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Clinical impact of an educational antimicrobial stewardship program associated with infectious diseases consultation targeting patients with cancer: Results of a 9-year quasi-experimental study with an interrupted time-series analysis

José Molina[a], Manuel Noguer[b], José Antonio Lepe[a], María Antonia Pérez-Moreno[c], Manuela Aguilar-Guisado[a], Roberto Lasso de la Vega[b], Germán Peñalva[a], Juan Carlos Crespo-Rivas[a], María Victoria Gil-Navarro[c], Javier Salvador[b], José Miguel Cisneros[a,*]

[a] Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Institute of Biomedicine of Seville (IBIS), University Hospital Virgen del Rocío/CSIC/University of Seville, Spain
[b] Clinical Unit of Oncology, Institute of Biomedicine of Seville (IBIS), University Hospital Virgen del Rocío/CSIC/University of Seville, Spain
[c] Clinical Unit of Pharmacy, Institute of Biomedicine of Seville (IBIS), University Hospital Virgen del Rocío/CSIC/University of Seville, Spain

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SUMMARY

Objectives: Antibiotic stewardship programs (ASP) have already demonstrated clinical benefits. However, their effectiveness or safety in immunocompromised hosts needs to be proved.
Methods: An ecologic quasi-experimental study was performed from January 2009 to June 2017 in the Oncology department of a tertiary-care hospital. A stable program of Infectious Diseases consultation (IDC) already existed at this unit, and an educational ASP was added in 2011. Its main intervention consisted of face-to-face educational interviews. Antibiotic consumption was assessed through quarterly Defined Daily Doses (DDD) per 100 occupied bed-days. Mortality was evaluated in patients with bloodstream infections through the quarterly incidence density per 1000 admissions, and the annual mortality rates at 7 and 30-days. Time-trends were analysed through segmented-regression analysis, and the impact of the ASP was assessed through before-after interrupted time-series analysis.
Results: Mortality significantly decreased throughout the study period (−13.3% annual reduction for 7-day mortality rate, $p < 0.01$; −8.1% annual reduction for 30-day mortality, $p = 0.03$), parallel to a reduction in antibiotic consumption (quarterly reduction −0.4%, $p = 0.01$), especially for broader-spectrum antibiotics. The before-after study settled a significant inflexion point on the ASP implementation for the reduction of antibiotic consumption (change in level 0.95 DDD, $p = 0.71$; change in slope −1.98 DDD per quarter, $p < 0.01$). The decreasing trend for mortality before the ASP also continued after its implementation.
Conclusions: The combination of an ASP with IDC improved antibiotic use among patients with cancer, and was accompanied by a reduction of mortality of bacteraemic infections. Implementation of the ASP was necessary to effectively change antibiotic use.

Introduction

Antimicrobial Stewardship Programs (ASPs) have proved significant benefits on the outcome of patients with infections.[1] However, the evidence supporting the effect of these interventions on immunosuppressed patients remains limited.[2] The impact of ASPs might be especially relevant in this setting, as long as they are especially exposed to the deleterious consequences of the inappropriate use of antibiotics, i.e. a superior mortality [3] and an increased risk of infections caused by multidrug-resistant microorganisms.[4] However, their implementation has been traditionally hindered by the reluctance of clinicians who may question the safety and effectiveness of narrower-spectrum agents or shorter courses of antibiotics when treating infections in immunocompromised patients.[5]

Indeed, very few studies have addressed the results of these interventions in patients with cancer, and their achievements have been mostly limited to reducing the economic costs or antibiotic

* Corresponding author.
E-mail address: josem.cisneros.sspa@juntadeandalucia.es (J.M. Cisneros).

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consumption, with scarce information on their clinical impact.[6–9] This is why the generation of good-quality evidence supporting the clinical benefits and feasibility of these initiatives has been demanded as a critical aspect to promote their application in this setting.[2]

In this article, we show the long-term results achieved by an educational ASP associated with Infectious Diseases consultation (IDC) on mortality and antibiotic use of hospitalized patients with solid cancer over a 9-year period.

Methods

Study design and period

A quasi-experimental ecologic study with a time-trend analysis was performed over 34 quarters from January 2009 to June 2017.

Setting

The intervention was implemented in the 20-bed Oncology ward of University Hospital Virgen del Rocío, a tertiary-care hospital in Seville (Spain). Patients with solid, non-hematological malignancies were attended in this unit. The same two senior oncologists attended hospitalized patients throughout the whole study period.

