

Impact of daily versus weekly service of infectious diseases consultation on hospital antimicrobial consumption: a retrospective study

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Abstract

Background: To verify whether daily service of Infectious Diseases consultation (ID-cons) is more effective than weekly service in reducing antibiotic (ABT) consumption without worsening of clinical outcomes.

Methods: Two-years observational analysis of all the ID-cons provided in a hospital in Milan. ID-cons resulted in: start-of-ABT; no-ABT; confirmation; modification-of-ABT. We evaluated the impact of weekly (09/2016-09/2017) versus daily (10/2017-10/2018) service of ID-cons on: time-from-admission-to-first-ID-cons, type of ABT-intervention and number-of-ID-cons per 100 bed days (bd). Primary outcomes: (i) reduction of overall hospital ABT consumption and (ii) reduction of ABT consumption by department and by ABT classes expressed as defined-daily-dose (DDD)/100bd (by Wilcoxon test for paired data). Secondary outcome: no significant increment of overall and sepsis-related in-hospital mortality (as death/patient's admissions) from 2017 to 2018.

Results: Overall 2552 ID-cons in 1111 patients (2.3 ID-cons/patient) were performed (18.6% weekly vs 81.4% daily). No differences in patient's characteristics were observed. In daily-service, compared to weekly, patients were seen by the ID-consultant earlier (time-from-admission-to-ID-cons: 6 days (IQR 2-13) vs 10 days (IQR 6-19), $p < 0.0001$) and ABT was more often started by the ID-consultant (Start-of-ABT: 11.6% vs 8%, $p = 0.02$). After switch to daily service, the number-of-ID-cons increased from 0.4/100bd to 1.5/100bd ($p = 0.01$), with the greatest increase in the emergency department (1.5/100bd vs 6.7/100bd, $p < 0.0001$). Total ABT consumption decreased from 62.1 to 59.3 DDD/100bd, $p = 0.02$. As for the number-of-cons, the consumption of ABT decreased mainly in the emergency area. According to ABT classes, glycopeptides consumption has been reduced from 3.1 to 2.1 DDD/100bd ($p = 0.02$) while carbapenem use decreased from 3.7 to 3.1 DDD/100bd ($p = 0.07$). No changes in overall-mortality (5.2% vs 5.2%) and sepsis-related mortality (19.3% vs 20.9%; $p = 0.7$) were observed among the two time-period.

Conclusions: Daily-ID-cons resulted in a more comprehensive taking charge of the infected patient by the ID-consultant, especially in the emergency area where we also observed the highest rate of reduction of ABT-usage. No change in mortality was observed.

Introduction

The development and spread of multidrug-resistant bacteria (MDR) is mainly due to misuse/overuse of antimicrobials and to the lack of effective infection control measures [1]. Antimicrobial resistance (AMR) leads to infections more difficult to treat and therefore to an increased number of inappropriate antimicrobial prescriptions [2]. AMR and consequent inappropriate antimicrobial therapy increase morbidity, duration of hospital stay and mortality [3–5]. Marquet et al., in a meta-analysis, have reported increased 30-day and in-hospital mortality in patients receiving inappropriate therapy. Other studies found better patient related outcomes, such as reduced thirty-day mortality and duration of hospital stay, when appropriate antimicrobial therapy was prescribed [6–10]. Given the impact of adequate antibiotic

treatment on patient's outcome, the infectious diseases specialist represents an added value, as suggested by several studies showing the positive effect of infectious diseases consultation [11–15].

Aim of the study is to verify whether a daily service of Infectious Diseases consultation (ID-cons) is more effective than a weekly service in reducing antibiotic consumption without worsening of clinical outcomes.

Methods

Design and study setting

The study consists in a two-years retrospective observational analysis of all the ID-cons provided in a large tertiary hospital in Milan, Italy. San Carlo Borromeo Hospital (HSC) is a non-teaching public hospital with 494 beds and 20,000 admissions/years. HSC does not contain a transplant or haematology-oncology unit but does have a neurosurgery unit. Thus, possible source and aetiology of infections might account for these characteristics. Additionally, HSC does not have an ID-unit but rather a consult service that is staffed by ID-specialists from the Unit of Infectious Diseases of San Paolo Hospital since 2016.

