts of Nigeria. Nonetheless, biomarkers are a viable adjunct to guide therapy especially in patients with suspected sepsis. They are particularly useful as a guide in the initiation of empirical antimicrobial therapy and monitoring of treatment (26,27). The documentation of antimicrobial stop or review dates further decreased in the post-intervention survey. Poor documentation of an antimicrobial review or stop date results in leaving patients on antimicrobial agents for inappropriate durations with possible enhancement of the development of AMR, development of adverse side effects and increased healthcare cost (7). Compliance with the guidelines was 67.8%. This is commendable as in the previous year, there was no antibiotic guideline available in the hospital. However, there is room for improvement. Other studies in Nigeria have also reported poor adherence to local guidelines (7,14–16,18).

The increased detection of MDR organisms in the post-

intervention survey might be due to increased utilization of the medical microbiology laboratory with the identification of the organism implicated in the infections which resulted in the prescription of the right antimicrobial agent thereby possibly favouring the patients' clinical outcome. This further emphasizes the need for targeted therapy along with its associated benefits.

Antibacterial agents were the most commonly prescribed agents in this study; this is similar to the observations of other studies possibly because bacteria are the commonest cause of infections in sub-Saharan Africa (3,28). The majority, 60.5% and 55.5% of the antimicrobials prescribed in pre- and post-intervention surveys respectively were in the Access group of antibiotics based on the WHO AWaRe classification of antibiotics (29). This is commendable, but there is room for improvement as WHO encourages a country-level target of at least 60% of total antibiotic consumption being Access group of antibiotics. A 5% decrease in the prescription of antimicrobial agents in the access group and a 10.4% increase in the antimicrobial agents in the Watch group of antibiotics observed was due to the increase in the isolation of MDR organisms (29). The increased prescription of quinolones (levofloxacin) and the lincosamide, clindamycin was due to the treatment of MRSA which was based on the microbiological data. It is worthy of note that there was no prescription of the fourth- and fifth-generation cephalosporins, carbapenems or colistin in both surveys. The carbapenems and colistin are antibiotics of the last resort and should be reserved for life-threatening infections by MDR microorganisms (28). This practice will limit the development of resistance to these antimicrobial agents and thereby conserve them for use when needed. There is a need for further improvement in the prescribing practices in this hospital and the utilization of the microbiology laboratory.

Limitations of this study include the inability to determine the duration of antimicrobial therapy, length of hospital stay, possible adverse drug effects and clinical outcome of the patients as this is difficult to achieve with a point prevalence survey.

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of antimicrobial therapy, length of hospital stay, possible adverse drug effects and clinical outcome of the patients as this is difficult to achieve with a point prevalence survey.

CONCLUSION

This study demonstrated the effectiveness of an antimicrobial stewardship program in the improvement of the antimicrobial prescription especially in a limited resource setting using the Global-PPS as a tool in the monitoring and evaluation. The development of an antibiotic guideline made an impact on prescribing patterns in the hospital. The success of the ASP highlights the importance of its implementation in combating AMR and ensuring the responsible use of antimicrobial agents. More efforts are needed in the utilisation of the medical microbiology laboratory to increase targeted therapy and limit the development of AMR. More rigorous research is however needed to look into the other aspects ASP addresses such as appropriateness of an antimicrobial agent, sub-therapeutic and excessive doses of antimicrobial agents, and the impact of ASP on length of hospital stay, clinical outcome as well as hospital cost.

Table I: Parameters evaluated in both surveys

Variables	Pre-intervention (2017)	Post-intervention (2018)	Difference Observed (%)
Age Range	1 day- 12 years	1 day -10 years	
Total Number of In-patients	70	72	
Number of Patients on at Least One Antimicrobial Agent	64 (91.4%)	60 (83.3%)	8.1%
Total Number of Antimicrobial Agents prescribed	119	112	
Number of Antimicrobial Agent/s per Patient			
1 Antimicrobial Agent	14 (20%)	14 (19.4%)	0.6%
2 Antimicrobial Agents	45 (64.3%)	40 (55.6%)	8.7%
≥3 Antimicrobial Agents	5 (7.1%)	6 (8.3%)	1.2%
Type of Antimicrobial Agent Prescribed			
Antibacterial Agent	116 (97.5%)	103 (92%)	5.5%
Antifungal Agent	1 (0.8%)	5 (4.5%)	3.7%
Antiviral Agent	Nil	Nil	
Antiparasitic Agent	2 (1.7%)	4 (3.6%)	1.9%