Ethics

The study was approved by the local Ethics Committee.

Intervention

A stable IDC program has been performed in the Oncology ward for the last 20 years, consisting of bedside advice on the management of complex infections and early report of all bloodstream infections (BSI). In January 2011, an educational ASP was prompted throughout the entire hospital, whose methodology and general results have already been published.[10,11] In brief, it consisted of a bundle of educative measures, designed and performed by a multidisciplinary team including Infectious Diseases physicians, Microbiologists, Pharmacists, Intensive Care physicians, Paediatricians and Preventivists. In the specific case of Oncology, the intervention included: a) development of consensual clinical guidelines for common infectious syndromes in patients with cancer [12]; b) face-to-face structured educational interviews with Oncologists on the basis of specific antibiotic prescriptions to reinforce the principles of the correct use of antibiotics (supplementary file 1); prescriptions employed for interviews were randomly selected (not targeted toward specific classes of antibiotics), and their aim was merely pedagogic (not auditing); c) periodical clinical sessions tackling practical aspects of the management of infections in Oncology; d) incorporation of the objectives of the ASP to the annual agreement signed by the department and the hospital director; and e) quarterly reports to the Head of department with the level of attainment of annual pre-agreed objectives. The usual Infectious Diseases consultant on the Oncology ward led the implementation of these tasks in the department. The main messages tackled in educational interviews were: identification and management of sepsis, interpretation of microbiologic results, de-escalation and sequential oral treatments whenever possible, diversification of antibiotic prescriptions and training in optimal duration of antibiotic courses (supplementary file 1).

No other interventions concerning antibiotic use (e.g. antibiotic policies, restrictions, etc.) were performed during the study period. The infection control program in this department consisted exclusively of the isolation of patients with resistant bacteria recovered from clinical samples. No new actions were implemented regarding the prevention of infections in these patients either.

Outcomes

The incidence of BSI produced by the six most relevant microorganisms was monitored (coagulase-negative *Staphylococci* excluded): *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida* spp., and specifically the incidence of multidrug-resistant strains in the Oncology ward (as defined in supplementary file 2). Surveillance data were stored and analysed using WHONET 5.3.

The impact of the intervention on the clinical management of serious infections was measured through the rate of early (7-day) and late (30-day) all-cause mortality among patients developing these BSI, which were recorded yearly. The magnitude of the effect on mortality was also evaluated through quarterly measures of the incidence density (ID) of early and late deaths among patients with BSI (i.e. number of deaths per 1000 admissions). Patients dying in less than 24 h after blood samples collection were not considered for the mortality analysis, as previously proposed,[13,14] for a better selection of patients actually benefitting from this intervention targeting an optimised use of antibiotics. Oncologic patients admitted in such severe condition that produces death in just a few hours are frequently not candidates for intensive support, which undercuts the effectiveness of any other therapeutic measure.

The potential changes in antibiotic use promoted by the intervention were evaluated through quarterly measures of the consumption of all-class antibiotics (ATC group J01 and J02), and specifically antipseudomonal betalactams. Consumption was calculated as Defined Daily Doses (DDD) per 100 occupied bed-days (OBD), according to the Anatomical Therapeutical Chemical Classification (ATC/DDD) methodology.[15] In order to evaluate the implementation of switching to oral treatments, the quarterly rate of oral antibiotic agents DDDs prescribed over the global number of DDDs was also recorded. The impact on direct costs was evaluated through the monitoring of quarterly pharmacy expenditures in antimicrobial drugs of the Oncology department.

Statistical analysis

Two different analyses were performed to evaluate the impact of both interventions (the IDC and the ASP). A time-trend study with a segmented-regression analysis was carried out during the whole study period (2009–2017) to assess the long-term impact of the combination of both interventions. Additionally, to evaluate the specific effect of the ASP, an interrupted time-series (ITS) regression analysis was performed to compare trends before and after the program, following Cochrane Effective Practice and Organization Care recommendations.[16] Two standardized effect sizes were estimated: changes in level (difference between the observed outcome at the first time point of the intervention and the point predicted by the pre-intervention trend), and changes in trend (difference between pre- and post-intervention slopes) following the intervention. A p value of <0.05 was considered statistically significant. Tests were 2-tailed. Statistical analyses were performed with Joinpoint Regression Program v.4.5.0.1 and R software v.3.4.3.