Infectious Diseases consultations were provided once a week from September 2016 to September 2017 (weekly ID-cons period) while from October 2017 the service of ID-consultation was provided on a daily basis (daily ID-cons period). All the ID-cons were performed by the same team of ID-consultants. ID-cons is defined as any request by the treating non-ID physician for ID advice with bed-side evaluation of the patient resulting in a written statement by the ID consultant.

This observational analysis received approval by our local Ethics committee (Comitato Etico Milano Area 1) in 01/17/2019 with number of protocol: 57183/2018. Written informed consent was obtained for enrolled patients.

Study procedures and definitions

We collected in a dedicated database demographics, clinical conditions and microbiological findings of all the hospitalized patients for whom an ID consultation was asked, from September 1st, 2016 to October 31st, 2018. Patients' medical histories and mortality were reviewed by clinical charts to identify risk factors of infections (alcoholism, radio-chemotherapy, use of steroids, injection drug use), and comorbidities (cardio-vascular disease, dementia, liver cirrhosis, cancer, chronic obstructive pulmonary disease, chronic renal failure, diabetes, HCV). Comorbidities were evaluated according to the Age-adjusted Charlson Comorbidity Index (ACCI), a validate prognostic tool that predict the risk of death of patients with several comorbidities [16].

Hospital Units were grouped into three departments:

- Medical Department, which includes: Cardiology, Gastroenterology, Internal Medicine Units, Oncology, Nephrology, Neurology, Pulmonary, Psychiatry and Rehabilitation Unit;

- Surgical Department: General Surgery, Neurosurgery, Obstetrics/gynecology, Orthopedic Unit, Urology and Vascular Surgery;
- Emergency Department: Coronary Unit, Intensive and Sub-intensive Units, Emergency Rooms, Emergency Medicine Unit and Stroke Unit.

Infections were classified as: 1) healthcare-associated infections (HAI), in case of infections associated with hospitalization or other medical treatment that appear 48 h or more after hospital admission; 2) community-acquired infections (CAI), in case of patients admitted for an infection acquired before hospitals' admission [17]. Classification of an infection into one of the two groups, HAI or CAI, was made by the ID consultant by combining clinical presentation with radiological and microbiological findings.

At each consultation all the antimicrobial therapies were reviewed and discussed with the treating physician. Interventions on antibiotic therapies were collected into the database according to the following classification: start of ABT, no need of ABT, confirmation of ABT and modification of ABT (including dosage optimization, change of ABT, de-escalation, intensification and discontinuation of ABT). De-escalation therapy was defined as: i) switching from combination to monotherapy; ii) narrowing spectrum of activity. An opposite definition was applied to intensification therapy.

A therapy was considered appropriate in case of "confirmation of ABT" by the ID consultant in terms of dose, duration, penetrability and choice of regimen. In case of microbiological findings, appropriateness was assessed based on of in vitro susceptibility data. Assessment of appropriateness was performed on the basis of internal guidelines that refers in turn to national and international guidelines. Conversely, "modification of ABT" was considered a marker of inappropriate therapy. In order to evaluate the appropriateness of antibiotics prescribed by the non-ID specialist physician, only first consultations per patient with an already ongoing antibiotic therapy were analyzed.

Inclusion/exclusion criteria and study period

All the hospitalized patients for whom the treating physician asked for ID consultation, from September 1st, 2016 to October 31st, 2018 were included in the. Age < 18 years was the only criteria for exclusion.

We evaluated the impact of one year of weekly service of ID-cons (09/2016-09/2017) versus one year of daily service of ID-cons (10/2017-10/2018).

Outcomes

Process outcomes estimate the performance of the study. Process outcomes of the study are: i) number-of-ID-cons per 100 bed days (bd), ii) days-from-admission-to-first-ID-cons, iii) type of ABT-intervention and iv) appropriateness of ABT prescription (evaluated only on first ID evaluation).

Primary outcomes of the study are: (i) the reduction of overall ABT consumption and (ii) the reduction of ABT consumption by department and by ABT classes expressed as defined-daily-dose (DDD)/100bd.

The secondary outcome is a non-significant increment of overall and sepsis-related in-hospital mortality (as death/patient's admissions) from 2017 to 2018.

