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Antimicrobial stewardship through telemedicine and its impact on multi-drug resistance

Rodrigo P dos Santos[1,2,3], Camila H Dalmora[2,3], Stephani A Lukasewicz[3], Otávio Carvalho[1,3], Caroline Deutschendorf[2,3], Raquel Lima[3], Tiago Leitzke[4], Nilson C Correa[4] and Marcelo V Gambetta[4]

Abstract

Introduction: Telemedicine technologies are increasingly being incorporated into infectious disease practice. We aimed to demonstrate the impact of antimicrobial stewardship through telemedicine on bacterial resistance rates.

Methods: We conducted a quasi-experimental study in a 220-bed hospital in southern Brazil. An antimicrobial stewardship program incorporating the use of telemedicine was implemented. Resistance and antimicrobial consumption rates were determined and analysed using a segmented regression model.

Results: After the intervention, the rate of appropriate antimicrobial prescription increased from 51.4% at baseline to 81.4%. Significant reductions in the consumption of fluoroquinolones (level change, $\beta = -0.80$; $P < 0.01$; trend change, $\beta = -0.01$; $P = 0.98$), first-generation cephalosporins (level change, $\beta = -0.91$; $P < 0.01$; trend change, $\beta = +0.01$; $P = 0.96$), vancomycin (level change, $\beta = -0.47$; $P = 0.04$; trend change, $\beta = +0.17$; $P = 0.66$) and polymyxins (level change, $\beta = -0.15$; $P = 0.56$; trend change, $\beta = -1.75$; $P < 0.01$) were identified. There was an increase in the consumption of amoxicillin + clavulanate (level change, $\beta = +0.84$; $P < 0.01$; trend change, $\beta = +0.14$; $P = 0.41$) and cefuroxime (level change, $\beta = +0.21$; $P = 0.17$; trend change, $\beta = +0.66$; $P = 0.02$). A significant decrease in the rate of carbapenem-resistant *Acinetobacter* spp. isolation (level change, $\beta = +0.66$; $P = 0.01$; trend change, $\beta = -1.26$; $P < 0.01$) was observed.

Conclusions: Telemedicine, which provides a tool for decision support and immediate access to experienced specialists, can promote better antibiotic selection and reductions in bacterial resistance.

Keywords

Antimicrobial stewardship, telemedicine, bacterial resistance

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Introduction

The Infectious Diseases Society of America (IDSA) has defined antibiotic stewardship as a coordinated intervention designed to improve antibiotic use by promoting the application of optimal drug regimens, as defined by the dosing, duration and route of administration. The benefits of antibiotic stewardship include better patient outcomes, reduced rates of adverse events and bacterial resistance, and cost savings.[1] Antimicrobial stewardship interventions, such as guideline-adherent empirical therapy and de-escalation therapy based on culture results, have been found to be associated with lower mortality.[2] The IDSA strongly recommends that stewardship programs be led by trained infectious disease physicians.[1] However, lack of funding and lack of trained personnel have been identified as the leading barriers to implementing a functional and effective antimicrobial stewardship program (ASP).[3]

Broad dissemination of electronic communication, advances in technology, and telemedicine have allowed institutions to have access to medical specialists who can

[1]Hospital Infection Control Committee, Hospital de Clínicas de Porto Alegre, Brazil
[2]Hospital Infection Control Committee, Instituto de Cardiologia de Porto Alegre, Brazil
[3]Qualis, Porto Alegre, Brazil
[4]Hospital Infection Control Committee, Hospital Regional do Alto Vale, Brazil

Corresponding author:
Rodrigo P dos Santos, Av. Ferdinand Kisslinger, 200 CEP: 91360054 Porto Alegre, RS, Brazil.
Email: Rodrigo@portalqualis.com.br

support healthcare professionals in remote areas through the real-time exchange of knowledge.[4-6] Telemedicine has been found to be associated with better patient outcomes. Critically ill patients have been found to have shorter intensive care unit stays and reduced hospital mortality rates when attended to by intensivists using telemedicine[7]. Telemedicine is being increasing incorporated into infectious disease practice. This technology has proven to be effective in the treatment of patients with acute infectious diseases, such as respiratory infections, bacteremia, skin and soft tissue infections, endocarditis, and urinary infections.[8,9] Several benefits of telemedicine have been identified in the infectious disease field, including decreased antimicrobial consumption and costs, fewer hospital stays, and reduced rates of bacterial resistance.[10–12] We describe a 2-year telemedicine intervention and its impact on antimicrobial consumption and multidrug bacterial resistance.

