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Research Article

The Effect of antibiotic stewardship targeted against vancomycin and carbapenems on antibiotic usage in PICU

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Abstract:

Introduction: Inappropriate and excessive usage of antibiotics has led to an ever-expanding drug resistance phenomenon, such that some bacterial diseases have recently become untreatable. Antibiotic stewardship (ABS) programs are important for rationalizing the administration of antibiotics in hospitals, and studies have proven their effects on reducing costs and microbial resistance.

Method: The present study was conducted in the form of a clinical trial in which the effect of ABS targeted against vancomycin and carbapenems usage was evaluated in terms of the length of hospital stay and mortality in the PICU of Dr. Sheikh Children's Hospital, Mashhad, Iran. This strategy implemented was reviewing the physicians' prescriptions and providing feedback.

Results: In the PICU of Dr. Sheikh Children's Hospital, vancomycin and carbapenems were inappropriately prescribed by the attending physicians in 78 and 48 % of cases, respectively. The mean number of days of both vancomycin and carbapenems usage decreased significantly in the intervention group in which the ABS program was implemented. However, no significant differences were observed between the two groups in the mean length of hospitalization and mortality.

Conclusions: Overall, it was concluded that pediatricians at Dr. Sheikh Children's Hospital highly accepted and strongly implemented the ABS program. Our findings demonstrated that the program yielded favorable results that were similar to those of advanced hospitals. ABS programs are thus recommended for implementation in other hospitals.

Keywords: antibiotic stewardship; vancomycin; carbapenems; PICU

Introduction

Inappropriate and excessive usage of antibiotics has led to an ever-expanding drug resistance phenomenon, such that some bacterial diseases have recently become untreatable. Inappropriate antibiotic use is one of the major causes of increased illness, mortality and treatment costs for patients [1, 2]. Antibiotic stewardship (ABS) programs are important for rationalizing the administration of antibiotics in hospitals, and studies have proven their effects on reducing costs and microbial resistance. However, even in the United States, ABS is currently implemented in only a few children's hospitals [3, 4]. The main strategies of ABS are: (a) Education & guidelines: providing guidelines for antibiotic usage and educating physicians; (b) Formulary restriction: restricting the usage of certain antibiotics by requiring the approval of an infectious disease specialist; (c) Review & feedback: reviewing prescriptions and providing feedback to doctors; (d) Computerized management: managing antibiotic prescription via computer software; (e) Antibiotic cycling: cycling the antibiotics used. Each of these strategies can be implemented individually or in combination with the others [5]. (Table 1)

Table 1: Summary of antibiotic stewardship strategies

Strategy	Procedure(s)	Personnel	Advantages	Disadvantages
Education / Guidelines	Production of guidelines for antibiotic usage. Group or individual	Antibiotic committee to produce guidelines. Educators (physicians, pharmacologists).	May alter behavior patterns. Avoids loss of autonomy for	Passive education is probably ineffective.

	education for clinicians by educators.		prescribers.	
Formulary Restriction	Restrict usage of targeted antibiotics to approval according to indications.	Antibiotics committee to create guidelines. Approval personnel (physicians, infectious diseases fellows, clinical pharmacologists).	Most direct control over antibiotic usage. Individualized educational opportunities.	Perceived loss of autonomy for prescribers. Need for full time consultant availability.
Review & Feedback	Daily review of prescribed antibiotics in terms of appropriateness & providing suggestions to physicians.	Antibiotics committee to create guidelines. Review personnel (usually clinical pharmacologists).	Avoids loss of autonomy for prescribers. Individualized educational opportunities.	Requires compliance with voluntary guidelines.
Computerized Management	Use of information technology to implement various strategies. Expert systems provide patient-specific recommendations at the point of care (order entry).	Antibiotics committee to create rules for computer systems. Personnel for approval or review (physicians, pharmacists), software programmers.	Provides patient specific data at the most probably point of impact (point of care). Facilitates other strategies.	Significant time and resource investment to implement sophisticated systems.
Antibiotic Cycling	Scheduled cycling of antibiotics used in hospital or unit (e.g., intensive care unit).	Antibiotics committee to create cycling protocol. Personnel to oversee adherence (pharmacist, physicians).	May reduce resistance by changing selective pressure.	Difficult to ensure adherence to cycling protocol. Theoretical concerns about effectiveness.