Statistical analysis

Categorical variables were presented as absolute numbers (percentages) while continuous variables as median (interquartile range; IQR). Clinical characteristics of patients were represented as median and interquartile range. Chi-square and Wilcoxon test were used as appropriate. ATB consumption was expressed as DDD/100bd. In order to evaluate the impact of our intervention on the outcome a sensitivity analysis including units with high number of ID cons/100bd (\geq 25th percentile of the ID-cons distribution) was performed. Differences in patients' characteristics and process outcomes were evaluated by Mann-Whitney and Chi-square tests while differences in antimicrobial consumption between the two time periods were evaluated by Wilcoxon test for paired data. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS software (version 9.2).

Results

Overall, 2552 ID-cons were performed in 1111 patients with a mean of 2.3 ID-cons per patient, including the follow-up visits. 18.6% (475/2552) of the ID-cons were performed in the weekly period versus 81.4% (2077/2552) in the daily period.

The 1111 patients included in the study were distributed as follows: 24.6% (273/1111) in weekly ID-cons and 75.4% (838/1111) in daily ID-cons.

An increment in the number of follow-up visits was observed switching from the weekly to the daily period. In fact, the mean of ID-cons per patient increased from 1.7 to 2.5.

Demographics and baseline characteristics of the study population are shown in Table 1. 40% of the population was female and median age was 73.5 (IQR 61-81) years. Median Charlson comorbidity index was 6 (IQR 4-8). The most common comorbidity was cardiovascular disease, followed by diabetes mellitus and neoplastic diseases. The patients in the two groups, weekly ID-cons and daily ID-cons, were comparable for sex, age and comorbidities.

Half of the infections evaluated during consultancies were healthcare-associated.

Overall, the most represented infection was pneumonia, followed by sepsis. Comparing daily vs weekly, a similar distribution of site of infections was observed except for UTIs and sepsis that were more represented in daily ID-cons (UTIs 15% vs 4%; sepsis 19% vs 15%) and CNS infections and bone and joint infections that were more common in weekly ID-cons (CNS 5% vs 2%; bone and joint 8% vs 6%) (tab.2).

Process outcomes

Four process outcomes were evaluated in the study: i) number-of-ID-cons per 100bd, ii) days-from-admission-to-first-ID-cons, iii) type of ABT-intervention and iv) appropriateness of ABT prescription (evaluated only on first ID evaluation).

As expected, switching from weekly to daily service the number of ID-cons performed significantly increased. In fact, the number-of-ID-cons/100bd increased from 0.4 to 1.5 ($p=0.01$) in the whole hospital. Analyzing the data by department, the greatest increase in the number of ID-cons was observed in the emergency department (from 1.5 to 6.7 number-of-ID-cons/100bd, $p<0.0001$) (fig. 1). Focusing only in ICU, ID-cons/100bd increased from 2 to 5 ($p<0.05$).

In daily service, patients were seen by the ID specialist earlier. In fact, days-from-admission-to-first-ID-cons decreased from 10 days in the weekly service (IQR 6-19) to 6 days in the daily service (IQR 2-13; $p<0.0001$). Furthermore, antibiotic therapy was more often started by the ID consultant (start of ABT: 11.6% (38/475) vs 8% (242/2077), $p=0.02$).

As previously stated, appropriateness was evaluated including only the first ID-cons per patient with an ABT prescribed by the non-ID treating physician. Switching to weekly service of ID-cons appropriateness rose from 26% to 34% (weekly 49/184 vs daily 191/559, $p=0.02$).

Primary outcomes

Primary outcome of the study was the reduction of hospital antibiotic consumption. In 2018, year of the daily service of ID-cons, as compared to 2017, weekly period, antibiotic consumption decreased from 64 DDD/100bd to 60 DDD/100bd ($p=0.07$). In order to include the units where the highest number of ID-cons were performed a sensitivity analysis was performed. In this analysis were excluded the units where less than 25th percentile of the ID-cons was performed (Oncology, Obstetrics/gynaecology and Psychiatry). Results from the sensitivity analysis showed that the consumption decreased from 67 DDD/100bd to 64 DDD/100bd ($p=0.01$).

Analysing the data by department, we obtained a small reduction of the consumption in the Medical Department (weekly 56 DDD/100bd vs daily 52 DDD/100bd) while the consumption wasn't reduced in the surgical department (weekly 56 DDD/100bd vs daily 52 DDD/100bd). The greatest reduction was observed in the Emergency Department where it was observed a reduction of 19% in the consumption of ABT (weekly 132 DDD/100bd vs daily 107 DDD/100bd, $p=0.07$) (fig.2). Focusing on ICU, ABT consumption was reduced from 131 DDD/100bd to 103 DDD/100bd ($p<0.05$).

