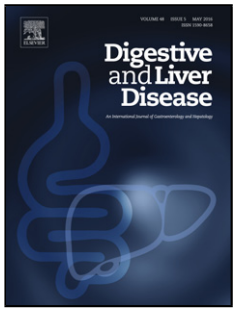

Title: Antimicrobial Stewardship in a Gastroenterology Department: Impact on Antimicrobial Consumption, Antimicrobial Resistance and Clinical Outcome

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TITLE PAGE

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Key Words: Antimicrobial stewardship, Gastroenterology, MDR-microorganisms, carbapenems, antifungals

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ABSTRACT

Background. A major cause of the increase in antimicrobial resistance is the inappropriate use of antimicrobials.

Aims. To evaluate the impact on antimicrobial consumption and clinical outcome of an antimicrobial stewardship program in an Italian Gastroenterology Department.

Methods. Between October 2014 and September 2015 (period B), a specialist in infectious diseases (ID) controlled all antimicrobial prescriptions and decided about the therapy in agreement with gastroenterologists. The defined daily doses of antimicrobials (DDDs), incidence of MDR-infections, mean length of stay and overall in-hospital mortality rate were compared with those of the same period in the previous 12-months (period A).

Results. During period B, the ID specialist performed 304 consultations: antimicrobials were continued in 44.4% of the cases, discontinued in 13.8%, not recommended in 12.1%, de-escalated 9.9%, escalated in 7.9%, and started in 4.0%. Comparing the 2 periods, we observed a decreased of antibiotics consumption (from 109.81 to 78.45 DDDs/100 patient-days, p=0.0005), antifungals (from 41.28 to 24.75 DDDs/100pd, p=0.0004), carbapenems (from 15.99 to 6.80 DDDsx100pd, p=0.0032), quinolones (from 35.79 to 17.82 DDDsx100pd, p=0.0079). No differences were observed in incidence of MDR-infections, length of hospital stay (LOS), and mortality rate.

Conclusions. ASP program had a positive impact on reducing the consumption of antimicrobials, without an increase in LOS and mortality.

Antimicrobial Stewardship in a Gastroenterology Department: Impact on Antimicrobial Consumption, Antimicrobial Resistance and Clinical Outcome

BACKGROUND

Infections caused by multidrug-resistant (MDR) microorganisms are difficult to treat, leading to significant mortality and morbidity, prolonged length of hospital stay, and excessive costs. The rise of antimicrobial resistance with a diminishing antibiotic pipeline poses a serious threat worldwide, especially concerning gram-negative microbes [1]. The overuse or misuse of antimicrobial agents is the vital component in the emergence and spread of MDR microorganisms. Unfortunately, Italy has a long tradition of widespread use of antibiotics and a high incidence of MDR microorganisms [2,3]. Antimicrobial stewardship programs (ASP) have been advocated by many to extend the life expectancy of the antimicrobial armamentarium. To date, there is growing evidence demonstrating the benefits of stewardship, including reductions of antimicrobial usage and costs [4-6]. During the past decades, the use of broad-spectrum antimicrobials in Gastroenterology Departments increased, particularly among patients with cirrhosis and spontaneous bacterial peritonitis (SBP). Bacterial infection is present in 32%-34% of hospitalized patients with cirrhosis, which is 4 to 5 fold higher than hospitalized patients in general, and it accounts for about 30%-50% of deaths [7-9]. Common types of infections in patients with cirrhosis include SBP (25%-31%), urinary tract infection (UTI) (20%-25%), pneumonia (15%-21%), bacteremia (12%), and soft tissue infection (11%)[10-12]. The major causative organisms are gram-negative bacteria, e.g., *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., whereas gram-positive bacteria comprise about 20%, and anaerobes only 3%[10]. In a large prospective study of cirrhotic patients with infections, multi-drug resistant (MDR) bacteria were isolated in 4%, 14%, and 35% of community-acquired,