Among the methods of antibiotic management presented in Table 1, the review and feedback method, which was utilized in our study, is the most desirable and effective strategy for ABS programs in pediatrics [1].

Material and Method:

The present study was conducted in the form of a clinical trial in which the effect of ABS targeted against vancomycin and carbapenems usage was evaluated in terms of the length of hospital stay and mortality in the PICU of Dr. Sheikh Children's Hospital, Mashhad, Iran. This strategy implemented was reviewing the physicians' prescriptions and providing feedback. The project was carried out over two phases, namely the pre-operational and operational phases. During the first phase, we reviewed patient records and collected data on the organisms that had caused nosocomial sepsis from April 2012 to September 2013, and recorded their antibiotic resistance. Based on the findings, guidelines were developed for the empirical treatment of nosocomial infections. In the operative phase, which was from November 1, 2014 to January 30, 2015, the files of PICU patients were reviewed every other day and recommendations about the compatibility of the prescriptions with the guidelines were provided to the prescriber. We evaluated the effects of antibiotic stewardship on antibiotic usage, hospital length of stay and mortality. Data from January (in the middle of the research) was used for the control group. In that month, patients' files were reviewed every other day and information related to antibiotics were recorded, but no recommendations were provided to the prescribers.

Results

In the preoperative phase we researched on blood cultures in Dr Sheikh Hospital and we found that (in the first five months of 2013), 326 blood cultures were performed for PICU patients of Dr. Sheikh Children's Hospital, from which 43 positive cultures were obtained (13% of cases). Gram-negative bacilli (69.7% of cases) were the main agents responsible for PICU sepsis. *Staphylococcus epidermidis* was the most common Gram-positive species obtained from blood cultures (18.6%). This was most likely due to contamination as central venous catheters were rarely used in the hospital during the mentioned time period. Therefore, minus *Staphylococcus epidermidis*, Gram-positives accounted for only 11.4% of ICU sepsis cases. Based on this, it was reasonable to include broad-spectrum antibiotics that cover resistant Gram-negatives in the

empirical treatment of nosocomial sepsis, while vancomycin usage was unnecessary (Tables 2 and 3).

Table 2: Bacteria identified via bacterial cultures before the start of the ABS program and during the 5 months when the ABS program was implemented in the PICU of Dr. Sheikh Children's Hospital

Bacteria	First 5 months of 2013 (%)	October 2014 to January 2015 (%)
Pseudomonas spp.	18.6	31
Acinetobacter spp.	6.9	15
Klebsiella pneumonia	25.5	10
Streptococcus pneumoniae	0	10
Staphylococcus epidermidis	18.6	4
Staphylococcus aureus	2	4
Klebsiella spp.	4.6	4
Enterobacter spp.	11.6	2
Enterococci spp.	9.3	2
Candida spp.	0	2
Total No.	43 (100%)	37 (100%)

Table 3: Guidelines for the use of vancomycin, carbapenems and tazocin in the PICU of Dr. Sheikh Children's Hospital