Clustering the data by antibiotic classes, we have obtained a reduction of 33% in glycopeptides use (weekly 3.1 DDD/100bd vs daily 2.1 DDD/100bd, $p<0.05$) and a reduction of 19% in fluoroquinolones use (weekly 11.9 DDD/100bd vs daily 9.6 DDD/100bd, $p<0.002$). A reduction, even though non statistically significant, was obtained in carbapenems use (weekly 3.7 DDD/100bd vs daily 3.1 DDD/100bd). This reduction in glycopeptides, fluoroquinolones and carbapenems use wasn't accompanied with an increase in other ABT classes (fig.3).

Secondary outcome

Secondary outcome of the study was a non-significant increment of mortality (as death/patient's admissions) from 2017 to 2018.

During the study period, no change in overall in-hospital mortality was observed (2017 5.2% vs 2018 5.2%). Regarding sepsis-related mortality, a non statistically significant increase in mortality was recorded (2017 19.3% vs 20.9%, $p=0.7$).

Discussion And Conclusion

In our study, the availability of daily ID-consultations resulted associated with a global reduction in antibiotic consumption in the whole hospital in spite of a similar distribution of infections among the two time periods. This reduction wasn't accompanied with a worsening of clinical outcomes.

The major reduction in the use of ABT was observed in the Emergency Department, especially in the ICU. It is worth to note, that this was the department where the greatest increase in the number of ID-cons was observed. ICUs are the settings where ID consultant is more needed because of the higher circulation of MDR, higher usage of broad-spectrum antibiotics and more difficult to treat infections. Indeed, in our study the daily availability of the ID-consultant resulted in a higher number of ID-cons asked by the clinicians and subsequently in a significant reduction in ABT use. This correlation strengths our finding on the impact of ID consultations.

These findings are concordant with several previous studies. ID intervention was proved to be effective in reducing antimicrobial use without affecting clinical outcome in a recent review by Pulcini et al. [11]. In other studies, ID intervention resulted associated with a decreased mortality [18, 19] and length of stay [20] and lowered healthcare-associated costs[45].

In our study, the use of glycopeptides and carbapenems was considerably reduced. These two classes often represent the only therapeutic weapon to treat severe infections due to MDR bacteria as MRSA and ESBL-Enterobacteriaceae. Therefore, the judicious use of these antibiotics is one of the main outcomes of several antimicrobial stewardship (AMS) programs as underlined in the Global Action Plan on AMR by WHO.

It is noteworthy that in our study we didn't observed an increment in the use of other antibiotic classes as consequence of the reduction of glycopeptides, carbapenems and fluoroquinolones. The so-called "squeezing the balloon effect" is an undesirable side effect of several AMS programs where the reduced use of one agent is associated with increased use of another [21, 22].

Another class that was reduced in a significant way in our study was the class of fluoroquinolones that has been reduced by 19%. Reducing fluoroquinolones use is crucial for at least two reason. From one side, FQ-resistance in Enterobacteriaceae in Italy is above 40; that means that the use of these agents as empirical therapy is no more justified nowadays as it was in the past. From the other side, in the last few

years have been published several warnings on the adverse effect of FQ. In 2018 the FDA released a Drug Safety Communication in which advises about the serious side effects associated with FQ use outweigh the benefits for certain uncomplicated infections [23]. Lastly, fluoroquinolones are strongly associated with *Clostridium difficile*-associated diarrhea [24]. Thus, reducing their use can be associated with a reduction in the rate of *Clostridium difficile*.

Concerning other outcomes, our intervention resulted in a more comprehensive take in charge of the patient with an infection by the ID-consultant; in fact, in 2018 ID-cons were asked sooner after hospital admission and more antibiotic therapies were decided by the ID-consultant. The importance of the Infectious Diseases Specialist for management of patients with severe infections has been clearly demonstrated in a recent meta-analysis by Vogel et al. In their study, they have evaluated the impact of ID-consultation on the management and outcomes of patients with *Staphylococcus aureus* bacteremia (SAB). Overall 30-day mortality, 90-day mortality and relapse risk were significant reduced in the group of the ID-consultation with a relative risk of 0.53, 0.77 and 0.62 respectively [25].