Results

252 episodes of BSI over 34 quarters were recorded. The ID of BSI remained stable (average incidence 4.37 episodes per 1000 OBD, quarterly percentage of change −1% CI95% −2.5, 0.5, $p = 0.17$), as well as the ID of BSI produced by multi-drug resistant bacteria, which kept low during all the study period (average incidence 0.62

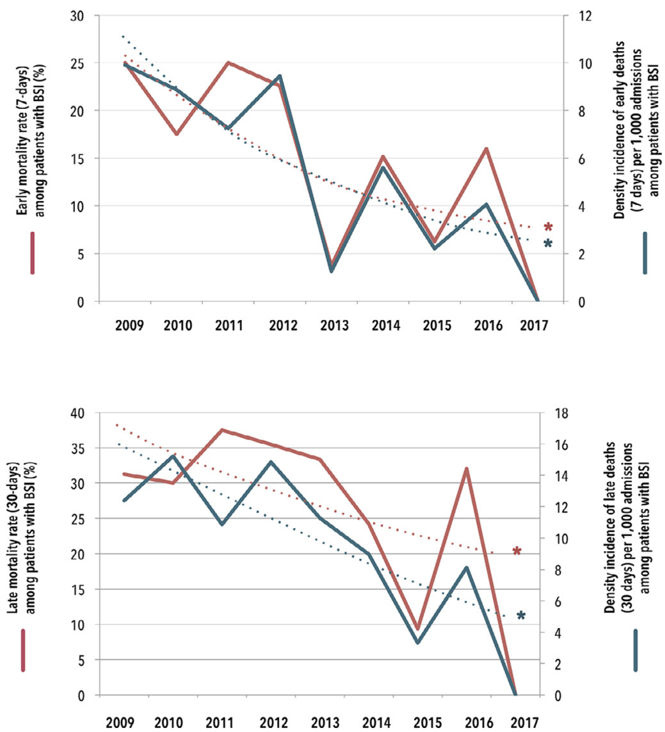

Fig. 1. Time trends of the early (7-day) and late (30-day) mortality of patients with bloodstream infections (BSI) throughout the study period.

* The decreasing trend was statistically significant for all indicators, including early mortality rate (−13.3% yearly reduction; CI95% −20.5; −5.4 p = 0.006), late mortality rate (−8,1% yearly reduction; CI95% −15;−0.7% p = 0.03), incidence density of early deaths (−18% annual reduction; CI95% −23.2; −12.5 p<0.0001) and incidence density of late deaths (−13.5% annual reduction; CI95% −19.9; - 6.5, p = 0.003) among patients with BSI.

2017 data refers to the months included in the study period (January 1st to June 30th).

episodes per 1000 OBD, quarterly percentage of change 0,2% CI95% −0.8, 1.2, $p = 0.70$) (see supplementary file 2).

A total number of 128 individual educational interviews (average 10 interviews per physician a year), 10 clinical sessions (1–2 per year) and 26 reports to the Head of department were delivered after the initiation of the ASP in January of 2011.

A significant reduction in early and late mortality of patients with BSI was observed over the whole study period. Seven and 30-day crude mortality rate decreased a 13.3% per year (CI95% −20.5; −5.4 $p < 0.01$) and −8.1% per year (CI95% −15;−0.7% $p = 0.03$) respectively. The ID of early deaths per 1000 admissions among patients with BSI was also reduced (−18% annual reduction; CI95% −23.2; −12.5 $p < 0.0001$), as well as the ID of late deaths (−13.5% annual reduction; CI95% −19.9; - 6.5, $p < 0.01$) (Fig. 1). A significant reduction in the global consumption of antibiotics was proved (quarterly reduction −0.4% CI95% −0.7; −0.1, $p = 0.01$), and specifically for antipseudomonal betalactams (quarterly reduction −1.23% CI95% −1.85; −0.61, $p < 0.001$). Direct expenditure in antimicrobials was also significantly reduced by the end of the study period (quarterly reduction −1484€ CI95% −2020 to −949€, $p < 0.01$). Conversely, the rate of oral antibiotics prescribed over the total number of DDDs increased progressively (quarterly increase 0.90% CI95% 0.10; 1.72, $p = 0.02$). The evolution of consumption for specific antibiotics can be found in supplementary file 3.