healthcare-associated, and nosocomial infections, respectively (P < 0.001) [13]. The main resistant organisms were extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, followed by *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and *Enterococcus faecium*[13]. There was a significantly higher incidence of septic shock and death from infections caused by resistant bacteria. Notably, the efficacy of empirical antibiotic treatment was decreased in nosocomial infections (40%), compared to community-acquired and healthcare-associated episodes (83% and 73%, respectively; P<0.0001), especially in SBP, UTI, and pneumonia (26%, 29% and 44%, respectively) [13]. Infectious diseases (ID) consultation has an important role in reducing inappropriate antimicrobial use [14-16]. To target this, an antimicrobial stewardship program (ASP) has been implemented at the Gastroenterology Department of the University Hospital of Modena, Italy. The ASP was based on case-audits: an ID specialist, member of the antimicrobial stewardship group, visited the Gastroenterology Department twice a week and controlled all antimicrobial prescriptions, finally deciding about the therapy in agreement with gastroenterologists. This department had a very high consumption of carbapenems (up 30 DDDs x100pd) in the recent years. Aims of this study were to evaluate the impact of the ASP on antimicrobial consumption, incidence of MDR micro-organisms infections and clinical outcome.

METHODS

This was an observational prospective study evaluating, after 12 months of intervention, the impact of newly implemented procedure (ASP) at the Gastroenterology Department of the University Hospital of Modena, Italy. Data for comparison with an historic cohort, were collected retrospectively from the hospital's data warehouse. The antimicrobial stewardship group is multi-disciplinary, consisting of clinical microbiologists, infectious disease (ID) physicians, and hospital pharmacists. The group reports to the hospital's

Antimicrobial Committee and Infection Prevention Committee, which have a mandate from the board of directors to implement and run the ASP. An ID specialist, member of the antimicrobial stewardship group, visited the ward twice a week, generally on Tuesday and on Friday, and discussed antimicrobial therapy bed-side with the treating physicians, face-to-face. During the case-audit, the therapy was discussed and the available diagnostics were reviewed. Using the expertise and experience of both the ID specialist and the ward physician, a decision on the antimicrobial therapy was made.

Final decisions were always based on local guidelines for antimicrobial therapy, which in turn are based on national and IDSA guidelines, and on rates of local resistance to antimicrobials.

Inclusion of patients in the ASP was done by a specialist in ID who controlled all therapies twice a week: all in-patients who received one or more antimicrobials at the time of the visit were included in the study. Patients' antimicrobial consumption was measured in defined daily doses (DDDs) per 100 patient days (DDDs/100pd), as stated by the WHO [17].

We evaluated and described the reasons for antimicrobial prescription. For diagnosis of pneumonia we considered the presence of respiratory symptoms (with or without fever) with $\geq$1 opacity on the chest radiographs; the presence of >250 polymorphonuclear leukocytes (PMN)/mm^3 in the ascitic fluid is used to define spontaneous bacterial periotonitis (SBP); cholangitis was suspected in any patient who appears septic, jaundiced, or who have abdominal pain, associated with an obstruction of the biliary tree. For the diagnosis of urinary tract infections (UTIs) and bloodstream infections, we considered the isolation of a bacteria/fungus from urine or blood culture in presence of symptoms compatible with the clinical syndrome. For cirrhotic patients, the presence of fever was not an essential criterion for infection.

We compared the DDDs of antimicrobials, the incidence of infections caused by MDR-

microorganisms, the mean length of stay and the overall in-hospital mortality rate with those of the patients admitted in the same Department during the previous 12-months (1 October 2013-30 September 2014, period A). We considered the following multidrug resistant (MDR)-microorganisms (using the criteria suggested by European Committee on Antimicrobial Susceptibility Testing – EUCAST) [18]: *Escherichia coli* ESBL-producing strain (MICs for cefotaxime >2 μg/ml), methicillin-resistant *Staphylococcus aureus* (MRSA; MICs for oxacillin ≥ 4 μg/ml), vancomycin-resistant *Enterococcus spp.* (VRE; MICs for vancomycin ≥ 4 μg/ml) and carbapenem-resistant bacteria (CRB; MICs for meropenem > 8 μg/ml).