Moreover, the quality of the antibiotic use was improved as witnessed by the increment in the rate of appropriateness of ABT prescriptions.

In the study, almost half of the infections were healthcare-associated. However, it has to be considered that those are exclusively the infections for which the clinician asked for ID advice. In our opinion, this is due to the fact the HAI are often more difficult to treat and clinicians are more confident in treating CAI without seeking for ID-advice. Therefore, the real incidence of healthcare-associated infections in our facility is inferior to the one observed in the study.

The study has some limitations. Firstly, we didn't evaluate all the prescriptions done in the hospitals but just the ones for whom ID-consultant was asked for advice. Hence, we couldn't evaluate properly the appropriateness of ABT use in the entire hospital. This is a direct consequence of the nature of the study and it is the reason why appropriateness is a process outcome instead of a primary outcome. Contrarily, the consumption of ABT was evaluated in the whole hospital including the prescriptions for which ID-consultant didn't have a direct impact resulting in an underestimation of the effect of the intervention. This was partly but not completely avoided by the use of the sub-analysis on the units in which an adequate number of ID-cons was performed. A second limitation is that we haven't evaluated the impact of the reduction in ABT consumption on the circulation of MDR. However, to observe a reduction in MDR circulation a longer time period is needed. Nonetheless, we could have evaluated the impact of the reduction of FQ use on the incidence of *Clostridium difficile*. This represents a future direction for our research. Similarly, we didn't evaluate the occurrence of adverse events due to the lack of follow-up visits in the weekly period. Another limit of the study is represented by the observational design of the study with its intrinsic risk of biases.

Infectious Diseases consultation was effective in reducing antibiotic use in the whole hospital and in the Emergency Department in particular without affecting in-hospital and sepsis-related mortality. These

findings further prove that ID-consultation is a valid tool for a successful large-scale stewardship program.

Declarations

Acknowledgments

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Authors' contributions

AC designed the study, collected the data, analyzed the data, and wrote the article. GCM and ADM designed the study, advised on analysis, and edited the manuscript. LD designed the study and analyzed the data. OV and TB reviewed the study designed and critically edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This observational analysis received approval by our local Ethics committee (Comitato Etico Milano Area 1) in 01/17/2019 with number of protocol: 57183/2018. Written informed consent was obtained for enrolled patients.

Competing Interests

The authors declare no conflicts of interest. Giulia Marchetti is a member of the Editorial Board of BMC Infectious Diseases.

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Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Authors' information

AD is a MD and a Ph.D. student. LD and OV are MDs and PhDs. TB is a MD. GCM and ADM are senior professors in Infectious Diseases at the University of Milan.

Consent for publication

Not applicable.

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Tables

Table 1: Demographics and baseline characteristics of the study population.

	Total pts. (1111)	Weekly (pts. 273)	Daily (pts. 838)
Female	460 (41.4%)	115 (42%)	345 (41%)
Age	73.5 (61-81)	72 (61-81)	75 (61-82)
Charlson Index Age ad.	6 (4-8)	6 (4-8)	6 (4-8)
Comorbidities, n (%):			
- Chronic Renal Failure	166 (14.9%)	36 (13.2%)	130 (15.5%)
- Cardiovascular disease	549 (49.4%)	125 (45.8%)	424 (50.6%)
- Diabetes mellitus	227 (20.4%)	51 (18.7%)	176 (21%)
- Dementia	122 (11%)	15 (5.5%)	107 (12.8%)
- Liver cirrhosis	89 (8%)	18 (6.6%)	71 (8.5%)
- Cancer	185 (16.7%)	42 (15.4%)	143 (17.1%)
- COPD	156 (14%)	36 (13.2%)	120 (14.3%)

Table 2: Characteristics and distribution of the infections (HAI: health-care associated infection; UTIs: urinary tract infection; ABSSSIs: Acute Bacterial Skin and Skin Structure Infections; CNS: Central Nervous System).

