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TRANSLATIONAL RESEARCH

Impact of antimicrobial stewardship programme on hospitalized patients at the intensive care unit: a prospective audit and feedback study

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AIMS

Inappropriate use of antibiotics is one of the most important factors contributing to the emergence of drug resistant pathogens. The purpose of this study was to measure the clinical impact of antimicrobial stewardship programme (ASP) interventions on hospitalized patients at the Intensive care unit at Palestinian Medical Complex.

METHODS

A prospective audit with intervention and feedback by ASP team within 48–72 h of antibiotic administration began in September 2015. Four months of pre-ASP data were compared with 4 months of post-ASP data. Data collected included clinical and demographic data; use of antimicrobials measured by defined daily doses, duration of therapy, length of stay, readmission and all-cause mortality.

RESULTS

Overall, 176 interventions were made the ASP team with an average acceptance rate of 78.4%. The most accepted interventions were dose optimization (87.0%) followed by de-escalation based on culture results with an acceptance rate of 84.4%. ASP interventions significantly reduces antimicrobial use by 24.3% (87.3 defined daily doses/100 beds *vs.* 66.1 defined daily doses/100 beds $P < 0.001$). The median (interquartile range) of length of stay was significantly reduced post ASP [11 (3–21) *vs.* 7 (4–19) days; $P < 0.01$]. Also, the median (interquartile range) of duration of therapy was significantly reduced post-ASP [8 (5–12) days *vs.* 5 (3–9); $P = 0.01$]. There was no significant difference in overall 30-day mortality or readmission between the pre-ASP and post-ASP groups (26.9% *vs.* 23.9%; $P = 0.1$) and (26.1% *vs.* 24.6%; $P = 0.54$) respectively.

CONCLUSIONS

Our prospective audit and feedback programme was associated with positive impact on antimicrobial use, duration of therapy and length of stay.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Inappropriate use of antibiotic has been associated with increased resistance, morbidity and hospital stay.
- Antimicrobial stewardship programmes (ASPs) aim to improve patient safety and outcomes whilst reducing adverse effects associated with antimicrobial use

WHAT THIS STUDY ADDS

- This study identified the current patterns of antibiotic prescribing and the impact of an ASP on these practices.
- ASP interventions are effective to manage the antimicrobial prescription according the local guidelines
- The ASP team can effectively participate in health education to promote the rational use of antimicrobial agents

Introduction

Much has been written about antimicrobial resistance (AR) as an important factor in both patient-safety and public-health [1]. Reports of AR bacterial infections are growing, and the ability of pharmaceutical industry to generate new classes of antibiotics is limited [2, 3]. Factors that are known to contribute to AR include the extent of antimicrobial exposure and consumption of antibiotics in a population [4–7]. A recent meta-analysis demonstrated a link between primary care physicians prescribing of antibiotics to AR in pathogens causing respiratory, urinary and skin infections [6].

The search for a way to improve antimicrobial prescribing practices has been addressed by the implementation of antimicrobial stewardship programmes (ASP) to control AR [7]. ASP includes measures to promote the appropriate use of antimicrobials. Such measures include: educational programmes for all clinical staff to ensure competency; evidence-based optimal treatment for routine infections; communication of issues related to antimicrobial use to stakeholders; and finally monitor the impact on change in clinical practice [8–11]. Ultimately, the aims of ASP are to improve efficacy, minimize adverse effects and limit AR. Infections caused by susceptible organisms are easier to treat than those caused by resistant organisms that may have poor clinical outcome (morbidity and mortality), extended hospital stay and higher cost [12].

Two core ASP strategies have been adopted by the Infectious Diseases Society of America to reduce the inappropriate use of antimicrobials: prospective audit and feedback interventions [11, 13]. The main attribute of prospective audit and feedback strategy is that acceptance of recommendations is voluntary; as such doctors maintain their prescribing autonomy [14]. It is therefore more acceptable to doctors and less likely to be opposed. In fact, due to the feedback mechanism, this type of intervention may be considered educational.

