Original article

Effects of a bundled Antimicrobial Stewardship Program on mortality: a cohort study

CrossMark

Lucas Miyake Okumura[a,*], *Monica Maria Gomes da Silva*[b], *Izelandia Veroneze*[b]

[a] *Hospital Pharmacy Department, Clinical Hospital, Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil*
[b] *Infectious Disease Control Service, Clinical Hospital, Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil*

ARTICLE INFO

ABSTRACT

Objectives: To assess a bundled Antimicrobial Stewardship Program and its effect on mortality.

Data: Eight months of clinical electronic medical records and Antimicrobial Stewardship Program registries were used as source of data.

Method: This is a historical cohort study conducted in a Brazilian University Hospital. Eligible patients were admitted to general wards or intensive care units and had an antimicrobial therapy prescribed and assessed by different strategies: Bundled Antimicrobial Stewardship Program (bundled intervention consisted of clinical pharmacist chart review, discussion with microbiologist and infectious disease physicians, local education and continuous follow-up) or Conventional Antimicrobial Stewardship Program (clinical pharmacist chart review and discussion with infectious disease physician). Primary outcome from this study was 30-day mortality, which was compared between groups, by using Kaplan–Meier survival curve and log-rank test. Other outcomes included Defined Daily Doses per 1000 patient-days and occurrence of resistant bacteria.

Results: From 533 patients, 491 were eligible for the study, of which 191 patients were included to Antimicrobial Stewardship Program and 300 to Conventional strategy. In general, they were likely to be male and age was similar in groups (58.9 vs 55.5 years, $p = 0.38$). Likewise, Charlson Comorbidity Index was not statistically different between groups (2.6 vs 2.7, $p = 0.2$). Bloodstream site infections were frequently diagnosed in both groups (30.89% vs 26%, $p = 0.24$). Other less common sites of infections were central nervous system and lungs. The ASP group had higher survival rates ($p < 0.01$) and the risk difference was 10.8% (95% CI: 2.41–19.14). There were less Defined Daily Doses per 1000 patient-days (417 vs 557.2, $p < 0.05$) and higher rates of resistant bacteria identified in the ASP group (83% vs 17%).

Conclusion: Bundled ASP was the most effective strategy, with reduced mortality and Defined Daily Doses per 1000 patient-days.

© 2015 Elsevier Editora Ltda. All rights reserved.

* Corresponding author.
  E-mail address: lucasokumura@yahoo.com.br (L.M. Okumura).

Background

Antimicrobial Stewardship Programs (ASP) seek to optimize clinical outcomes and to reduce unwanted events related to inappropriate use of antimicrobial drug therapy (ADT).[1,2]

According to the Infectious Disease Society of America and Society for Healthcare Epidemiology of America,[1] the collaboration between an Infectious Diseases Medical Doctor (ID MD), a clinical pharmacist, and other professionals improves patient outcomes by conducting prospective audits/feedback, formulary restriction, local education, implementing evidence-based guidelines, de-escalation and escalation of ADT, dose optimization, and intravenous-to-oral therapy switch.

Common outcomes used to assess the effectiveness of Stewardship Programs include specific indicators such as drug waste, days of therapy, Defined Daily Doses (DDDs), reduction of antimicrobial resistance, and rate of *Clostridium difficile* infections.[3,4] ASP-related research has also reported positive effects on hospital length of stay and mortality,[5,6] but still they are scarce in international literature because such outcomes can be influenced by multiple confounders.

Recently, one systematic review has evaluated a single intervention – ADT de-escalating – on mortality.[7] In fact, such evidence was poorly planned and it does not illustrate what Stewardship Programs are all about. Despite the importance of ADT de-escalating and its large applicability to preserve large spectrum antibiotics, other interventions such as switch therapy (intravenous-to-oral) and ADT initiation are largely performed by Stewardships.[8] Current research have evidenced that they play a role in reducing resistant bacteria and other undesired events.[8–11]

There is a demand to conduct ASP researches that illustrate what is performed during daily clinical practice. Notwithstanding, ID societies[1,2] endorse the need to assess whether a "bundled" ASP strategy, with as many as possible interventions, improves patients' outcomes.[2]

Objectives

This research aimed to assess the effects of a bundled ASP strategy on 30-day mortality. Secondary objectives from this study assessed bundled ASP effects on DDD and occurrence of resistant bacteria.