	Total pts (1111)	Weekly (pts. 273)	Daily (pts. 838)
HAI	575 (52%)	118 (43.2%)	457 (54.5%)
Site of Infection:			
- UTIs	126 (11.3%)	10 (3.8%)	116 (14.4%)
- Cardio-vascular	32 (2.9%)	11 (4.1%)	21 (2.6%)
- Bone and joint	66 (5.9%)	20 (7.6%)	46 (5.7%)
- ABSSSIs	74 (6.7%)	17 (6.4%)	57 (7.1%)
- Intra-abdominal	138 (12.4%)	35 (13%)	103 (12.9%)
- Pneumonia	220 (19.8%)	46 (17.5%)	174 (21%)
- CNS	29 (2.6%)	13 (4.9%)	16 (2.0%)
- Sepsis	193 (17.3%)	40 (15.2%)	153 (19.1%)
- Other	182 (16.4%)	70 (26%)	112 (14%)

Figures

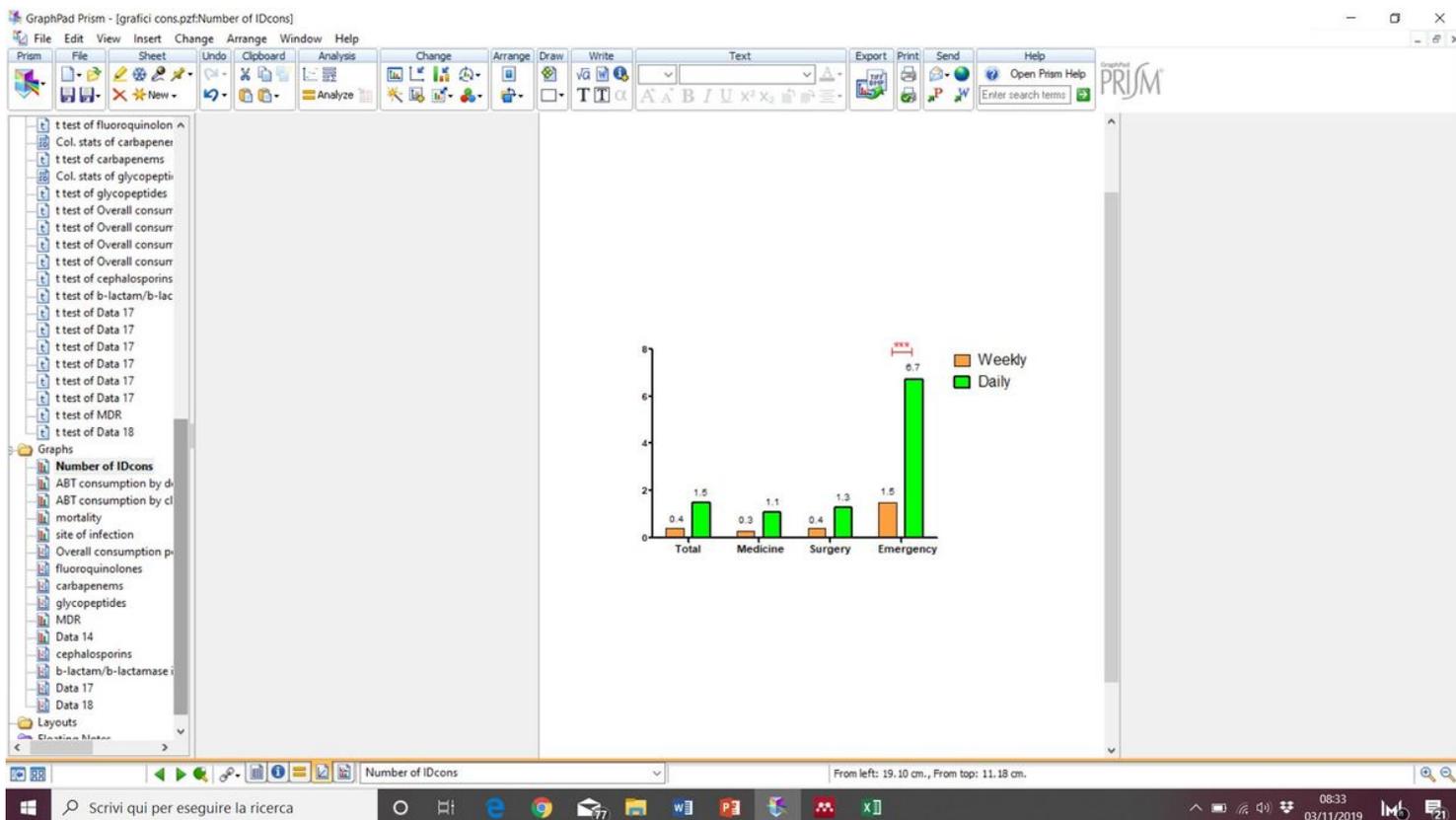


Figure 1

Number of ID-cons per 100 bed-days performed over the study period (LEGEND: in orange weekly ID-cons, in green daily ID-cons).

