Antibiotic stewardship team in a Tunisian university hospital: A four-year experience

Equipe mobile d'antibiothérapie dans un hôpital universitaire Tunisien: Une expérience de quatre ans

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Abstract

Background: Association between antibiotic use and antimicrobial resistance has been demonstrated in several studies; hence the importance of antibiotic stewardship programs (ASPs) to reduce the burden of this resistance.

Aim: To describe the antibiotic stewardship team (AST) interventions in a Tunisian university hospital.

Methods: a cross-sectional study was conducted in the infectious diseases department in Sousse-Tunisia between 2016 and 2020. Hospital and private practice doctors have been informed of the existence of an antibiotic stewardship team. Interventions consisted of some helps to antibiotic therapy (i.e.; prescription, change or discontinuation) and/or diagnosis (i.e.; further investigations).

Results: Two thousand five hundred and fourteen interventions were made including 2288 (91%) in hospitalized patients, 2152 (86%) in university hospitals and 1684 (67%) in medical wards. The most common intervention consisted of help to antibiotic therapy (80%). The main sites of infections were skin and soft tissues (28%) and urinary tract (14%). Infections were microbiologically documented in 36% of cases. The most frequently isolated microorganisms were Enterobactriaceae (41%). Antibiotic use restriction was made in 44% of cases including further investigations (16%), antibiotic de-escalation (11%), no antibiotic prescription (9%) and antibiotic discontinuation (8%). In cases where antibiotics have been changed (N=475), the intervention was associated with an overall decrease in the prescription of broad-spectrum antibiotics from 61% to 50% with a decrease in the prescription of third generation cephalosporins from 22% to 15%.

Conclusions: The majority of antibiotic stewardship team's interventions were made in hospitalized patients, university hospitals and medical wards. These interventions resulted in an overall and broad-spectrum antibiotic use reduction.

Key words: antimicrobial resistance, Enterobacteriaceae, antibiotic stewardship.

Résumé

Introduction: L'association entre l'usage des antibiotiques et la résistance bactérienne a été démontrée dans plusieurs études d'où l'importance des programmes de bon usage des antibiotiques pour réduire la fréquence de cette résistance.

Objectif: Décrire les interventions de l'équipe mobile d'antibiothérapie dans un hôpital universitaire Tunisien.

Méthodes: Une étude transversale a été réalisée au service de Maladies Infectieuses de Sousse-Tunisie entre 2016 et 2020. Les médecins hospitaliers et de libre pratique ont été informés de l'existence d'une équipe mobile d'antibiothérapie. Les interventions consistaient en l'aide à l'antibiothérapie (prescription, changement ou arrêt) et/ou au l'aide au diagnostic (demande d'examens complémentaires).

Résultats: Deux milles cinq cents quatorze interventions ont été faites incluant 2288 (91%) chez des patients hospitalisés, 2152 (86%) dans des hôpitaux universitaires et 1684 (67%) dans des services médicaux. L'intervention la plus fréquente était l'aide à l'antibiothérapie (80%). Les principaux sites d'infection étaient la peau et les tissus mous (28%) et l'appareil urinaire (14%). Les infections étaient documentées microbiologiquement dans 36% des cas. Les microorganismes les plus fréquemment isolés étaient les entérobactéries (41%). Une réduction de la prescription des antibiotiques a été réalisée dans 44% des cas incluant la demande d'examens complémentaires (16%), la désescalade antibiotique (11%), la non prescription d'antibiotiques (9%) et l'arrêt de l'antibiothérapie (8%). Dans les cas où l'antibiothérapie a été changée (N=475), l'intervention était associée à une diminution dans la prescription d'antibiotiques à large spectre de 61% à 50% avec une diminution dans la prescription de céphalosporines de troisième génération de 22% à 15%.

Conclusions: La majorité des interventions de l'équipe mobile d'antibiothérapie ont été faites chez des patients hospitalisés, dans des hôpitaux universitaires et dans des services médicaux. Ces interventions ont abouti à une réduction de la prescription globale des antibiotiques et de la prescription des antibiotiques à large spectre.

Mots-Clés : résistance bactérienne, Entérobactéries, bon usage des antibiotiques.

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INTRODUCTION

Emergence and diffusion of antimicrobial resistance (AMR) is a serious public health concern with a considerable human and economic cost worldwide (1). It is estimated that by 2050, continued rise in AMR would result in 10 million deaths in the world every year and would cost up to 100 trillion USD (1).