Another point to consider is the method for implementation and evaluation of such programmes. Some of the options include; the selection of audit cases based on surgical or medical fields and/or based on pre-defined antibiotics. Monitoring for consumption can be done in the form of defined daily doses (DDD) or days of therapy [15, 16]. This may identify high prescription areas and maximize the impact of interventions.

To date, there has been no programme or evaluation of ASP in Palestinian hospitals. Hence, in this study, the aim is to evaluate the impact of ASP on the following outcomes: (i) antibiotic consumption; (ii) duration of therapy; (iii) length of hospital stay; (iv) intervention acceptance rate; (v) readmission within 30 days of discharge; and (vi) mortality within 30 days of ASP audit.

Methodology

Patients and setting

This was a single-centre, prospective, pre- and postintervention study at Palestinian Medical Complex (PMC) in Ramallah. The PMC consists of five hospitals; Ramallah Public Hospital; Al-Sheikh Zayed Hospital; National Center for Blood Diseases; Bahrain Pediatrics Hospital; and Kuwaiti Specialized Surgery Hospital. The PMC has 214 beds. It provides a wide range of services, including neonatal care, maternity care, internal medicine, paediatrics, general surgery and cardiovascular surgery.

All patients admitted to the intensive care unit (ICU) and administered any antimicrobial drug were included in the study. A review of the ASP database was conducted, for interventions made between September 2015 and December 2015.

Description of the ASP

The ASP team, consisting of an infectious diseases physician, clinical microbiologist, clinical pharmacists at the 12-bed ICU, drew up new antibiotic guidelines for empirical treatment of common infections. Evidence for these guidelines was drawn from international published guidelines and was adapted to Palestinian Medical complex microbial susceptibility patterns. The clinical pharmacists performed the primary review, screened cases for appropriateness and made therapeutic recommendations; for example, dosage optimization, or switch from intravenous to oral antibiotics. These recommendations were reviewed by the ASP team on the 2nd, 4th and 7th days, allowing for bacterial culture to be processed with recommendations for de-escalation, change, dose adjustment of antibiotics where appropriate (Figure 1). Criteria used to determine if antimicrobial was inappropriately prescribed include:

- If hospital antibiotic guidelines were not followed without reasonable explanation;
- If empiric treatment was less than optimal per guideline including dose level, dose duration or dosing regimen;
- If cultures results indicate that a narrower-spectrum antibiotic may be more appropriate;
- If culture results show that there was no infection and an alternative reason for the fever is identified.