Indications for the onset of empirical therapy with vancomycin: 1. Clinical suspicion (significant) of CNS bacterial infections 2. Staphylococcal pneumonia (rapidly progressive with empyema). 3. Fever and neutropenia (in case of severe mucositis or shock) 4. Nosocomial soft tissue infections 5- Ventriculoperitoneal shunt infection 6- Peritonitis caused by peritoneal dialysis catheter 7- Clinical infection of central venous catheter (cellulitis in the catheter, fever and shiver during the use of catheter, shock in the patient)
Cases in which vancomycin usage is not recommended or should be discontinued after 48-72 hours: 1- Non-nosocomial sepsis 2- In fever, neutropenia, severe mucositis, and bacterial meningitis, if the cultures from samples that were obtained before the start of vancomycin are negative, vancomycin should be discontinued. 3- In cases where the onset of vancomycin has occurred, vancomycin should be discontinued if blood culture indicates that the responsible organism is susceptible to another antibiotic agent.
Indications for the onset of empirical therapy with carbapenems, tazosin and ceftazidime: 1. Hospital–acquired pneumonia 2. Fever and neutropenia 3. Patient deterioration after at least 48 to 72 hours of admission to the PICU (isolated fever is not an indication for such emperical therapy)
Indications for continuation of therapy with carbapenems and tazosin 48-72 hours after onset: 1. Positive culture for resistant gram negatives from blood, urine, peritoneal fluid, joint fluid, or CSF fluid. 2. Fever and neutropenia with negative blood culture.
Indications for reviewal of therapy with carbapenems and tazocin 48-72 hours after onset: 1. Ventilator-associated pneumonia: If the patient responds to the treatment and the culture from the endotracheal aspirate is negative, or if the culture is positive for a Gram-negative organism that is sensitive to a narrower spectrum antibiotic, carbapenems should be stopped and therapy should continue with the other antibiotic. Cultures from endotracheal aspirates should be requested (before starting or changing the antibiotic) in suspected VAP patients. Negative cultures from endotracheal aspirates (in patients who have not had their antibiotics changed 72 hours prior to sampling) are strongly against VAP (due to typical bacterial agents). In such cases, given rapid clinical improvement, discontinuation is recommended after 48-72 hours. In patients who have cultures of organisms susceptible to narrower spectrum antibiotics, therapy should be deescalated and treatment should continue for 6 to 10 days. 2. Patients with deteriorating conditions: In patients who have a negative culture and good clinical recovery after 48-72 hours, carbapenems can be continued or switched to a third–generation cephalosporin+aminoglycoside or to tazosin. In patients who have a negative culture but are non-responsive to therapy, blood culture should be repeated, focal infections should be reconsidered, and colistin and/or antifungal agents should be considered.

In the operative phase During the three months of the implementation of the ABS program and during the one month used as the control, 199 patients (1676 patient days) and 59 patients (673 patient days) were hospitalized in the PICU , respectively. Table 4

shows a comparison of the basic characteristics of these two groups. (Table 4)

Table 4: Comparison of the basic characteristics of the intervention and control groups in the management plan for vancomycin and carbapenems usage in the PICU

	ABS (intervention)	Pre-ABS (control)	P
Total No.	1676 patient days	673 patient days	
Age			
0-1 month	41.2 %	42.3 %	0.967
1 month to 1 year	44.2 %	40.6 %	
Above 1 year of age	14.5 %	16.7 %	
Boy to girl ratio	52.47	47.52	0.474
Cause of hospitalization			
Surgery	60.3 %	55.9 %	0.268
Sepsis	11.5%	13.5 %	
Pneumonia	10.5%	13.5 %	

And the result was this Vancomycin was started for 59 patients (29.6 %) in the intervention group and for 30 patients (50.8%) in the control group, while carbapenems were started for 50 patients (25.1 %) in the intervention group and for 27 patients in the control group. According to our guidelines, the administration of vancomycin and carbapenems was inappropriate in 78 and 48 % of cases, respectively, with the recommended discontinuation being approved by the attending physician in 61 and 59 % of cases, respectively. The mean number of days of vancomycin usage for each patient in the intervention and control groups was 1.5 and 3.3 days, respectively (P= 0.001). The corresponding values for carbapenems were 1.6 and 4.9 days, respectively (P= 0.001).