In Tunisia, which was the second largest consumer of antibiotics in the world in 2015 (2), the use of antibiotics has increased by 38% between 2005 and 2013 (3). During the last decade, the resistance rates of Escherichia coli have increased from 5% to 19% for the third-generation cephalosporins and from 14% to 25% for the fluoroquinolones; those of Klebsiella pneumoniae have increased from 27% to 43% for the third-generation cephalosporins and from 0% to 12% for imipenem, while the resistance rate of Enterococcus faecium to vancomycin has increased from 0% to 38% (4-6).

Association between antibiotic use and AMR has been demonstrated in several studies, hence the importance of ASPs to reduce the burden of AMR (7, 8). Antibiotic stewardship is defined as the systematic effort to increase appropriate use of antimicrobials (7). It has proven efficacy in improving patient outcomes, reducing both use and costs of care (7-10).

Since 2012, the World Health Organization and the Infectious Diseases Society of America have recommended implementing antibiotic stewardship programs in healthcare system, and many experiences have been reported in high, middle and low-income countries (11,12). In Tunisia, a national action plan against AMR, including antibiotic stewardship, has been developed since 2018 (13), but to the best of the authors' knowledge, no study on antibiotic stewardship has been published in Tunisia.

The aim of this study was to describe the antibiotic stewardship team interventions in a Tunisian university hospital.

METHODS

Study site

This study was conducted by the infectious diseases specialists of the department of Infectious Diseases at Farhat HACHED university hospital, Sousse, Tunisia. Tunisia is a developing upper/middle income North-African country (10), and Sousse is a central-eastern Tunisian city which contains two university hospitals, Farhat HACHED and Sahloul, seven private clinics, and 645 medical offices. Farhat HACHED is a 698-bed hospital with 13 medical departments, 4 surgical departments and 2 intensive care units (ICUs). Sahloul is a 632-bed hospital located 5 km from Farhat HACHED with 7 surgical departments, 6 medical departments and 2 ICUs.

Study design

A cross-sectional study was carried out to describe AST interventions between January 2016 and January 2020, before the emergence of COVID-19 epidemic in March 2020.

In our department, advices on antibiotic use have been given to other departments of the hospital since 2011 but this activity was not organized in AST. In January 2016, an AST consisting of an infectious diseases specialist and a postgraduate medial trainee, either an intern or a resident, has been implemented. The mission of AST was to help doctors to antibiotic therapy (prescription, change or discontinuation) and to diagnosis (further investigations), by phone call, bedside consultation or notes in patients' records.

Inclusion criteria: Interventions made in hospitals, private clinics and medical offices in Sousse were included in this study.

Non-inclusion criteria: Interventions made in the Emergency department and at the outpatient clinic were not included in this study because they were part of the department activities before implementation of AST.

Study protocol: Hospital and private practice doctors have been informed of the existence of AST. For each intervention, collected data were as follows: date of intervention, primary physician healthcare setting, ward, specialty and grade; communication of intervention (phone calls, bedside consultation or notes on patients' records), site and microbiological confirmation of infection, type of intervention (help to antibiotic therapy, help to diagnosis, antibiotic prophylaxis/chemoprophylaxis, or vaccination) and antibiotics received before and after intervention. Antibiotic use reduction was defined by any of the following interventions: no antibiotics, discontinuation of antibiotics, de-escalation (change to antibiotics with narrower spectrum) or further investigations. The study protocol is described in Figure 1.