Methods

Hospital Regional Alto Vale is a 220-bed hospital that serves clinical and surgical patients in Rio do Sul, southern Brazil. It has an intensive care unit for clinical, cardiac, pediatric and neonatal patients. The teleinfectology base was located in Porto Alegre, which is located 400 km from the remote hospital.

We conducted a quasi-experimental study to assess the impact of an antimicrobial stewardship program incorporating immediate post-prescription reviews and the provision of feedback through telemedicine tools. A web-based platform designed to facilitate the review of clinical data and provision of feedback to physicians working at the remote hospital was created and has been described elsewhere.[9]

The consultation service was available from May 2014. Hospital physicians were trained on how to use the platform, and remote professionals (four infectious disease (ID) specialists) provided feedback through the platform, e-mails and text messages. The ID specialists were divided according day-shifts and responded to all consultation during their work shifts. All initiated antimicrobial prescriptions had to be reported, and patient data were entered into the web platform to be evaluated remotely by the ID specialists. The web platform enabled every case to be discussed, and the suggestions provided by ID specialists could be refuted. Therefore, medical staff had the choice to accept or reject the specialist advice. The physicians had unlimited access to the ID specialist either through the web platform or by phone (as needed) 7 days a week.

The appropriateness of antimicrobial prescribing practices was evaluated based on antimicrobial choice, dose, route of administration, and number of prescription days. The ID team categorised their recommendations for prescriptions into the following categories: (1) adequate (no change needed), (2) length of therapy adjustments, (3) dose adjustments, (4) change of administration route, (5) selection of another antimicrobial, (7) overlapping spectrums of activity, and (8) treatment cessation.

Each month, data on the consumption of antimicrobial drugs were recorded as the number of defined daily doses (DDDs) per 100 patient-days. Data were collected on the consumption of the following antibiotics: first-, second-, third- and fourth-generations cephalosporins; penicillin with beta-lactamase inhibitors; quinolones; aminoglycosides; carbapenems and vancomycin.

The rate of antimicrobial resistance in isolates obtained from hospitalised patients was evaluated for the following bacteria: *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., *Pseudomonas* aeruginosa, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., and *Acinetobacter* spp. Multiresistant bacteria were classified as follows: carbapenem-resistant Enterobacteriaceae (CRE); carbapenem-resistant *P.* aeruginosa, carbapenems-resistant *Acinetobacter* spp, vancomycin-resistant *Enterococcus* spp. (VRE) and methicillin-resistant *S. aureus* (MRSA). The incidence density of multiresistant bacteria was defined as the number of resistant isolates recovered per 1000 patient-days. Susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Consumption of overall alcohol-based hand rub and chlorohexidine soap for the entire hospital was measured in millilitres per 100 patient-days and reported on a monthly basis.

Time to ID consultation was reported in minutes. Adherence to teleinfectology recommendations was also recorded.

Statistical analysis

Categorical variables are reported as percentages, and medians with interquartile ranges (i.e. 25th and 75th percentiles) are reported for continuous variables. Two-sided *P*-values less than 0.05 were considered statistically significant.

A time series segmented regression analysis was performed to evaluate the presence of significant changes in antibiotic consumption before (January 2013 to April 2014) and after (May 2014 to April 2016) the stewardship program intervention was implemented. According to Wagner et al., two parameters define each segment of a time series model: level and trend. A change in level, e.g. a post-intervention increase or drop in the rate of the evaluated outcome, was considered to be an abrupt intervention effect. A change in trend was defined by an increase or decrease in the slope of the post-intervention segment relative to that of the slope of the segment preceding the intervention.[13]

The two-rate chi-square test was performed to compare the pre- and post-intervention rates of bacterial resistance. A linear regression model was generated to measure trends in prescription appropriateness during the intervention period. All *P*-values less than 0.05 were considered statistically significant. Platform data were exported from the web repository and stored in Excel 2011. Data were analysed using SPSS version 18.0.