We analysed the specific impact of our ASP on these results through a before-after ITS analysis (Table 1). After the implementation of the ASP, the descending trend in the ID of mortality observed in the pre-intervention period was maintained, with no significant changes in slope proved in this case (Table 1, Fig. 2). When variables assessing antibiotic use were analysed, a significant inflection point was demonstrated after the ASP initiation for all of them, except for the rate of oral antibiotic prescriptions, for which a non-significant improvement was also observed (Table 1 and Fig. 3). Evaluation of the quality of the prescriptions was not systematically performed, but the educational interviews allowed describing some of the most frequent reasons for inappropriate use of antibiotics in the unit. An incorrect selection of the agent according to the clinical diagnosis (28.6%) in the case of empiric treatments, and failing to de-escalate or inappropriate duration in the case of definite therapies (19.6% for both causes) motivated most of the inadequate prescriptions (see supplementary file 4).

Discussion

Our results show that the association of an educational ASP with IDC was able to achieve long-term improvements in antibiotic use, and was accompanied by a reduction of the mortality of bacteraemic infections among patients with solid tumours. To our knowledge, this is the first study proving such benefits for these interventions in the setting of immunocompromised hosts.

A maintained reduction in both the incidence and the mortality rate of patients with BSI (Fig. 1) was observed throughout the study period. The 30-day mortality rate described at the beginning of the study (mean rate 39%) was similar to other large cohorts,[3,17] but by the end of the intervention, it had significantly decreased to a mean mortality rate of 20%. Noticeably, our results also show a significant reduction in early crude mortality throughout the study period (Fig. 1), which would correlate better to an improved management of these acute infections, and should not be expected to be modified by other improvements in general care of cancer patients (e.g. chemotherapy schemes).

IDC had already proved beneficial to the survival of patients with BSI produced by *S. aureus*[18] and *Candida* spp. [14]. However, other studies with a wider scope, analysing all-cause BSI, have only observed better antimicrobial use with no impact on mortality when assessing the role of the counselling.[19,20] Moreover, none of these studies have assessed the impact of IDC in the specific setting of patients with cancer. Our results provide valuable information in this regard, showing a significant improvement in survival parallel to maintained IDC in a large cohort of cancer patients with BSI, which was not limited to specific aetiologies.

With this study, we aimed to evaluate the specific impact of the ASP on mortality. The pre-intervention decreasing trend in mortality was maintained after the implementation of the stewardship program, but no significant changes in the slope were established (Fig. 2). These results prevent us from definitely establishing a causality relationship between the ASP itself and the reduction of mortality, but seems likely that the combined effect of both interventions (the IDC and the ASP) contributed significantly for this sustained trend. At least, these data should highlight the safety of the strategies of rational use of antibiotics promoted by the ASP, also in this population of immunosuppressed hosts. These results are consistent with that obtained by a recent clinical trial developed by our group, which demonstrated the safety of interrupting antibiotic treatment in hematologic patients with febrile neutropenia after confirming the clinical cure.[21] We believe this new information to be relevant, since most studies on ASP developed in immunosuppressed populations have limited their results to the reduction in the consumption of certain antibiotics with no information on their clinical effects or, at best, showing an absence of an increase in mortality.[6–9] To our knowledge, before ours only two ASPs developed in patients with cancer have reported a reduction in mortality.[22,23] They both based their conclusions on two-group comparison tests which directly measured differences before and after the intervention, but this kind of analyses have been strongly discouraged in the assessment of ASPs due to their high

Table 1
Interrupted time-series analysis of the clinical outcomes and antibiotic use changes observed after the implementation of the antimicrobial stewardship program.

	Change in level[a] (CI95%)	Change in slope[b] (CI95%)
Deaths per 1000 admissions (7 days)	−0.43 (−7.07; 6.20)	−0.07 (−1.43; 1.29)
Deaths per 1000 admissions (30 days)	−0.34 (−9.71; 9.01)	−0.77 (−2.69; 1.15)
DDD of all-class antimicrobials (J01+J02) /100 OBD	0.95 (−4.04; 5.96)	**−1.98 (−3.31; −0.64)**[*]
DDD of antipseudomonal betalactams /100 OBD	**−4.04 (−7.61; −0.46)**[*]	**−1.08 (−1.96; −0.21)**[*]
Pharmacy expenditures in antimicrobial agents(€)	**−4770 (−7360; −2180)**[*]	**−1484 (−2020; −949)**[*]
Rate of DDD of oral antimicrobials over all DDD (%)	−2.14 (−10.48; 6.20)	0.51 (−1.41; 2.42)

OBD: Occupied bed-days; DDD: defined daily dose.
[a] Reduction in the first quarter after the intervention with respect to the expected value.
[b] Average reduction per quarter after the intervention.
[*] ***p*<0.05**.