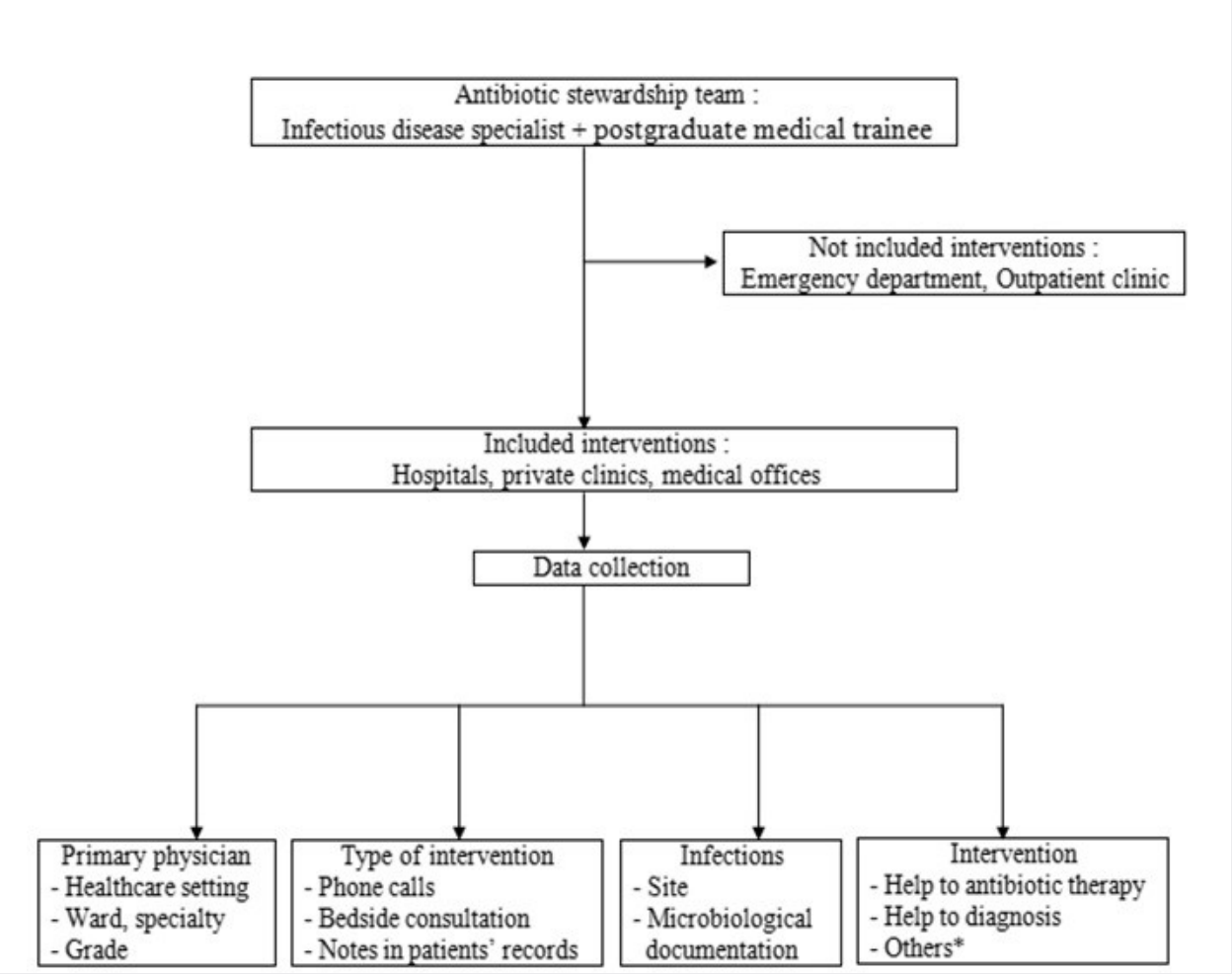

Figure 1. Study protocol. *antibiotic prophylaxis/ chemoprophylaxis, vaccination

Statistical study

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 10.0. All variables were categorical, therefore, they were expressed as percentages, and significance was tested by using the Chi-square test. A p value < 0.05 was considered to be statistically significant.

Ethical considerations: As the interventions of AST were expected to be either beneficial or not to change patients management, no study protocol has been submitted to the hospital Ethics Committee approval.

RESULTS

During the period study, two thousand five hundred and fourteen interventions were made by the AST. Baseline characteristics of the study are summarized in Figure 2. Two thousand two hundred and eighty eight interventions (91%) were made for hospitalized patients (inpatients). The mean number of interventions was 628 per year (620-654). Two thousand one hundred and fifty two interventions (86%) were made in university hospitals, including 1546 (61%) in Farhat HACHED hospital. Primary physicians' wards were medical in 1684 cases (67%), surgical in 729 cases (29%) and ICUs in 101 cases (4%). Twenty four specialties were involved, mainly endocrinology (10%). Primary physician was an attending doctor in 1299 cases (52%). Interventions were made via phone calls in 1109 cases (44%) and after patient bedside consultation in 815 cases (33%). Interventions of the AST consisted of help to antibiotic therapy in 2012 cases (80%) (Table1).