Results

From May 2014 to April 2016, 11,088 prescriptions for 6163 patients were submitted to the web platform for real time consultation. During morning shifts 4502 (40.6%) prescriptions were included; 4857 (43.8%) during afternoon shifts; and 1729 (15.6%) during night shifts. Of 160 physicians, 127 (79.3%) actually used the platform.

The most commonly identified indication for antibiotic use was surgical prophylaxis (19.3%; $n = 2135$), followed by pneumonia (19.2%; $n = 2126$), urinary tract infections (10.6%; $n = 1200$), sepsis (8.6%; $n = 952$), appendicitis (2.9%; $n = 326$), cholecystitis (2.3%; $n = 251$), chronic obstructive pulmonary disease (2.2%; $n = 240$), open wound fracture prophylaxis (2.2%; $n = 240$), and diabetic foot disease (2.0%; $n = 221$).

Overall, most prescribed drugs were amoxicillin + clavulanate (20.4%; $n = 2686$), first-generation cephalosporins (18.3%; $n = 2416$), cefepime (12.2%; $n = 1605$), cefuroxime (5.8%; $n = 768$), metronidazole (5.3%; $n = 694$), meropenem (4.4%; $n = 576$), ampicillin (4.0%; $n = 531$), gentamicin (3.6%; $n = 475$), vancomycin (3.5%; $n = 460$), ceftriaxone (2.6%; $n = 348$), and clindamycin (2.4%; $n = 314$), comprising 82.4% of all prescriptions.

Over the course of the entire period, 79.7% ($n = 8833$) prescriptions were considered appropriate. Dose adjustments were the second most common recommendation (12.3%; $n = 1360$); other therapeutic options were suggested for 6.3% of prescriptions ($n = 697$); adjustments in the length of therapy were suggested for 0.8% of prescriptions ($n = 84$); and suggestions to stop therapy comprised 0.6% of interventions ($n = 69$). The rate of appropriateness did not differ according to ID specialist response, varying from 77.0% to 83.0% among the four specialists. However, according to remote physicians the rate varied from 11.0% to 100% of appropriateness.

A significant increase in prescription appropriateness was identified over the time period. The rate of prescription appropriateness increased from 50.4% during the first month of follow-up to 81.4% during the last month of the intervention (peak of adequacy of 89.4% in January 2016) (see Figure 1).

In the segmented regression analysis, a significant reduction in quinolone use (level change, $\beta = -0.80$; $P < 0.01$; trend change, $\beta = -0.01$; $P = 0.98$) was identified. For intravenous ciprofloxacin, a significant and immediate reduction in consumption (level change, $\beta = -0.82$; $P < 0.01$) was observed; subsequently, a sustainable decrease in the rate of intravenous ciprofloxacin consumption was identified (trend change, $\beta = -0.29$; $P = 0.46$). For intravenous levofloxacin, a similar pattern was observed in the consumption trends (level change, $\beta = -0.59$; $P < 0.01$; trend change, $\beta = +0.08$; $P = 0.77$). Otherwise, for intravenous moxifloxacin, a significant and immediate decrease in the consumption of this antibiotic was identified (level change, $\beta = -1.13$; $P < 0.01$; trend change, $\beta = -0.83$; $P < 0.01$) (Figure 2).

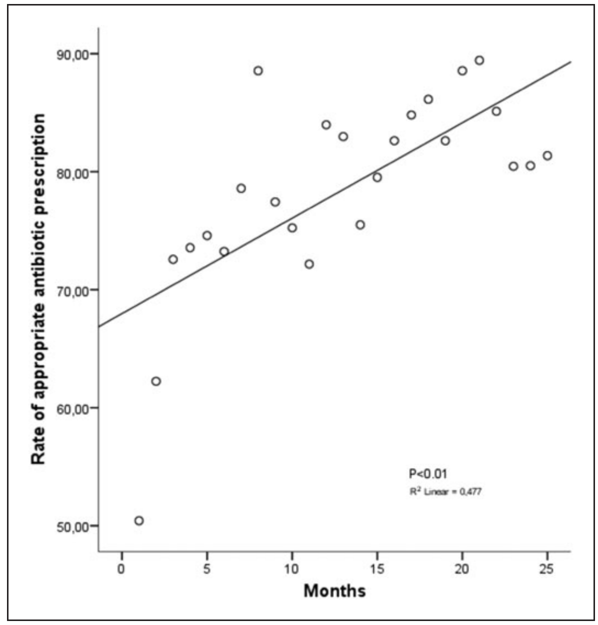

Figure 1. Rate (%) of appropriate antibiotic prescription.