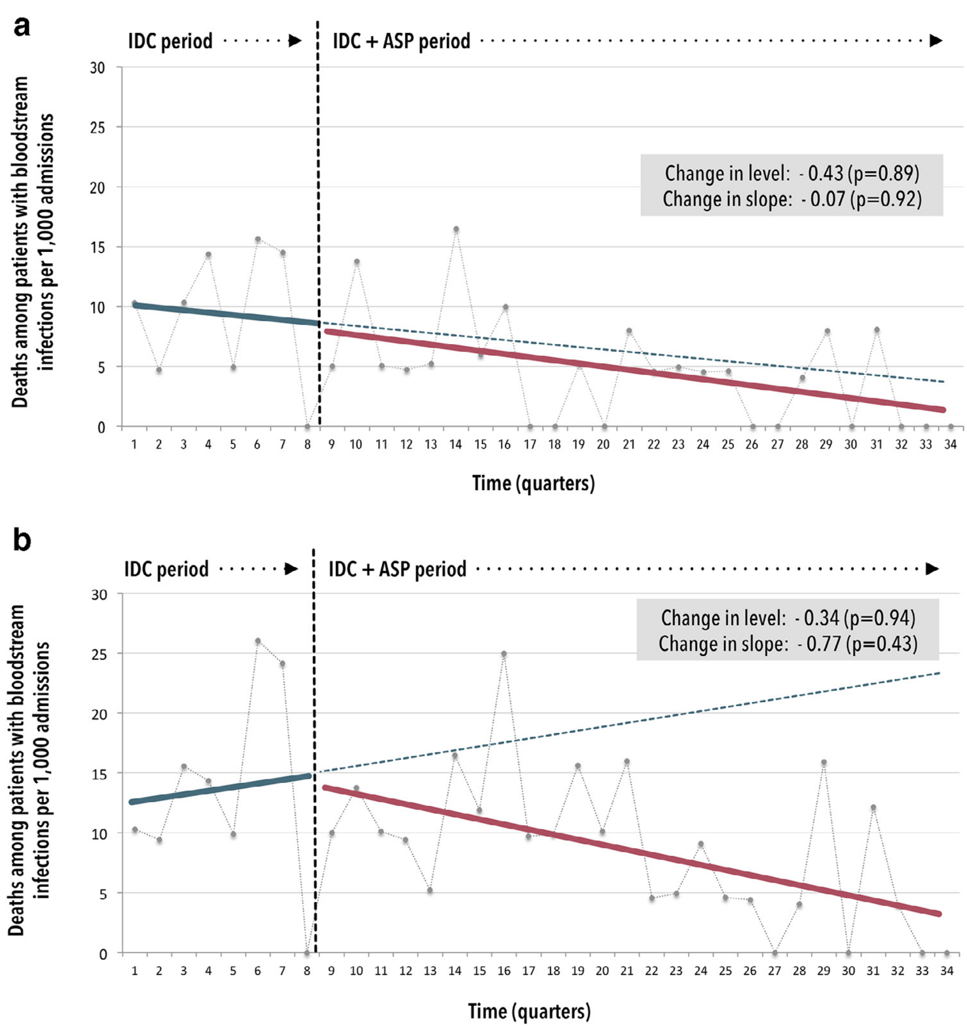

Fig. 2. Interrupted time-series analysis of the trends in mortality among patients with bloodstream infections (BSI) observed before and after the implementation of the antimicrobial stewardship program.
(a) Before-after trends in incidence density of early deaths per 1000 admissions among patients developing bloodstream infections, measured at the 7th day after the BSI diagnosis. **(b)** Before-after trends in incidence density of late deaths per 1000 admissions among patients developing bloodstream infections, measured at the 30th day after the BSI diagnosis.
Solid blue lines show the observed trend during the pre-intervention period. Dashed blue lines show the expected trend after the intervention according to the pre-intervention values. Solid red lines show the observed trend after the intervention.
Change in level: indicates the reduction in the first trimester after the intervention with respect to the expected value.
Change in trend. Indicates the average reduction achieved per quarter after the intervention.
IDC*: Infectious Diseases Counseling;* ***ASP****: Antimicrobial Stewardship Program.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