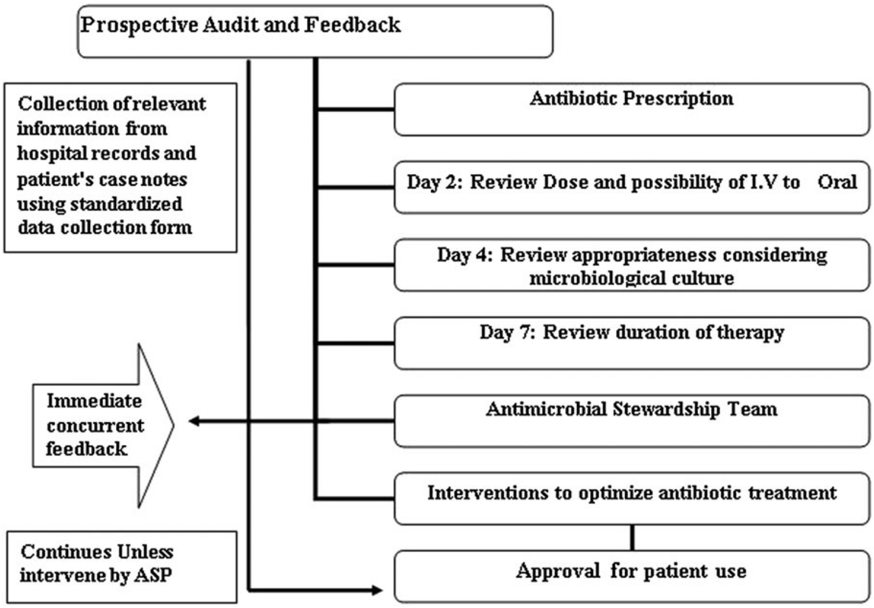

Figure 1

Schematic diagram of the antimicrobial stewardship programme prospective audit with immediate concurrent feedback workflow

The prospective audit with intervention and feedback made by the ASP team within 48–72 h of antibiotic administration began in September 2015. Four months of pre-ASP data were compared with 4 months of post-ASP data. Data collected included clinical and demographic data; as well as use of antimicrobials which was calculated using DDD.

Data collections and outcomes

Compliance with or rejection of ASP recommendations was determined via review of patient's medical record/chart at 24 and 48 h after antibiotic recommendation. During the study period, hospital pharmacy records were used to obtain drug prescription data for the audited antibiotics. DDD/100 beds for each drug or drug category prescribed monthly were calculated following the World Health Organization Anatomical Therapeutic Chemical classification system [17]. All recommendations made by ASP team were recorded on a standardized form.

Ethics

The study was approved by Palestinian Medical Complex ethical committee. Informed consent was deemed unnecessary since ASP constituted routine clinical practice and medical record analysis was analysed anonymously.

Data analysis

All statistical calculations were analysed using SPSS version 16.0 (SPSS Inc., Chicago, IL). Data were expressed as the mean ± standard deviation for continuous variables, and unpaired Student *t* test was performed to determine differences between mean values. For noncontinuous variables data were expressed as median [interquartile range (IQR)]. Mann–Whitney test was performed; for categorical variables, data were expressed as number and percentage and were analysed by chi-square test or Fisher exact test, as appropriate.

Results

Demographics and comorbid conditions

There were no statistically significant differences in terms of age, number of comorbid conditions, previous hospitalization and previous antibiotic use between the pre-ASP group and post-ASP group (Table 1). Patients in the post-ASP period had more episodes of sepsis and respiratory infections. Types of infection were defined based on the International Classification ICD-10 [17].

Interventions

During the post-ASP period, a total of 356 antimicrobial prescriptions for 142 patients were revised during a 4-month period. Of these, 49.4% were considered inappropriate in 101 patients. The majority of interventions recommended by ASP team were: de-escalating 64 (36.4%); discontinue antibiotics 53 (30.1%); and intravenous to oral switch intervention 32 (18.2%). Overall, 176 interventions were made by ASP team with an average acceptance rate of 78.4% by the ICU team. The most accepted interventions were dose optimization based on pharmacokinetic and dynamics of antibiotics with an acceptance rate of 87.0% followed by de-escalation based on culture results with an acceptance rate of 84.4% (Table 2). Changing the antibiotic was the most common reason for non-acceptance, another key reason was the ICU team did not view the recommendations; therefore, the recommendations were no longer applicable.

Table 1

Patient demographics and comorbid conditions by period

Demographic characteristics	Pre-ASP period (n = 115)	Post-ASP period (n = 142)	P
Mean age (years)	68.4 (15.3)	70.1 (16.6)	0.35
Male sex	55 (47.8)	82 (57.7)	0.01
Previous hospitalization within 3 months	53 (46.1)	68 (47.9)	0.43
Previous antibiotic use within 3 months	79 (68.7)	90 (63.4)	0.17
Comorbid conditions			<0.01
No comorbidities	9 (7.8)	21 (14.8)	
1–2	47 (40.8)	65 (45.8)	
3–4	43 (37.4)	44 (30.9)	
>5	16 (14.0)	12 (8.5)	
Median (IQR)	4 (0–13)	4 (0–12)	
Respiratory infection	44 (38.3)	62 (43.7)	<0.01
Sepsis	27 (23.5)	29 (20.4)	<0.01
Genitourinary	10 (8.7)	19 (13.4)	<0.01
Skin, joint bone, soft tissue	11 (9.6)	14(9.9)	0.88
Infection of the central nervous system	9 (7.8)	10 (7.0)	0.68
Infection of cardiovascular system	4 (3.5)	6 (4.2)	0.28
Others	10 (8.6)	2 (1.4)	<0.01