Statistical Analysis. Analysis was performed by using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). The comparison between the incidence rate of the infections caused by MDR-bacteria was performed by a two-sample test of proportions. For antibiotic consumption of the total Department, including patients without intervention(s), monthly DDDs were grouped in pre-intervention and during intervention periods. Pooled median DDDs were compared between periods using Wilcoxon (Mann-Whitney) U-test. Univariate linear regression analyses were performed to assess means and slopes of variations of DDDs during pre- and during intervention. Significance threshold was set for a $p<0.05$. Analysis was performed by using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA).

RESULTS

Between October 2014 and September 2015, 784 patients were admitted to the Gastroenterology Department of the University Hospital of Modena, Italy. During this period (period B), 176 (22.4%) patients received at least one ID consultation and have been enrolled in the study. Overall, 304 ID consultations were performed. Sixty-one percent of the patients were males and the mean age was 63 years (range: 19-95 years). Case-audits took on average between 10 and 15 minutes, including administration time.

Demographic characteristics of the patients, underlying diseases and type of infection are shown in the Table 1. The most common infections were pneumonia (24.43%), bloodstream infection (BSI; 18.75%) and cholangitis or cholecystitis (17.04%). Thirty-two (18.18%) patients received antimicrobials without a proven infection (11 patients for pancreatitis, 8 for prophylaxis after variceal bleeding and 13 for encephalopathy in cirrhosis).

ID consultations. During period B, the ID specialist performed 304 consultations for 176 patients (Figure 1): the antimicrobial prescription was unchanged in 135 cases (44.4%), interrupted in 42 (13.8%), not recommended in 37 (12.1%), de-escalated in 30 (9.9%), escalated in 24 (7.9%), and started in 12 (4.0%). In 13 cases (4.3%) the dosage of antimicrobials was corrected and in another 11 cases (3.6%) the class of antimicrobials was changed. In the 98.02% of the cases, the ID consultant and the medical team of the department found an agreement on antimicrobial therapy to be prescribed.

Antimicrobial consumption. During period B, there was an overall significantly decrease of antibiotics from 109.81 to 78.45 DDDs per 100 patient-days, p=0.0005, and antifungals from 41.28 to 24.75 DDDsx100pd, p=0.0004. The greatest impact of the ASP was observed on carbapenems (Figure 2), which decreased from 15.99 to 6.80 DDDs/100pd (p=0.0032), and quinolones, which decreased from 35.79 to 17.82 DDDs/100pd (p=0.0079). Also the overall consumption of glycopeptides and echinocandins decreased (Table 2), but not significantly (p=0.193 and p=0.440, respectively). This reduction in broad-spectrum antibiotic use was accompanied by a slight increase in the consumption of penicillins (from 44.29 to 47.75 DDDs/100pd, p=0.729), but not of other antibiotics as aminoglycosides, macrolides, linezolid, daptomycine and tigecycline (data not shown). Third and fourth generation cephalosprins moderately decreased from 13.46 to 12.60 DDDs/100pd, p=0.488.

Infections, LOS and mortality rate. Table 2 shows the clinical, microbiological and

pharmacological data of the patients admitted to the Gastroenterology Department during the Period A (October 2013-September 2014) and the Period B (October 2014-September 2015) of the study. No significant differences were evidenced in the number of admissions, LOS and in-hospital mortality rate. It should be noted that all patients who had an infectious cause of death (12/176, 6.81%) were performing an antibiotic therapy effective on the basis of the microbiological isolates. Furthermore, we observed that, in comparison with non cirrhotic patients, individuals with liver cirrhosis (90/176, 51.13%) had higher mortality rate due to infectious causes (2.32% and 11.11%, respectively; $p<0.033$), and a higher LOS (16.51 and 20.88 days, respectively; p: n.s.). In the 50.0% of the cases, the death for bacterial infections occurred, in cirrhotic patients, within 15 days after infection. It is noteworthy, however, that the incidence of MDR bacteria infections decreases after the implementation of ASP, but without reaching a statistical significance. Only the incidence of *K. pneumonia* carbapenem-resistant moderately increased (p=0.823).