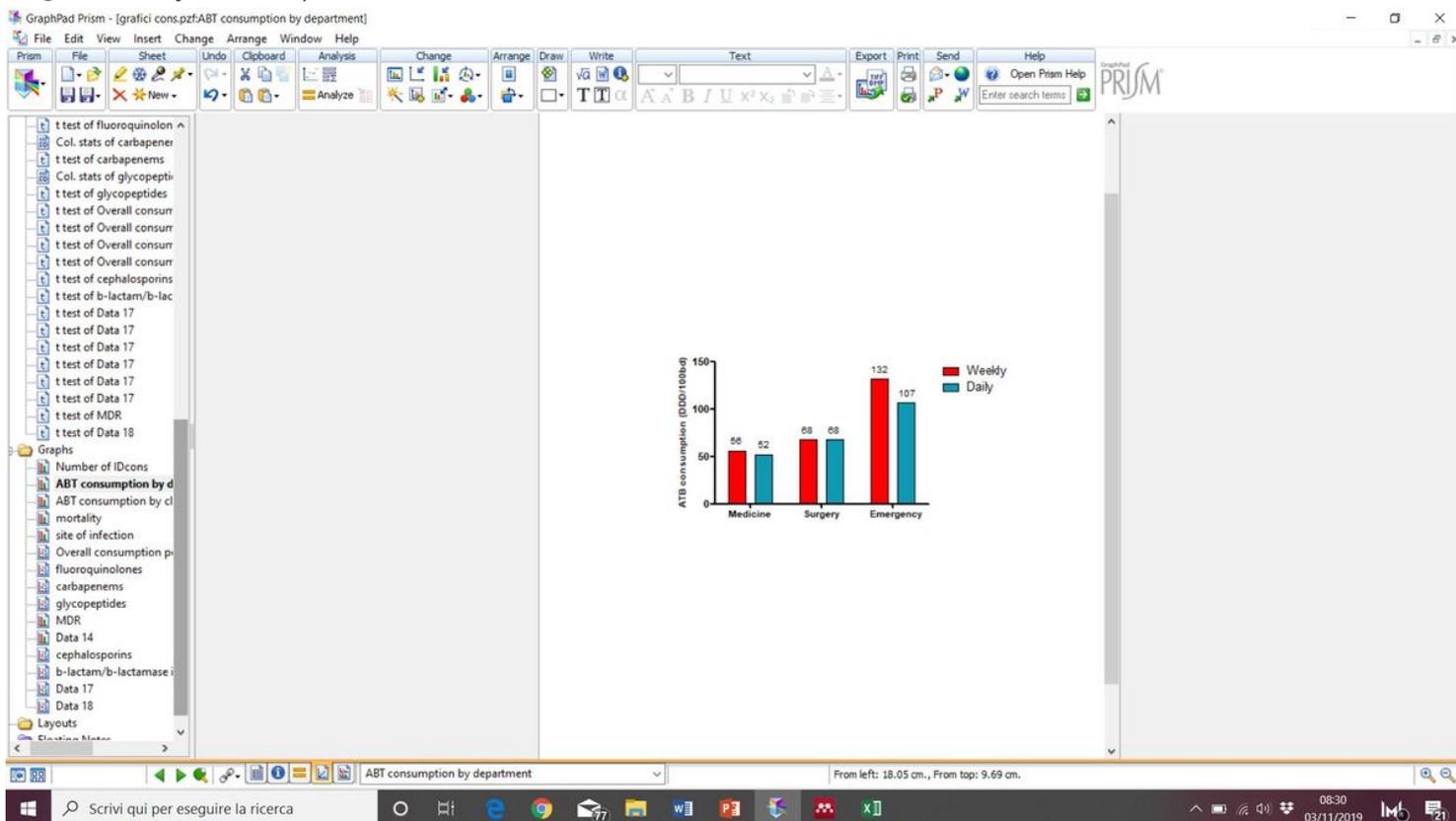


Figure 2

Antibiotic consumption by department (LEGEND: in red weekly ID-cons, in blue daily ID-cons; ATB: antibiotic).