Route of Administration			
Parenteral	115 (96.6%)	99 (88.4%)	8.2%
Oral	4 (3.4%)	13 (11.6%)	8.2%
Indication of Therapy			
CAI	58 (48.7%)	56 (50.0%)	1.3%
HAI	18 (15.1%)	19 (17.0%)	1.9%
MP	37 (31.1%)	32 (28.6%)	2.5%
SP	4 (3.4%)	Nil (0.0%)	3.4%
Unknown	1 (0.8%)	5 (4.5%)	3.7%
Other	1 (0.8%)	Nil (0.0%)	0.8%
Quality Indicators			
Empirical Therapy	115 (96.6%)	88 (78.6%)	18.0%
Targeted Therapy	4 (3.4%)	24 (21.4%)	18.0%
Use of Biomarker	2 (1.7%)	6 (5.4%)	3.7%
Stop/Review Date	24 (20.2%)	18 (16.1%)	4.1%
Guideline Compliance	NA	76 (67.8%)	
Drugs Prescribed based on Microbiological Data	4 (3.4)	24 (21.4)	18%

CAI: community-acquired infection, HAI: healthcare-acquired infection, MP: medical prophylaxis, SP: surgical prophylaxis, NA: not available

Table II: Evaluation of Microbiological Parameters

Variables	Frequency (%)	Frequency (%)
Non-MDR Organisms	4 (100)	10 (41.7)
MRSA	Nil	12 (50)
MDR Enterobacteriaceae	Nil	2 (8.3)

MDR: multidrug-resistant, MRSA: methicillin-resistant *S. aureus*

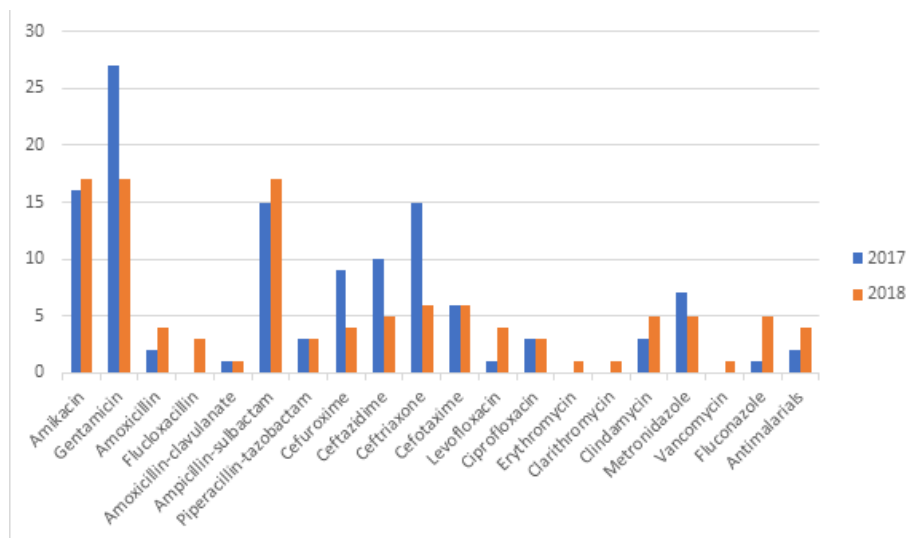


Figure 1: Chart showing antimicrobial agents prescribed

ABBREVIATION

AMR Antimicrobial resistance
AMS Antimicrobial stewardship
ASP Antimicrobial Stewardship program
ESBL Extended spectrum beta-lactamase
G-PPS Global Point Prevalence Survey
HAI Healthcare-associated infections
MDR Multidrug-resistant
MRSA Methicillin-resistant *Staphylococcus aureus*
WHO World Health Organization

Conflict of Interest: The authors declare no conflicting interest.

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