DISCUSSION

ID services play an important role in improving antimicrobial use by providing expert advice on the appropriate use of antimicrobial agents, education to prescribers, and developing and implementing evidence-based guidelines. It was suggested that consultation with an ID specialist is one of the six clinical strategies to reduce inadequate antimicrobial treatment in the hospital setting [19]. Many studies demonstrated improved patient outcomes when ID physicians were involved in the care of patients with bacteraemia, with the advantage of reducing morbidity, mortality, and cost of care [14]. Indeed, a previous study from our institution showed that ID consultation led to cost reduction by advising less expensive antibiotics and reducing third- and fourth-generation cephalosporins, piperacillin/tazobactam, teicoplanin, and parenteral quinolones [20]. To our knowledge, this is the first study on antimicrobial stewardship in a Gastroenterology

Department. Our data demonstrate important results. First, antimicrobial therapy was changed in 21.4%, discontinued completely in 13.8%, and not recommended in 12.1% of cases. Similarly, in a Urology Department in Netherlands, the therapy was changed in 37.7% and discontinued in 23.7% of patients [21], and in a Turkish hospital the therapy was changed in 57.4% of patients and antibiotics were not necessary for 9.8% [22]. This finding is consistent with previous studies where the use of antimicrobial therapy was judged to be inappropriate or required change. In a study by Yinnon et al [23] there was a change of therapy or discontinuation of antibiotics in 46%. Other studies found that 41–66% of antibiotic was changed after ID consultation [24,25].

Second, the ASP had a positive impact on the consumption of antibiotics and antifungals, especially as regards carbapenems, quinolones, glycopeptides and echinocandins. One of the main reasons why we selected the Gastroenterology Department forthe ASP was that it had a very high consumption of carbapenems (up 30 DDDs /100pd) during the past years. This was mainly due to the fact that since 2011 an increase of infection and colonization rates of ESBL-positive Enterobacteriaceae was observed in our hospital and the first-line empirical treatment in cirrhotic patients with sepsis or PBS was changed from ceftriaxone to meropenem. Therefore, the ASP was focused especially in reducing the carbapenems and quinolones consumption. An important result of our study is that the reduction in broad-spectrum antibiotic consumption was not associated with an increase in LOS and, in mortality rate. Moreover, the incidence of MDR bacterial infections decreased during the ASP implementation period, even if it did not reach statistical significance. This could indicate that a reduction in the use of broad-spectrum antibiotics may have contributed a lower selection of MDR bacteria.

Objective of the case-audit was to reach a consensus-based agreement between the ID specialist and the physician at the ward, using (local) guidelines, available diagnostics and the expertise and experience of both physicians. This should optimize antimicrobial

treatment. The case-audit focused on the improvement of patient care through relatively easy to achieve improvements after a few days of therapy, such as early de-escalation of antimicrobial therapy and stop when there was no longer an indication. Furthermore, the face-to-face case-audit on the ward provided an extra opportunity for questions about appropriateness of therapy and requesting additional consultations for other patients on the ward.

Our study confirms that cirrhosis is one of the main reasons for admission in Gastroenterology Department. The patients with cirrhosis accounted for the 51.13% of the study population and resulted to have a higher LOS and in-hospital mortality rate. Arvaniti *et al.* demonstrated that bacterial infections in cirrhosis are associated with poorer outcome and that mortality increased about 4 fold [26]. Both short- and long-term mortality rates of sepsis in cirrhotic patients are very high; 26%-44% of patients die within 1 month after infection and another 33% die in 1 year [26,27]. Also we observed a poorer outcome in the patients with cirrhosis and bacterial infections, and despite an effective antimicrobial treatment, 50.0% of these patients died within 15 days after infection. Factors that must to be taken into account as predictors of death during or following infection are: advanced liver disease, nosocomial origin, gastrointestinal haemorrhage, encephalopathy, liver cancer, presence of shock and organ failure (especially renal failure) [26,27].