For cephalosporins, a significant and immediate decrease (level change, $\beta = -1.23$; $P < 0.01$) and subsequent increase in use (trend change, $\beta = +1.03$; $P < 0.01$) was observed. For the first-generation cephalosporins, there was a significant and immediate decrease in use (level change, $\beta = -0.91$; $P < 0.01$; trend change, $\beta = +0.01$; $P = 0.96$). For intravenous cefuroxime, a significant increasing trend (level change, $\beta = +0.21$; $P = 0.17$; trend change, $\beta = +0.66$; $P = 0.02$) was observed (Figure 2). There was a significant immediate decrease in ceftriaxone consumption (level change, $\beta = -0.76$; $P < 0.01$; trend change, $\beta = +0.01$; $P = 0.93$). Initially, a significant increase in cefepime consumption was observed; however, a subsequent decrease was identified (level change, $\beta = +0.38$; $P < 0.01$; trend change, $\beta = -0.94$; $P < 0.01$).

For amoxicillin + clavulanate, an immediate increase in consumption was observed (level change, $\beta = +0.84$; $P < 0.01$; trend change, $\beta = +0.14$; P = 0.41) (Figure 2). Consumption of ampicillin + sulbactam did not change (level change, $\beta = +0.14$; $P = 0.54$; trend change, $\beta = -0.24$; $P = 0.52$).

For piperacillin + tazobactam, there was a significant increase in the rate of consumption (level change, $\beta = +0.14$; $P = 0.33$; trend change, $\beta = +0.01$; $P = 0.93$).

No changes in the rates of carbapenem consumption were identified (level change, $\beta = -0.38$; $P = 0.18$; trend change, $\beta = -0.03$; $P = 0.94$) (Figure 2). For vancomycin, an immediate consumption reduction was observed (level change, $\beta = -0.47$; $P = 0.04$; trend change, $\beta = +0.17$; $P = 0.66$). For polymyxins, there was a decrease in post-intervention relative to pre-intervention consumption