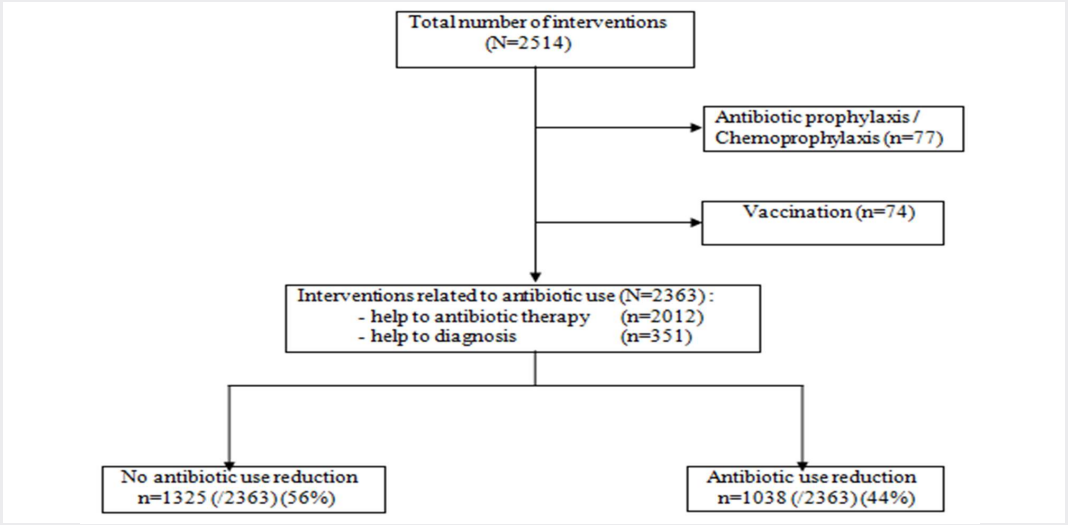

Figure 2. Baseline characteristics of the study.

Table 1. Primary physicians and interventions characteristics.

Characteristics	n (%)
Primary physician healthcare setting :	
Hospital (inpatients)	2288 (91)
Ambulatory (outpatients)	226 (9)
Primary physician healthcare setting :	
Tertiary (**university** hospital)	2152 (86)
Farhat HACHED hospital	1546 (61)
Sahloul hospital	493 (20)
Others	113 (5)
Private clinic / medical office	276 (11)
Secondary / primary	86 (3)
Primary physician specialty :	
Medical	1684 (67)
Surgical	729 (29)
Intensive care	101 (4)
Primary physician ward :	
Endocrinology	240 (10)
Otorhinolaryngology	180 (7)
Internal medicine	177 (7)
Carcinology	171 (7)
Dermatology	154 (6)
Rheumatology	134 (5)
Cardiology	126 (5)
Gynecology	122 (5)
Others	1210 (48)
Primary physician grade :	
Attending doctor	1299 (52)
Assistant professor	522 (21)
Associate professor / professor	381 (15)
General practitioner	282 (11)
Specialist	114 (5)
Postgraduate trainee	1215 (48)
Intern	825 (33)
Resident	390 (15)
Communication of the intervention :	
Phone calls	1109 (44)
Bedside consultation	815 (33)
Notes in patients' records	590 (23)
Type of the intervention :	
Help to antibiotic therapy	2012 (80)
Help to diagnosis	351 (14)
Antibiotic prophylaxis / chemoprophylaxis	77 (3)
Vaccination	74 (3)
Total	**2514 (100)**

When the intervention consisted of help to antibiotic therapy (N=2012), the main sites of infections were skin and soft tissues in 555 cases (28%), urinary tract in 277 cases (14%) (Table 2), and 719 infections (36%) were microbiologically documented including 582 (82%) bacterial infections. Among bacterial documented infections, the most isolated microorganisms were Enterobactriaceae (41%) (Table 2).

Table 2. Sites of infections and isolated microorganisms

Infections characteristics	n (%)
Sites of infection	2012 (100)
Skin and soft tissues	555 (28)
Urinary tract	277 (14)
Upper respiratory tract	159 (8)
Lower respiratory tract	159 (8)
Osteoarticular	159 (8)
Neuromeningeal	141 (7)
Gastrointestinal / hepatic	91 (4)
Brucellosis / tuberculosis	83 (4)
Others	388 (19)
Microbiologically confirmed infections	719 (100)
Bacterial	586 (82)
Enterobacteriaceae	296 (41)
Pseudomonas aeruginosa / Acinetobacter baumannii	91 (12)
Staphylococcus aureus	90 (12)
Streptococcus spp	21 (3)
Enterococcus spp	20 (3)
Others	68 (9)
Fungal	74 (10)
Viral	43 (6)
Parasitic	16 (2)

When AST intervention was help to antibiotic therapy or help to diagnosis (N=2363), it consisted of further investigations in 388 cases (16%), antibiotic de-escalation in 251 cases (11%), no antibiotic prescription in 212 cases (9%), and antibiotic discontinuation in 187 cases (8%). Thus, antibiotic use reduction was made in 1038 cases (44%) (Table 3).