Data are mean ± standard deviation, median (interquartile range, IQR), or number (%) of patients
Differences assessed by Fisher's exact or χ^2 test (categorical data), t test (continuous data) as appropriate
ASP, antimicrobial stewardship programme

Table 2

Types of interventions recommended by the antimicrobial stewardship programme team

Intervention	n (%)	Accepted, n (%)
De-escalation based on culture results	64 (36.4)	54 (84.4)
Discontinue antibiotic	53 (30.1)	41 (77.4)
Dose optimization	23 (13.1)	20 (87.0)
Intravenous-to-oral switch	32 (18.2)	21 (65.6)
Adding an antibiotic	4 (2.3)	2 (50.0)
Total	176 (100)	138 (78.4)

Antibiotic use

There were seven drugs in the drug use 90% segment selected for audit out of 21 drugs prescribed in the ICU (Figure 2). Overall utilization was reduced by 24.3% (87.3 DDD/100 beds *vs*. 66.1 DDD/100 beds; $P < 0.001$), specifically driven by third generation cephalosporins, carbapenems and fluroquinolones. Ceftriaxone use was reduced by 34.2% (18.4 DDD/100 beds *vs*. 12.1 DDD/100 beds; $P <$ 0001), piperacillin/tazobactam use decreased by 17.7% (12.4 DDD/100 beds *vs*. 10.2 DDD/100 beds; $P < 0.001$), and meropenem use decreased by 22.2 (10.8 DDD/100 *vs*. 8.4 DDD/100 beds; $P < 0.001$).

Clinical outcomes

The median (IQR) lengths of hospital stay before and after implementation of the ASP were 11 (3–21) days and 7 (4–19) days, respectively ($P < 0.01$). Also, there was a statistically significant difference in duration of therapy between the median (IQR) of pre-ASP group [8 (5–12) days] and the post-

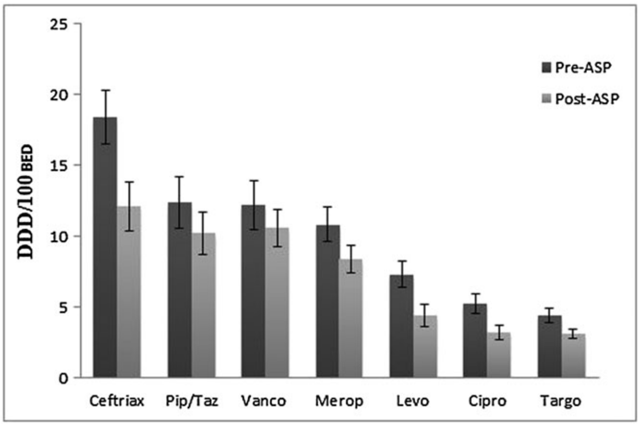

Figure 2

Antimicrobial use pre- and post-antimicrobial stewardship programme intervention

ASP group [5 (3–9) days; $P = 0.01$]. There was no significant difference in overall mortality between the pre-ASP group (31, 26.9%) and the post-ASP group (34, 23.9%; $P = 0.1$).

Regarding readmission, independent samples *t* test showed no significant differences between pre- and post-ASP (Table 3). Of the 84 surviving patients in the pre-ASP group 30 (26.1%) were re-admitted within 30 days of discharge and 17 (14.8%) were re-admitted within 60 days of discharge. Of the 108 surviving patients in the post-ASP, 35 (24.6%) were re-admitted within 30 days and 18 (12.7%) within 60 days of discharge ($P = 0.54$, $P = 0.28$ respectively).