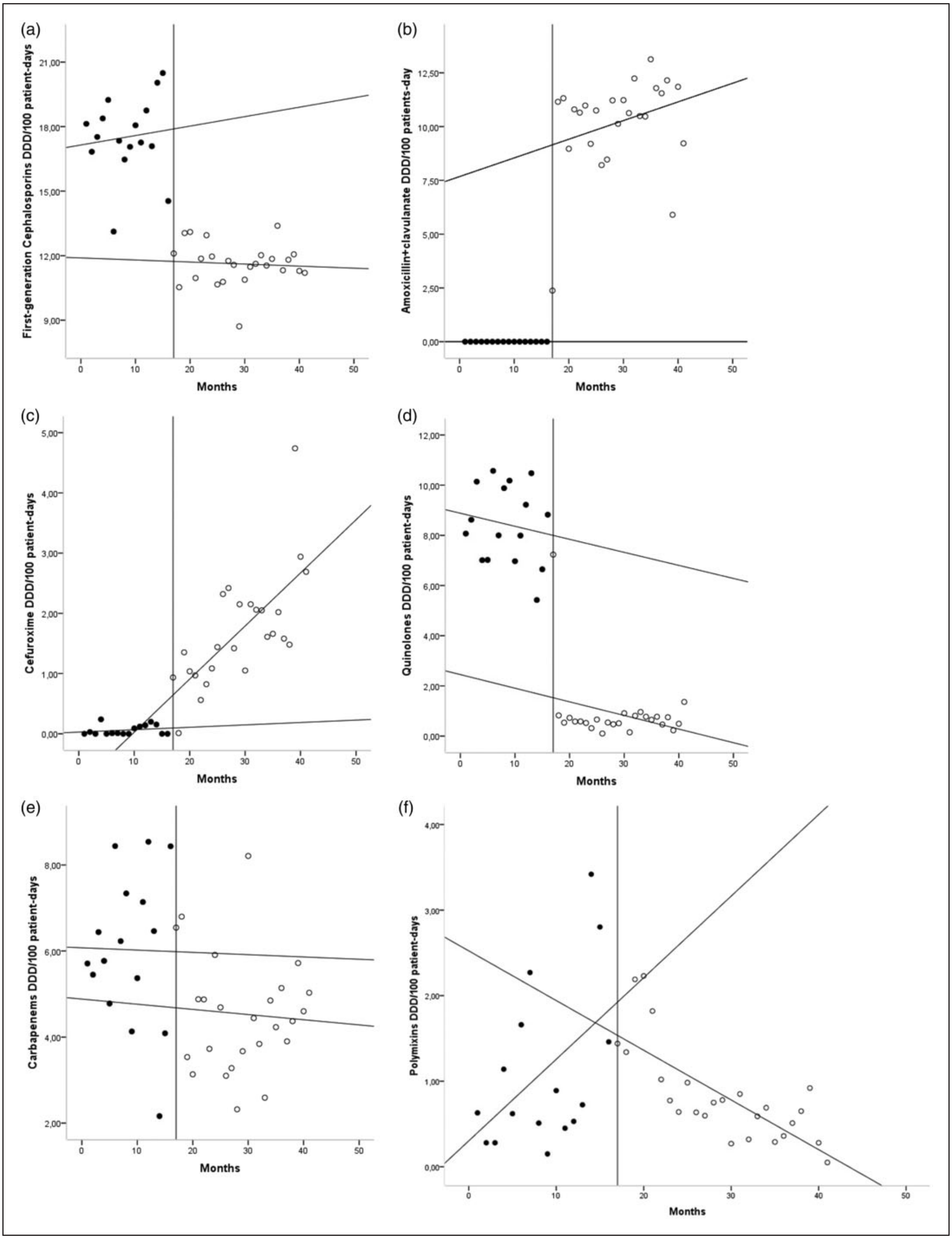

Figure 2. Pre- and post-intervention consumption of antimicrobials in DDD/100 patient-days. (a) DDD per 100 patient-days for first-generation cephalosporins; (b) DDD per 100 patient-days for amoxicillin +clavulanate; (c) DDD per 100 patient-days for cefuroxime; (d) DDD per 100 patient-days for quinolones; (e) DDD per 100 patient-days for carbapenems; (f) DDD per 100 patient-days for polymyxins.

(level change, $\beta = -0.15$; $P = 0.56$; trend change, $\beta = -1.75$; $P < 0.01$) (Figure 2).

The following bacteria were most frequently identified as resistant: carbapenem-resistant *Acinetobacter* spp. (median rate = 1.31/1000 patient-days; $n = 255$); CRE (median rate = 0.23/1000 patient-days; $n = 51$); MRSA (median rate = 0.0/1000 patient-days; $n = 9$); carbapenem-resistant *P. aeruginosa* (median rate = 0.0/1000 patient-days; $n = 8$); and *VRE* (median rate = 0.0/1000 patient-days; $n = 1$).

The results of the segmented regression analysis suggested that there was a significant and immediate increase in the rates of bacterial resistance followed by a subsequent and significant reduction; these changes were related primarily to increases and decreases in the rates of *Acinetobacter* spp. resistance (level change, $\beta = +0.66$; $P = 0.01$; trend change, $\beta = -1.26$; $P < 0.01$) (Figure 3). The rates of resistance in other bacteria were not found to differ significantly in the segmented regression analysis.

For overall hospital alcohol-based hand rub consumption, the regression linear model indicated that there was no increase in post-intervention consumption ($\beta = -0.10$; $P = 0.64$). For chlorhexidine soap, there was a significant increase in consumption after program implementation (trend change, $\beta = +1.28$; $P = 0.01$; level change, $\beta = -0.25$; $P = 0.93$).

The median time to receiving a second opinion via tele-infectology consultation was 3 min and 36 sec (25th–75th percentiles; 1 min and 48 sec – 8 min and 16 sec), and the starting point of this variable was defined as beginning with antimicrobial prescription at the remote hospital.

There was a significant reduction in antimicrobial costs, which reduced immediately (level change, $\beta = -0.73$; $P < 0.01$; IC) and continued to decrease after program implementation (trend change, $\beta = -2.11$; $P = 0.01$). The mean antimicrobial cost before ASP implementation was 19,525 US dollars per month (range: 13,034–32,681 US dollars), and the mean antimicrobial cost after ASP implementation was 15,965 US dollars per month (range: 13,288–24,429 US dollars) after implementation of the program.