Table 3. Interventions of the antibiotic stewardship team on antibiotic use.

Characteristics	n (%)
Antibiotic use reduction	1038 (44)
Further investigations	388 (16)
Antibiotic change / de-escalation	251 (11)
No antibiotic	212 (9)
Antibiotic discontinuation	187 (8)
No antibiotic use reduction	1325 (56)
Antibiotic prescription	605 (26)
Continuation of the same antibiotic	364 (15)
Antibiotic change / wider spectrum	190 (8)
Other anti infectious prescription	132 (6)
Antifungal	74 (3)
Antiviral	43 (2)
Antiparasitic	16 (1)
Antibiotic change / same spectrum	34 (1)

In cases where antibiotics have been changed (N=475), intervention of the AST was associated with an overall decrease in the prescription of broad-spectrum antibiotics from 61% to 50% (p=0,02), with a decrease in the prescription of third-generation cephalosporins from 22 to 15% (p=0,31) (Figure 3).

DISCUSSION

During the study period, 2514 interventions were made by AST. The majority of interventions were made in hospitalized patients (91%), university hospitals (86%) and medical wards (67%), while outpatients (9%), private clinics (11%), secondary/primary care settings (3%), surgical wards (29%) and ICUs (4%) were less frequently involved. The frequency of interventions in university hospitals especially Farhat HACHED hospital could be explained by their geographical proximity with AST members, but additional efforts should be undertaken to make more interventions in outpatients, secondary/primary care settings and private clinics. In a French study, university hospitals accounted for only 10% of the AST interventions, while non-university public hospitals and private clinics accounted for 52% and 38% of the interventions, respectively (14). Outpatient prescriptions comprise up to 60% of antibiotic use and an American study showed that 40% of outpatient antibiotic prescriptions were not indicated (15). This could be explained by demand from patients or their parents, uncertainty of diagnosis, delays in getting laboratory results and lack of guidelines (14-16).

Low involvement of surgical wards and especially of ICUs in AST interventions has been observed in several studies (17-20).

Surgeons, who are primary caregivers of operated patients, may believe their opinions should count more than infectious diseases specialists whose interventions could be perceived

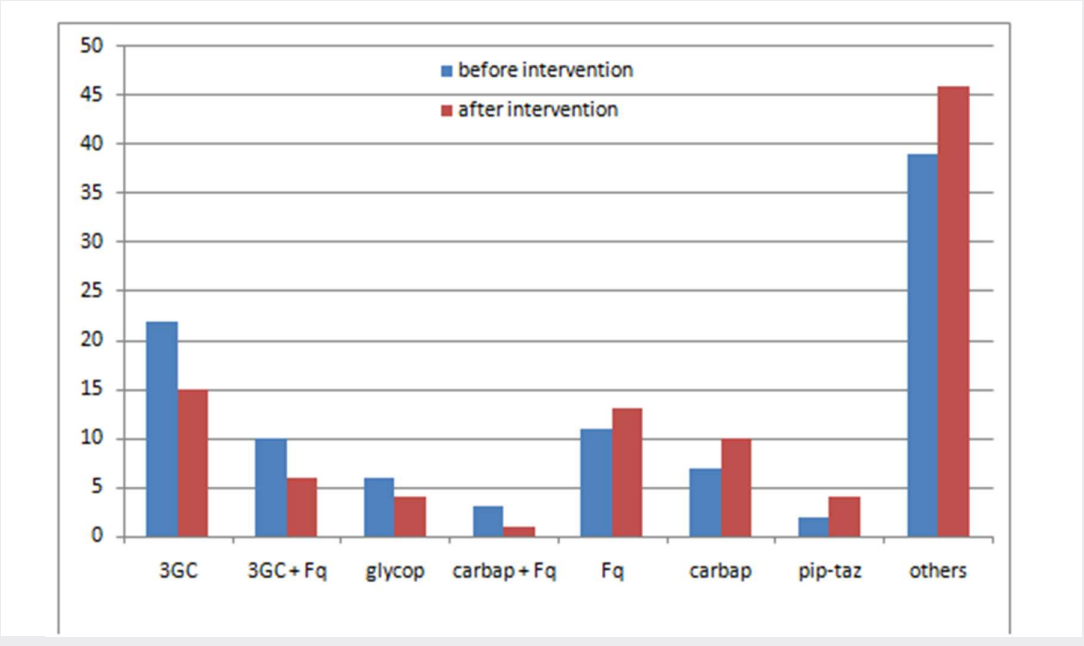

Figure 3. Changes in antibiotic prescriptions after the antibiotic stewardship team intenventions.
3GC: third generation cephalosporins, Fq: fluoro quinolones, glycop: ghycopeptides, carbap: carbapenems, pip-taz: piperacillin-tazobactam.