Discussion

Little is known about the impact of implementing an ASP and monitoring of antimicrobial prescribing in Palestinian hospitals. Moreover, most drug related problems in hospitals are caused by anti-infective medications [18]. To the best of our knowledge this study was the first in West Bank to focus on the clinical impact of implementing ASP on patient clinical outcomes. One important core strategy of ASP, the prospective audit and feedback strategy will probably be the most widely implemented in view of its clear advantages particularly with regards to lack of opposition from prescribers [19]. One of the desirable targets of an ASP is to control inappropriate and overuse of broad spectrum antibiotics. It is estimated that 50% of antimicrobial use in hospitals is inappropriate [20]; our study confirms this number since 49.4% of antibiotic prescriptions were deemed to require intervention.

Consumption of restricted antibiotics was significantly reduced after implementation of ASP. Previous studies have shown that ASPs have consistently been effective in reducing prescriptions of restricted antibiotics [21–24]. Our study showed that consumption of all seven audited antimicrobials decreased due to ASP intervention. Ceftriaxone consumption was noticeably high at baseline and ASP intervention resulted in a significant decrease in its use. This may be attributed to the fact that approximately 40% of patients in the study suffered from respiratory diseases and chest infections. Based on local and international management standards on pneumonia, it is likely that the empirical therapy doctors selected was a cephalosporin [25, 26]. Other broad-spectrum antibiotics that had significant reductions in consumption include fluoroquinolones and carbapenems. Out of the five interventions evaluated in this study, de-escalation of antibiotic based on culture results antibiotic were the most commonly encountered, if no resistant organism (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* spp. or methicillin-resistant *Staphylococcus aureus*).

It was observed from this study that the ICU physicians were more likely to accept ASP interventions; however, approximately 22% of the ASP interventions were rejected by the physicians. The main reason for rejection is changing the antibiotic. This may be expected considering that many physicians have personal preferences with no clear reasons indicated. Another possible reason for rejection of the recommendation may be the fact that some of the cases developed complications. In such situations, physicians may opt to be cautious and reject ASP interventions that may deviate from their opinions. Moreover, physicians are not

Table 3

Outcomes: post-antimicrobial stewardship programme (ASP) period compared with pre-ASP period

Outcome	Pre-ASP period (*n* = 115)	After-ASP period (*n* = 142)	*P*-Value
Duration of therapy (days), median (IQR)[a]	8 (5–12)	5 (3–9)	0.01*
Length of stay (days), median (IQR)[a]	11 (3–21)	7 (4–19)	0.01*
30-day readmission[b]	30 (26.1)	35 (24.6)	0.54
60-day readmission[b]	17 (14.8)	18 (12.7)	0.28
30-day all-cause mortality[b]	31 (26.9)	34 (23.9)	0.10

[a]Mann–Whitney *U* test,
[b]Student *t* test,
*significant $P < 0.05$
IQR, interquartile range

keen to change antibiotics despite microbiology results suggesting that narrower-spectrum antibiotics can be prescribed, as the patients had responded to the initial empiric antibiotics.

It should be noted that our recommendations were made through written notes. On some occasions, the ICU team did not view the recommendations within the specified 48 h; therefore, the recommendations were no longer applicable and were considered a rejection. One consideration may be that direct face-to-face communication with the providers may have had a greater impact or acceptance. One of the more common interventions made by ASP was to switch to oral therapy intervention, which has two main benefits: first, it reduces the cost of treatment for the patients as it is less expensive than parenteral antibiotic; second, it has fewer incidences of catheter-related infections and may lead to a shorter hospital stay.