Our study has some limitations. Effects of ASP were evaluated for a Gastroenterology Department in a single academic setting and it does not allow general considerations. Nevertheless, we think that in the absence of any data even a study conducted on a single Gastroenterology department could give important information. Moreover, a Gastroenterology department due to the severity of its case mix and the peculiarity of cirrhotic patients could represent a good example of how ASP could be implemented also in setting treating more complicated patients.

Another important limitation was that the comparison of LOS and the mortality rate in the 2

periods of the study considered all the patients admitted to the department during the period A and the period B, and not only the patients that received or needed antimicrobial treatment. Finally, we did not perform a cost benefit analysis.

In conclusion, ASP interventions are beneficial without showing any negative impact on survival by reducing the use of broad-spectrum antibiotics and for this reason it should be promoted throughout the hospital departments.

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Characteristics	N (%) 176 (100)
Sex - Male - Female	 108 (61.4) 68 (38.6)
Age (mean; min-max)	63 years (19-95)
Underlying diseases - Cirrhosis - Gallstones - HCC - Pancreatitis - Liver transplant - IBD/diverticulitis? - Neoplasia (different by HCC) - Other	 90 (51.13) 34 (19.31) 22 (12.50) 11 (6.3) 10 (5.68) 13 (7.38) 13 (7.38) 8 (4.5)
Type of infection - Pneumonia - BSI - Cholangitis/cholecystitis - UTI - Peritonitis - Others - More infections - None • Encephalopathy in cirrhosis • Pancreatitis	 43 (24.43) 33 (18.75) 30 (17.04) 28 (15.90) 18 (10.22) 20 (11.36) 37 (21.02) 32 (18.18) 13 (7.38) 11 (6.25) 8 (4.54)

• Prophylaxis for variceal bledding	

Table 1. Demographic characteristics, underlying diseases and type of infection of the 176 patients admitted to the Gastroenterology Department at the University Hospital of Modena that received at least 1 ID consultation between October 2014 and September 2015.

	Period A Oct 2013-Sep 2014	Period B Oct 2014- Sep 2015	P
Admissions	761	784	-
Bed-occupation rate (%)	109%	118 %	
Patients evaluated by ID specialist for the ASP* (%)	0 (0.0)	176 (22.44)	-
Days of hospitalization	5298	5502	-
Length of stay (mean in days)	7.11	7.01	-
Infections due to MDR-microorganisms: **N; incidence (episodes /100 admissions), (95%CI)**			
- MRSA**	7; 0.92 (0.37–1.89)	3; 0.89 (0.36–1.84)	0.204
- *E. coli* ESBL+	20; 2.63 (1.60-4.06)	13; 1.66 (0.88–2.83)	0.196
- CRB***	13; 1.71 (0.91–2.92)	9; 1.14 (0.52–2.17)	0.359
i. K. pneumoniae KPC+	6; 0.79 (0.29–1.71)	7; 0.89 (0.36–1.84)	0.823
ii. P. aeruginosa Carba+	4; 0.52 (0.14–1.34)	1; 0.12 (0.003–0.71)	n.a.
iii. A. baumannii Carba+	3; 0.39 (0.08–1.15)	1; 0.12 (0.003–0.71)	n.a.
- VRE****	11; 1.44 (0.72–2.58)	9; 1.14 (0.52–2.17)	0.608
Deaths (mortality rate %)	23 (3.0)	26 (3.31)	0.742
DDDs /100pd of antibiotics	109.81	78.45	**0.0005**
- All penicillins	44.29	47.75	0.729
- 3rd -4th G Cephalosporin	13.46	12.6	0.488
- Carbapenems	15.99	6.80	**0.0032**
- Quinolones	35.79	17.82	**0.0079**
- Glycopeptides	17.15	9.09	0.193
DDDs /100pd of antifungals	41.28	24.75	**0.0004**
- echinocandins	2.84	1.66	0.440