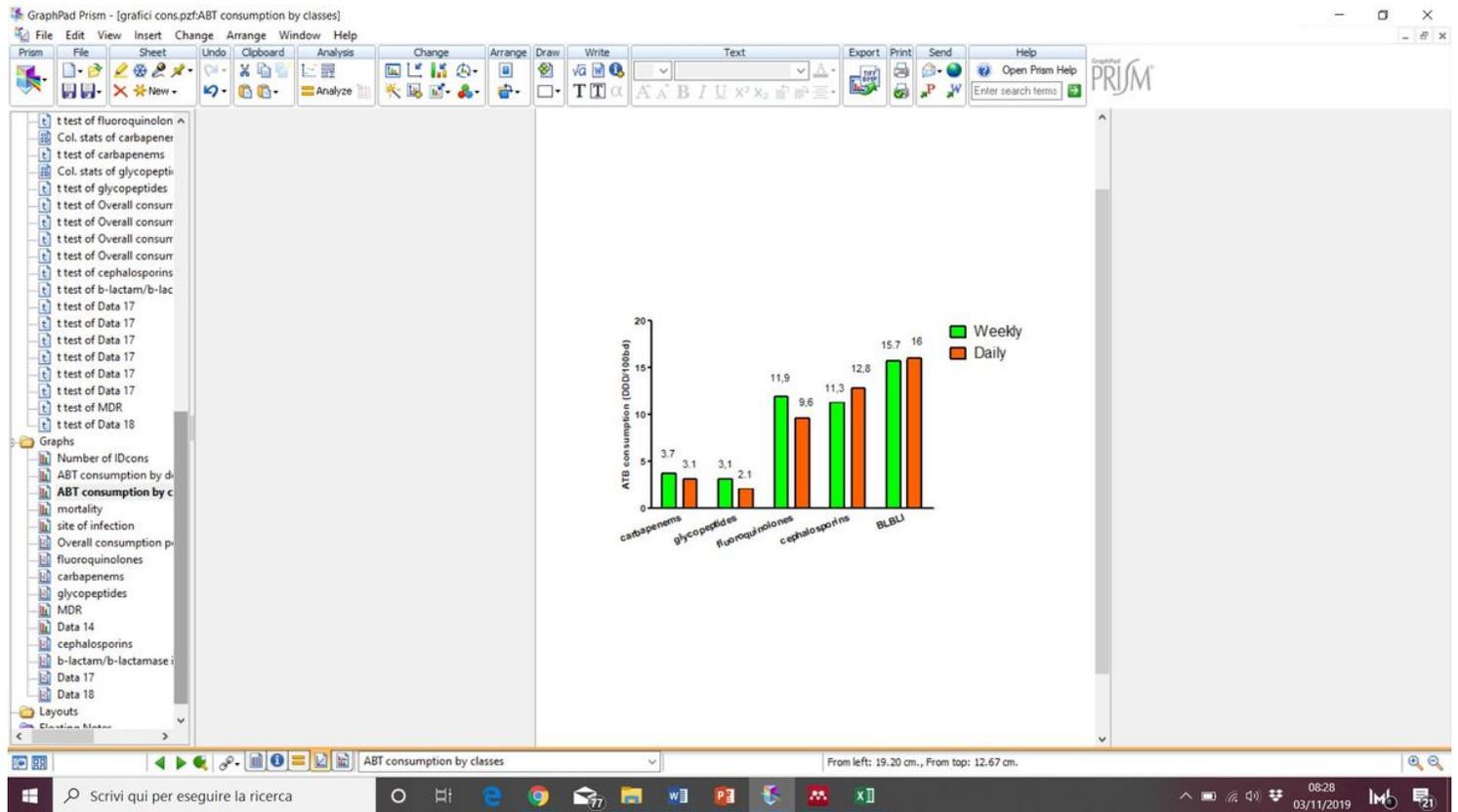


Figure 3

Antibiotic consumption by classes (LEGEND: in green weekly ID-cons, in orange daily ID-cons; BLBLI: beta-lactam/beta-lactamase inhibitors).