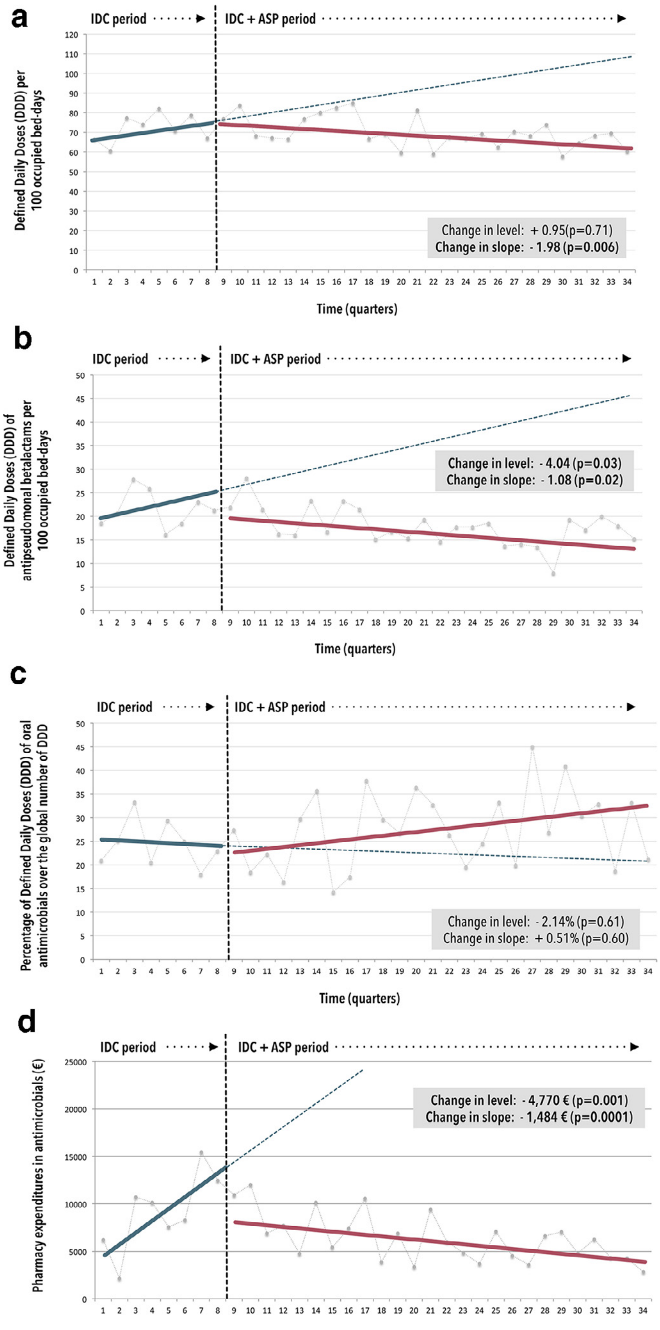

Fig. 3. Interrupted time-series analysis of the trends in antibiotic use observed after the implementation of the antimicrobial stewardship program.
(**a**) Before-after trends in global consumption of antibiotics; (**b**) Before-after trends in consumption of antipseudomonal betalactams; (**c**) Before-after trends in the rate of DDD of oral antibiotics prescribed over the total number of DDDs; (**d**) Before-after trends in the direct Pharmacy expenditures in antimicrobials.
Solid blue lines show the observed trend during the pre-intervention period. Dashed blue lines show the expected trend after the intervention according to the pre-intervention values. Solid red lines show the observed trend after the intervention.
Change in level: indicates the reduction in the first trimester after the intervention with respect to the expected value.
Change in trend. Indicates the average reduction achieved per quarter after the intervention.
IDC: *Infectious Diseases Counseling;* ***ASP***: *Antimicrobial Stewardship Program.*

risk of bias.[24] Indeed, the internal validity of both studies seems to be undercut by a limited sample size and study period, and a seemingly uneven distribution of basal characteristics and clinical presentation of the infections evaluated between groups.[22,23] ITS have been pointed out as the preferential method to assess the impact of interventions, as we did.[16,25]

The ASP had a significant impact on the use of antibiotics in the unit. Our data show how the implementation of structured interventions is necessary to change the way antibiotic are used in these kinds of units, suggesting that the sole clinical counselling may be insufficient to achieve this goal. In fact, when variables regarding antimicrobial consumption were analysed, we observed stable or even worsening trends in antibiotic use during the years preceding the ASP (Fig. 3). This might be explained because in traditional IDC, the intervention of the expert is limited to the patients attended by the consultant, and this may not necessarily change the use of antibiotics in the entire unit. Our ASP consisted of a bundle of educational interventions aiming to improve the knowledge of all Oncologists on the principles of a correct antimicrobial treatment,[10] and it was only after their implementation when global antibiotic use in the unit was truly improved.