Table 2. Clinical, microbiological and antimicrobial consumption data of patients admitted to the Gastroenterology Department in Period A (October 2013-September 2014) and Period B (October 2014-

September 2015). *ASP: Antimicrobial Stewardship Program **MRSA: *methicillin-resistant S: aureus*; ***CRB: carbapenem-resistant bacteria; ****VRE: vancomycin-resistant *Enterococcus* spp.

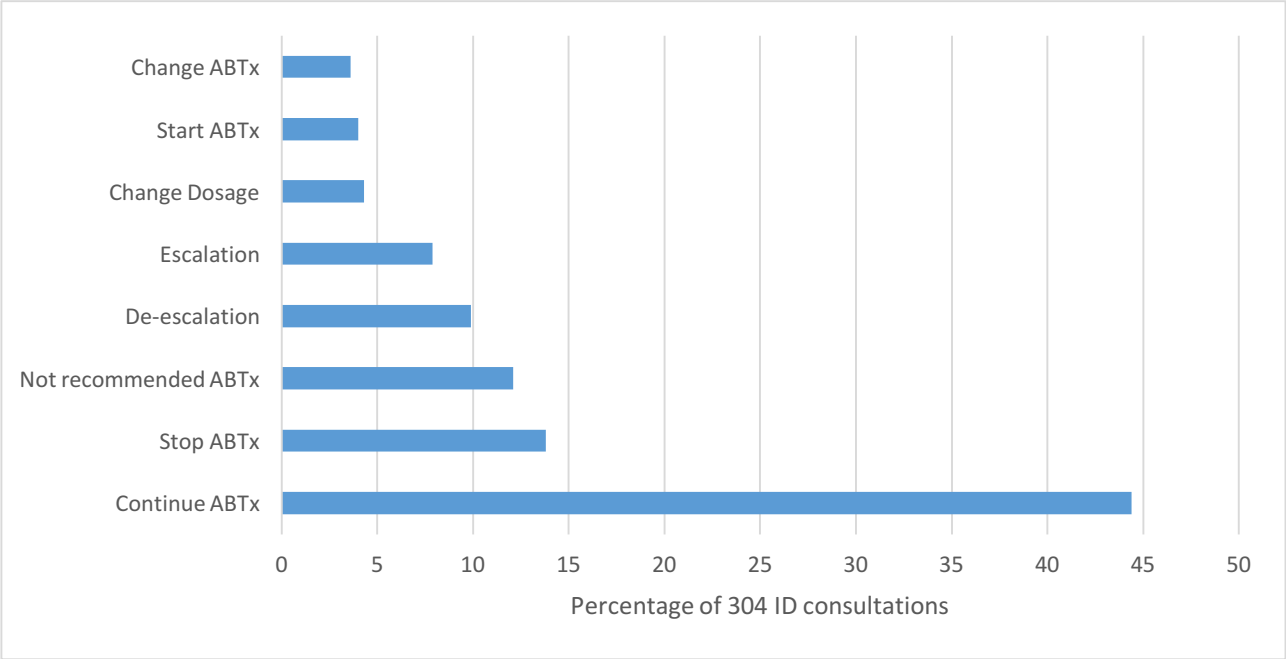

Figure 1. Advice of the ID specialist about antimicrobial treatment for the 176 patients admitted to the Gastroenterology department between October 2014 and September 2015 (ABTx: antimicrobial treatment).