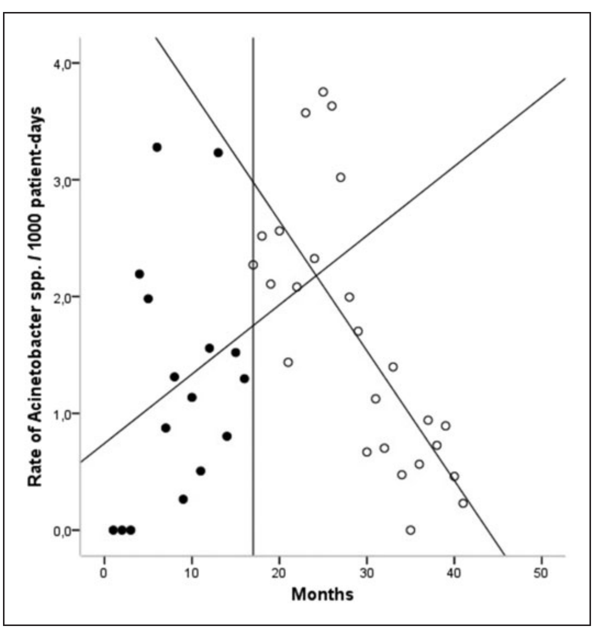

Figure 3. Pre- and post-intervention rates of positive culture results (infection or colonization) for carbapenem-resistant *Acinetobacter* spp. per 1000 patient-days.

Discussion

The performance of post-prescription audits and provision of real-time feedback to prescribers using telemedicine tools promoted the implementation of rapid changes in prescribing behaviours in the evaluated institution. Concurrently, the rate of resistance in the most prevalent bacteria in the institution reduced significantly. Recently, Tamma et al. conducted a quasi-experimental crossover trial, the results of which suggested that undergoing post-prescription review were more effective in reducing antibiotic consumption than were pre-prescription audits.[14] On the other hand, Mehta et al., identified a significant increase in antimicrobial use after the implementation of a post-prescription audit intervention to an ASP based on prior authorisation.[15] Telemedicine tools with the capacity to provide immediate feedback to physicians have the potential to combine these ASP's two core strategies in the sense that post-prescription evaluations are utilised, but feedback can also impact prescriptions before antibiotic administration.

Increases in the rates of bacterial resistance are fuelling the post-antibiotic era worldwide. In some bacterial species, such as *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* species (ESKAPE pathogens), the rates of resistance to currently available antibiotic drugs are increasing in many parts of the world.[16] This increase may change some practices in medicine. Surgery prophylaxis, and even simple medical interventions, may become unsafe procedures. Additionally, immunosuppressed patients and premature babies are at greater risk of developing resistance and have poorer outcomes, as new antibiotic options have become scarce. The IDSA has called for a global commitment to drug discovery through the "10×20" initiative. This initiative has resulted in the approval of two novel antibiotics and clinical development of seven drugs, but none have addressed the clinical need new drugs for Gram-negative resistant bacteria.[17] Therefore, new initiatives have supported the need for interventions to prevent resistance, such as ASP programs, hand hygiene and isolation precautions, and the prevention of new and horizontal transmission of resistant bacteria.[18]

Antimicrobial stewardship has been found to be associated with improved antimicrobial utilisation, appropriate initial therapy, use of narrower-spectrum drugs, earlier switch from intravenous to oral routes, shorter length of therapy, and reductions in antimicrobial resistance and adverse events without short-term compromises.[1] Previously developed guidelines for the implementation of ASPs have not formally included telemedicine as a tool to promote antimicrobial stewardship.[1] Few publications have addressed the effect of antimicrobial interventions including telemedicine. Yam et al. demonstrated that the implementation of an ASP incorporating the use of remote interventions in a rural hospital increased de-escalation therapy and reduced *Clostridium difficile* infections (CDI) and costs.[11] We identified increased rates of appropriate prescription in a small study conducted in a community hospital in Brazil. During the 4 months in which the teleinfectology program was carried out, the rate of antimicrobic prescription appropriateness increased from 36% to 60%.[9] In the uninterrupted time-series analysis performed by Beaulac et al., a significant reduction of 43% in the rate of hospital-acquired CDI was identified.[12] In the current study, in which a teleinfectology program was implemented in a complex institution and we remotely evaluated more than 10,000 antibiotic prescription consultations, we observed consistent changes in prescription habits. The antimicrobial stewardship program incorporated the restriction of fluoroquinolone use, implementation of a protocol for surgical antibiotic prophylaxis, use of penicillins and beta-lactamase inhibitors for community respiratory infections, use of second-generation cephalosporins for urinary infections, judicious use of vancomycin and carbapenems, and use of broad-spectrum cephalosporins for healthcare-associated infections.