The study has some limitations. The possibility of an ecologic bias is inherent to the design, and causality should be cautiously considered. We analysed in detail any possible interference from potential confounding factors, and recorded no significant changes in the incidence of all-cause BSI or multi-drug resistant microorganisms, no significant modifications in the portfolio of services of the Oncology department occurred, and no other interventions affecting antibiotic policies, infection control or antibiotic prophylaxis were implemented during the study period. A more complex methodology for the statistical analyses was also chosen to prevent some of these potential biases,[24] showing consistent results throughout all the variables evaluated. Causality cannot be definitely established by this design (especially for mortality variables), but the consistency between all these data supports the feasibility of this hypothesis. Of note, the expiration of the patent of imipenem (March 2010) and meropenem (April 2011), as well as minor changes in the costs of other antimicrobials throughout the study period may have explained some part of the reduction in Pharmacy expenditure reported. The effect of this circumstance on final results should be expected secondary, since the reduction in antibiotic consumption was not limited to carbapenems, and continued throughout the whole study period, years after the patent expiration. The close interrelation between both interventions evaluated (the IDC and the ASP) made it difficult to measure the precise weight of each one on the final outcomes achieved. Nonetheless, the significance of this precise information may be less relevant, since they are usually also carried out together in real-life. Finally, the single-centre design of the study makes it necessary to confirm the reproducibility of our results in different healthcare centres; in this sense, we believe that our work may serve as a solid proof-of-concept to encourage the implementation of similar programs, and offer new arguments to avoid the reluctance of clinicians still unsure of the safety of these initiatives.

To sum up, this study suggests a substantial contribution of the IDC and ASPs for improving the outcome of BSI in patients with solid cancer, and for promoting better use of antibiotics in this setting. Our results also show the safety of the strategies of rational use of antibiotics among immunocompromised hosts, and define the necessity of implementing structured ASPs beyond sole clinical counselling to achieve this goal.

CRediT authorship contribution statement

José Molina: Conceptualization, Formal analysis, Writing - review & editing. **Manuel Noguer:**

Writing - review & editing. **José Antonio Lepe:** Data curation, Writing - review & editing. **María Antonia Pérez-Moreno:** Data curation, Formal analysis, Writing - review & editing. **Manuela Aguilar-Guisado:** Writing - review & editing. **Roberto Lasso de la Vega:** Writing - review & editing. **Germán Peñalva:** Data curation, Formal analysis, Writing - review & editing. **Juan Carlos Crespo-Rivas:** Writing - review & editing. **María Victoria Gil-Navarro:** Data curation, Writing - review & editing. **Javier Salvador:** Writing - review & editing. **José Miguel Cisneros:** Conceptualization, Funding acquisition, Writing - review & editing.

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Transparency declaration

None to declare.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.07.002.