A decrease in both length of hospital stay and duration of therapy after implementation of the ASP was observed. However, the relationship between the decrease in hospital stay and the decrease in antimicrobial consumption is not clear. The study cannot distinguish if the decrease in antimicrobial consumption is caused by the shorter hospital stay or if ASP intervention resulted in better treatment and shorter hospitalization duration or duration of therapy. Many ASP studies have shown a reduction in hospital stay [27]. Many potential confounders affect the overall hospital stay and it is difficult to determine the impact of ASP precisely. Future research needs to focus on hospital stay as it appears to be an important measure of the impact of an ASP.

Regarding mortality and re-admissions, our findings are similar to most studies, which have demonstrated little to no impact of prospective audit and feedback ASPs on mortality [28–30] and 30-day readmission [29, 31]. This may be because of the large number of factors that may affect clinical response and outcomes. As ASPs continue to evolve, they may include some of the confounding factors such as resistance rate, drug costs, and total costs of care. Addition of those factors may allow for better characterization of the relationship between ASP and mortality and/or re-admissions.

The results of our study are in line with other programmes that studied the impact of ASP in critical care and showed that ASP interventions were associated with shorter duration of antibiotic therapy, less inappropriate antimicrobial use [32].

In general, ASPs studies have consistently shown a reduction in the average length of hospital stay, infection-related re-admissions and 14-day re-infection rate. By contrast, assessment of 30-day mortality has shown little or no difference [33]. The reason for such observation appears to be that many factors affect mortality (and length of hospitalization) while the effect of intervention by antimicrobial stewardship (i.e. shortened duration of therapy or choice of a narrower-spectrum antibiotic) appears negligible.

This study showed that ASP can be introduced successfully into hospitals in low- and middle-income countries with limited human resources, which never practiced stewardship before [34, 35]. Pharmacists would need to be trained in monitoring antibiotic use, and would be allowed time in partnership with other healthcare professionals according to the size of hospital [36].

The prospective audit and feedback methodology allows for a team-based approach to patient care with a focus on both individual patient outcomes and global hospital outcomes. Here, practitioners initiate therapy, and the ASP team intervenes only in select cases. These programmes address both over- and under-treatment. This method allows the ASP team to interact directly with prescribers to tailor specific antibiotic therapy for each patient.

Practitioners may be more receptive to the stewardship programme when suggestions are not only limited to a reduction of antibiotic usage but are also focused on optimal patient care [37].

Implementation of an ASP in a Palestinian hospital over a relatively short time achieved results that appear consistent with other publications in this field of science [33–36]. This finding is particularly interesting, considering that most hospitals do not have a clinical pharmacist with formal training in infectious diseases to provide antimicrobial consultation. Other practices that may improve antimicrobial use may include: implementation of antimicrobial guide with empiric treatment recommendations. Certainly, the addition of routine education programmes for health care professional may improve overall antimicrobial use and provide update on new treatment options.

Limitations

There are several limitations to our study. The study design pre- and postintervention is associated with a number of inherent limitations, including the potential for confounding bias.

The ASP study duration was 4 months; it is possible that this study duration is not long enough to characterize the full effect of ASP. In addition, the study attempted to provide accurate definitions for outcomes and potential confounders, yet misclassification bias may still affect the results. Finally, it is unclear how changes in antimicrobial consumption may affect resistance rates and clinical outcomes.

Competing Interests

There are no competing interests to declare.

The authors thank Dr Ahmad Bitawi, Head of the PMC for facilitating this study and use of their database.

Approval for the study was granted by Ethical research committee at the Palestinian Medical Complex Requirement for consent was waived because the data were analyzed anonymously.

Contributors

M.R.K., H.O.H. and M.G.S. jointly conceived designed and coordinate the study. M.R.K. and H.O.H. critically revised the manuscript for important intellectual content. M.A.N., A.A.D., M.B.K. and A.M.K. contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content. M.B.K. wrote code, ran the model and analysed output data. M.G.S. and H.O.H. edited the manuscript and provided conceptual advice. All authors read and approved the final manuscript.

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