as only consultative (17,18). This could explain that surgeon compliance to antibiotic guidelines is low. However, the "Global Alliance for Infections in Surgery" (19) including experts from 87 countries worldwide has been recently founded to promote the rationale use of antimicrobials in surgical infections and showed that a surgeon was a component of AST in surgical departments in 59% of cases (19). Thus, a collaborative relationship based on education, mutual respect and willingness to compromise should be built between surgeons and other members of ASTs (19, 20).

In ICUs, over 70% of patients receive antibiotics (21). However, intervention of ASTs is limited because patients are critically ill, and broad-spectrum antibiotics are often prescribed empirically since shorter times to initiation of appropriate antibiotic therapy are associated with better outcomes (21). The best interventions to improve adherence to infectious diseases advices in ICUs are enabling interventions, while restrictive interventions are less effective (22-23).

In this study, most interventions were made with medical trainees (48%) and via phone calls (44%), while complex cases were discussed with attending doctors after patient bedside assessment and within multidisciplinary meeting.

Although the most common intervention of AST was help to antibiotic therapy (80%), help to diagnosis and preventive interventions (i.e. vaccination and chemoprophylaxis) were made in 20% of cases and could be developed more.

The most common sites of infections were skin and soft tissues (28%), urinary tract (14%), upper respiratory tract (URT) (8%), lower respiratory tract (LRT) (8%), osteoarticular (8%) and neuromeningeal (7%), while ocular, pelvic and intra abdominal infections accounted together for only less than 5% of interventions. Based on these findings, AST interventions should be either consolidated or reinforced depending on the implications of different settings.

Among microbiologically documented infections (36%), Enterobactriaceae (41%) were the most commonly isolated followed by Pseudomonas aeruginosa /Acinetobacter baumannii (12%) and Staphylococcus aureus (12%). Gram negative bacilli were mainly isolated in urinary tract infections and Staphylococcus aureus in skin and soft tissue infections. By providing susceptibility testing of the isolated microorganism, the Microbiology laboratory played a key role in decreasing time to appropriate antibiotic therapy and consequently improving patient outcome (24). Fungal infections were not rare since they accounted for 10% of documented infections, which was underestimated since invasive fungal infections which occured mainly in Hematology and ICUs were most often managed by primary physicians without AST intervention. Antifungal stewardship should be reinforced since it has proven efficacy in limiting safely antifungal consumption and prescription of advanced antifungal agents such as B echinocandins, then reducing costs of care (25,26).

In this study, AST interventions resulted in antibiotic use reduction including antibiotic discontinuation or de-escalation in almost half of cases (44%). For wide spectrum antibiotics, an overall decrease from 61 to 50% has been noted. This decrease concerned mainly third-generation cephalosporins and third- generation cephalosporin - fluoroquinolone combination prescription while an increase in fluoroquinolones and carbapenems prescription has been noted. The prescription of wider spectrum antibiotics should improve the outcome in patients with severe infections or documented infections with multidrug resistant organisms.

Several studies have demonstrated that implementation of ASPs in care settings shortened length of stay, improved appropriate use of antibiotics and reduced overall antibiotic prescribing and prescription of broad spectrum antibiotics such as third-generation cephalosporins, fluoroquinolones and carbapenems (27-32).

This study is a pilot Tunisian study which provided data based on a high number of interventions during a long period of time. However, it has some limitations. It was a monocentric study, most interventions were limited to the two university hospitals of the region, the application of AST interventions by primary care physicians was not followed and the impact of interventions on antibiotic resistance, mortality or cost of care was not measured. More efforts including educational meetings and implementation of multidisciplinary practice guidelines should be made to improve the impact of AST interventions.

CONCLUSION

The present study reported that the majority of AST interventions were made in hospitalized patients, university hospitals and medical wards. These interventions resulted in an overall and broad-spectrum antibiotic use reduction, but their impact on antibiotic resistance, mortality or cost of care was not measured. To contribute to the national ASP, more efforts should be made to reinforce AST interventions in secondary/primary care settings, outpatients, surgical wards and ICUs.

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