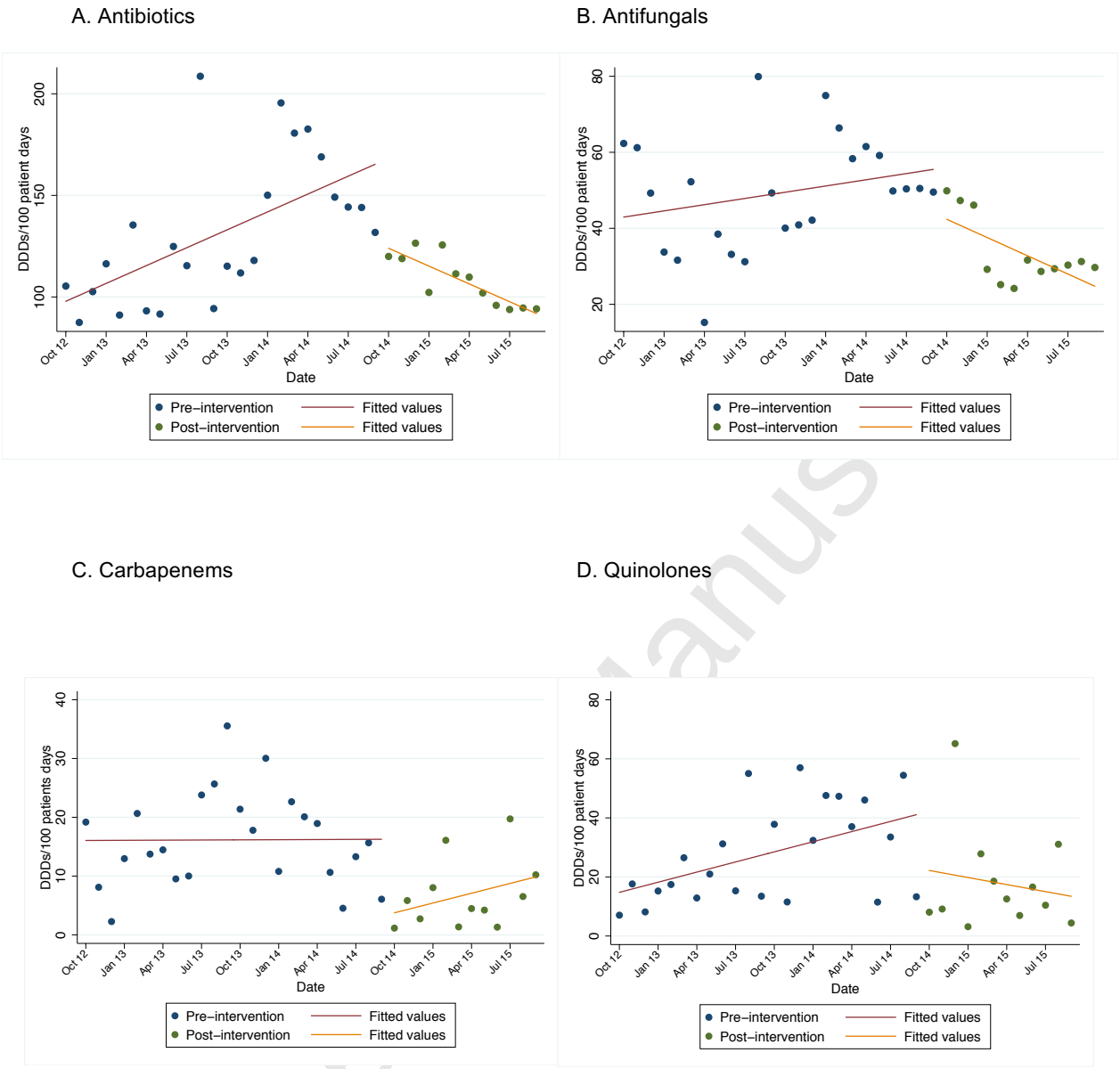

FIGURE 2. Antimicrobial Stewardship Program (ASP) effects on the antibiotic and antifungal consumption at the Gastroenterology Department between October 2014 and September 2015 in comparison with the previous 24 months, analyzed using univariate linear regression models.(A. All antibiotics; B. All antifungals; C. Carbapenems; D. Quinolones).