The average lengths of PICU hospitalization in the intervention and control groups were 8.4 and 11.4 days, respectively. However, the Mann-Whitney test revealed no statistically significant difference (P= 0.06) between these values. Mortality rates in the intervention and control groups were 7 and 10.2%, respectively, though Fisher's test revealed no statistically significant difference (P= 0.4) (Table 5).It is cleared that the increase of patients and the days of control will give a good and satisfaction result.

Table 5: Comparison of the effect of the 3 month ABS program on vancomycin and carbapenems administration relative to the 1 month of control in the PICU of Dr. Sheikh Children's Hospital

	ABS (Intervention)	Pre-ABS (Control)	P
Mean vancomycin usage (days)	1.5	3.36	0.001
Mean carbapenems usage (days)	1.63	4.95	0.001
Mean length of hospitalization (days)	8.42	11.40	0.06
Mortality rate (%)	7%	10.2%	0.4

Discussion

The present study showed that Gram-negative bacilli are the main cause of nosocomial sepsis in the PICU of Dr. Sheikh Children's Hospital in Iran. Gram-negative bacilli are also most responsible for nosocomial sepsis in other developing countries, while staphylococcal infections are the most common cause of nosocomial infections in hospitals of advanced nations [6].so in treatment we must have attention to this problem. In North America, Gram-positive bacteria caused more than 70% of blood infections in an NICU in 2013 [7]. In Greece, Gram-positive bacteria are responsible for 59% of PICU infections [8]. In Latin America, the share of Gram-negative bacilli in PICU and NICU sepsis varies from 31% in Colombia to 65% in Mexico [6]. In the PICU of Bahrami Hospital, Tehran, *Escherichisa coli* and *Pseudomonas aeruginosa* were the most commonly isolated organisms from all clinical specimens in 2011 [9].

In a study of the prevalence and effectiveness of ABS programs in children's hospitals across the United States, it was found that few children's hospitals have implemented comprehensive ABS programs. Additionally, based on the results of blood cultures, the researchers concluded that ABS programs led to is e rational use of antibiotics in 76% of cases and the shortening of the duration of antibiotic therapy in more than 40% of cases. They also concluded that ABS effects broad-spectrum antibiotic usage more compared to other antibiotics [10].so as we can see our research in Iran have had the same result.

The only antibiotic management article in Iran that has been published in Pubmed is a study by Dr. Sistanizad, which was conducted in the ICU of a teaching hospital in Tehran. In that study, carbapenems were only prescribed during the intervention period with the supervision of an ICU specialist and the consultations of both an infectious disease specialist and a clinical pharmacist. The use of carbapenems also required a positive culture (with agents resistant to other

antibiotics). Such management led to a 64% reduction in carbapenem usage. Also, the sensitivity of *Pseudomonas aeruginosa* to imipenem significantly increased during their intervention period [11] and he had the same result in that we have had.

In the PICU of Dr. Sheikh Children's Hospital, vancomycin and carbapenems were inappropriately prescribed by the attending physicians in 78 and 48 % of cases, respectively. A study conducted at four NICUs in New York showed that vancomycin and carbapenems were inappropriately used in 32 and 43 % of cases, respectively [12]. In that study, vancomycin usage was 267 days per 1000 patient days in the intervention group, compared to 294 days per 1000 patient days in the control group [11]. In the present study, the ABS program resulted in 39.5 and 55.5 % reductions in vancomycin and carbapenems usage (patient days). At Boston Children's Hospital, ABS programs reduced the use of vancomycin in two NICUs by 35 and 65 %, without increasing the rate of mortality [13].

Over 3 years, ABS programs reduced the use of broad-spectrum antibiotics to 21% at the DuBont Children's Hospital in the United States [3].

Conclusion

Overall, it was concluded that pediatricians at Dr. Sheikh Children's Hospital highly accepted and strongly implemented the ABS program. Our findings demonstrated that the program yielded favorable results that were similar to those of advanced hospitals. ABS programs are thus recommended for implementation in other hospitals.

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