References

1. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017(2). doi:10.1002/14651858.CD003543.pub4.
2. Robilotti E, Holubar M, Seo SK, Deresinski S. Feasibility and applicability of antimicrobial stewardship in immunocompromised patients. *Curr Opin Infect Dis* 2017;**30**(4):346–53. doi:10.1097/QCO.0000000000000380.
3. Marín M, Gudiol C, Garcia-Vidal C, Ardanuy C, Carratalà J. Bloodstream infections in patients with solid tumors: epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. Med *(Baltimore)* 2014;**93**(3):143–9. doi:10.1097/MD.0000000000000026.
4. Alevizakos M, Gaitanidis A, Andreatos N, Arunachalam K, Flokas ME, Mylonakis E. Bloodstream infections due to extended-spectrum β-lactamase-producing enterobacteriaceae among patients with malignancy: a systematic review and meta-analysis. *Int J Antimicrob Agents* 2017;**50**(5):657–63. doi:10.1016/j.ijantimicag.2017.07.003.
5. Seo SK, Lo K, Abbo LM. Current state of antimicrobial stewardship at solid organ and hematopoietic cell transplant centers in the uS. *Infect Control Hosp Epidemiol* 2016;**37**(10):1195–200. doi:10.1017/ice.2016.149.
6. Horikoshi Y, Kaneko T, Morikawa Y, Isogai M, Suwa J, Higuchi H, et al. The north wind and the sun: pediatric antimicrobial stewardship program combining restrictive and persuasive approaches in hematology-oncology ward and hematopoietic stem cell transplant unit. *Pediatr Infect Dis J* 2018;**37**(2):164–8. doi:10.1097/INF.0000000000001746.
7. Snyder M, Pasikhova Y, Baluch A. Early antimicrobial De-escalation and stewardship in adult hematopoietic stem cell transplantation recipients: retrospective review. *Open Forum Infect Dis* 2017;**4**(4):ofx226. doi:10.1093/ofid/ofx226.
8. So M, Mamdani MM, Morris AM, Lau TTY, Broady R, Deotare U, et al. Effect of an antimicrobial stewardship programme on antimicrobial utilization and costs in patients with leukaemia: a retrospective interventional controlled study. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2017. doi:10.1016/j.cmi.2017.11.009.
9. Wattier Rachel L, Levy Emily R, Sabnis Amit J, Dvorak Christopher C, Auerbach Andrew D. Reducing second gram-negative antibiotic therapy on pediatric oncology and hematopoietic stem cell transplantation services. *Infect Control Hosp Epidemiol* 2017;**38**(9):1039–47. doi:10.1017/ice.2017.118.
10. Molina J, Peñalva G, Gil-Navarro María V, Praena J, Lepe JA, Pérez-Moreno MA, et al. Long-term impact of an educational antimicrobial stewardship program on hospital-acquired candidemia and multidrug-resistant bloodstream infections: a quasi-experimental study of interrupted time-series analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2017. doi:10.1093/cid/cix692.
11. Cisneros JM, Neth O, Gil-Navarro MV, Lepe-Jiménez JA, Jiménez-Parrilla F, Cordero E, et al. Global impact of an educational antimicrobial stewardship program on prescribing practice in a tertiary hospital center. *Clin Microbiol Infect* 2014;**20**(1):82–8.
12. PRIOAM Guidelines for the diagnosis and treatment of the infectious diseases. Infectious syndromes in patients with malignancies. University Hospital Virgen del Rocío (Seville, Spain). Available at: www.guiaprioam.com. Accessed 01 April 2019.
13. López-Cortés LE, Del Toro MD, Gálvez-Acebal J, Bereciartua-Bastarrica E, Fariñas MC, Sanz-Franco M, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of staphylococcus aureus bacteremia. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2013;**57**(9):1225–33. doi:10.1093/cid/cit499.
14. Lee Rachael A, Joanna Z, Camins BC, Griffin RL, Rodriguez JM, McCarty TP, et al. Impact of infectious disease consultation on clinical management and mortality in patients with candidemia. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2018. doi:10.1093/cid/ciy849.
15. WHO collaborating center for drug statistics methodology. Available at https://www.whocc.no/ddd/definition_and_general_considera/. Accessed 24 December 2017, n.d.
16. Norwegian Knowledge Cent. Effective practice and organisation of care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors 2013.
17. Williams MD, Braun LA, Cooper LM, Johnston J, Weiss RV, Qualy RL, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care Lond Engl* 2004;**8**(5):R291–8. doi:10.1186/cc2893.
18. Vogel M, Schmitz RPH, Hagel S, Pletz MW, Gagelmann N, Scherag A, et al. Infectious disease consultation for staphylococcus aureus bacteremia - A systematic review and meta-analysis. *J Infect* 2016;**72**(1):19–28. doi:10.1016/j.jinf.2015.09.037.
19. Kerremans JJ, Verbrugh HA, Vos MC. Frequency of microbiologically correct antibiotic therapy increased by infectious disease consultations and microbiological results. *J Clin Microbiol* 2012;**50**(6):2066–8. doi:10.1128/JCM.06051-11.
20. Fluckiger U, Zimmerli W, Sax H, Frei R, Widmer AF. Clinical impact of an infectious disease service on the management of bloodstream infection. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2000;**19**(7):493–500.
21. Aguilar-Guisado M, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol* 2017;**4**(12):e573–83. doi:10.1016/S2352-3026(17)30211-9.
22. Rosa RG, Goldani LZ, dos Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. *BMC Infect Dis* 2014;**14**:286. doi:10.1186/1471-2334-14-286.
23. Madran B, Keske Ş, Tokça G, Dönmez E, Ferhanoğlu B, Çetiner M, et al. Implementation of an antimicrobial stewardship program for patients with febrile neutropenia. *Am J Infect Control* 2018;**46**(4):420–4. doi:10.1016/j.ajic.2017.09.030.
24. Shardell M, Harris AD, El-Kamary SS, Furuno JP, Miller RR, Perencevich Eli N. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2007;**45**(7):901–7. doi:10.1086/521255.
25. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;**27**(4):299–309.