Given the rates of inappropriate antibiotic use in surgical patients, these antibiotics were identified as one of the targets of ASPs.[19] Sometimes it may be difficult to intervene in the prescription of these antibiotics using institutional protocols or educational tools, as most prophylactic prescriptions are single dose, a circumstance that does not permit prompt implementation of interventions. We could, however, monitor each prescription's indication, dose, re-dose, infusion interval and duration of use through the use of mandatory real-time consultations. During the 3-min response process, it is possible for the physician to implement rapid interventions and quick changes in prescription habits, even in the case of antimicrobial prophylaxis following surgery.

Although fluoroquinolones are usually regarded as safe, the Food and Drug Administration recently issued an alert for the use of this class of drugs, recommending the use of alternative options when this class was previously indicated.[20] Cardiac arrhythmias and musculoskeletal dysfunctions are major adverse events related to fluoroquinolone use. In addition, the use of fluoroquinolones has been found to be closely associated with the emergence of drug resistance, including carbapenem-resistant *A. baumannii*.[21,22] In the study conducted by Chusri et al., the use of fluoroquinolones, broad-spectrum cephalosporins and carbapenems increased the risk of carbapenem-resistant *A. baumannii* infection by 81.2, 31.3 and 112.1 times, respectively.[23] In our study, an immediate reduction in fluoroquinolone use could have resulted in a significant reduction in multidrug resistant *Acinetobacter* spp. Consequently, this reduction contributed to the reduction observed in polymyxin use.

In conjunction with antimicrobial stewardship, the prevention of horizontal transmission of bacterial resistance are necessary. Hand hygiene, environmental cleaning, and use of contact precautions are recommended to prevent the spread of resistance. We measured the consumption of alcohol-based hand rub and chlorhexidine soap as a proxy for hand hygiene. An increase in the consumption of chlorhexidine soap, which occurred in conjunction with ASP implementation, might also have contributed to the reduction observed in antimicrobial resistance.

Slayton et al. reported a reduction of 74% in CRE infections when a coordinated approach to antimicrobial stewardship was implemented in 10 facilities and compared with the rates observed when independent institutional efforts were used.[24] Telemedicine has the potential to create a net of ASPs across institutions, which may result in even greater reductions in antimicrobial resistance. This redesign of the post-prescription audit process and provision of immediate feedback to the prescriber may improve the performance of the hospital team. When incorporated by hospital staff, such interventions can guide the prescription process, thereby increasing the selection of safe options, especially in diverse teams including a broad range of physicians; such interventions may be particularly useful in supporting less experienced staff and reducing the stress associated with decision-making.

Recently, the Infectious Diseases Society published a statement on telehealth and telemedicine as they relate to infectious disease. The society supports the incorporation of telehealth technologies in ASPs. These programs will provide greater efficiency and flexibility to remote staff working in community hospitals that lack resources. Telehealth program require access to the facility resistance profiles, interactions between ID physician and pharmacy committees, access to patient medical records, and access to staff and patients, when needed; additionally, telehealth programs must follow the IDSA guidelines for ASP.[25]

Our article has several limitations. First, this study was a non-controlled single centre trial. Second, although we used alcohol-gel preparations and chlorhexidine soap consumption as a measure of hand hygiene, we did not observe hand hygiene, adherence to contact precautions, and environmental cleaning, which could have impacted the rate of resistant bacteria. Finally, we did not access patient outcomes data, such as length of stay, cure rate and patient mortality.

Given the global commitment to the reduction of bacterial resistance, telemedicine tools that facilitate net construction, teleconsultation, decision support, and immediate access to and easy communication with experienced specialists should be included as cost-effective approaches to promoting changes in antimicrobial consumption and reductions in bacterial resistance.

Declaration of Conflicting Interests

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