Methods

Study design and setting

This is a retrospective cohort study conducted in a Brazilian public university hospital with 550 beds and an average of 60% occupation.

This hospital has a five day/week ASP and the core members from this team include two ID physicians (preceptor and ID resident) and one pharmacist (resident).

Patients

From February to September 2013, patients who were more than 18 years old were included in this study when admitted to adult general ward or intensive care unit (ICU). To meet eligibility criteria, they also needed to have a drug-related problem in their ADT prescription evaluated by a clinical pharmacist at the first or second day of drug therapy. Exclusion criteria for this study were: admission to other wards (cardiac, oncology and hematology wards and other specialty units); patients not assessed by clinical pharmacist; non-acceptance of interventions suggested by ASP.

During the study period, patients were assigned to different Stewardship Programs according to human resources availability. Thereby, two strategies were concomitantly performed and patients could receive either a conventional ASP or a bundled ASP.

Bundled strategy consisted in daily clinical pharmacist ADT problems screening by using chart reviews, lab results and electronic system review; discussion with ID MD and microbiologist (i.e. daily visits to laboratory to discuss possibilities to narrowing or increasing antibiotics spectrum); local education to prescribers to improve drug therapy use; and provide continuous follow-up (until clinical resolution or discharge, when applicable).

Conventional strategy consisted of a passive ASP, whereby a clinical pharmacist performed the same drug therapy problems screening and discussed each case with ID physicians. Whenever an intervention was necessary, a phone was used to communicate with prescribers.

Data collection, baseline characteristics and outcomes

One pharmacist (LMO) collected data from ASP interventions registries, hospital's medical record and pharmacy dispensing registries.

To compare baseline ASP strategies, we considered demographic variables (age and sex), clinical conditions (primary site of infection, Charlson's Comorbidity Index – CCI, admission to ICU or general ward)[12] and days of follow-up/per patient.

The primary outcome from this study was 30-day mortality, which was compared between groups. Other assessed outcomes included: DDD reduction, interventions performed to improve ADT and occurrence of resistant bacteria in blood cultures. In order to assess such outcomes the following definitions were used:

- 30-day mortality: time period since patient assessment by conventional or bundled ASP strategy, till discharge (survive) or event of death.
- DDD was expressed as DDD/thousand patient-days and was calculated according to World Health Organization criteria.[13]
- Resistant bacteria were all types of isolated organisms that had a documented drug resistance in a sterile biological sample (only blood culture was considered). We did not consider in this outcome drug sensitive bacteria.

Finally, we conducted a subgroup analysis by including all patients who had not accepted intervention by ASP to analyze the impact on mortality.

Study sample

The calculated sample size for the present study was 186 patients in each study arm based on a previous study[14] and considering a relative risk of 0.57 on mortality, two-sided hypothesis, 5% alpha and 80% power. We chose this study because it was conducted in a critical care setting, which is also part of our inclusion criteria. Moreover, such a study was also conducted in a Brazilian hospital and showed impact on mortality.

Data analysis and statistical methods

Descriptive statistics were used to analyze continuous and dichotomous variables. Inferential analyses were performed to compare patient characteristics, whereby continuous variables were assessed with t-test (normal curve assumed with Komolgorov–Smirnov test) and proportion variables were analyzed with chi-square or Fisher's exact test, as adequate.

To assess the primary outcome, a survival analysis (non-parametric Kaplan–Meier method and log-rank test) compared the occurrence of fatal events between groups. We also determined point estimate values, such as absolute risk reduction (ARR), relative risk (RR), number needed to treat (NNT) and 95% confidence intervals (CI). Incidence rates (IR) of 30-day mortality per thousand patient-days were also reported by means of comparison to other epidemiological studies.

At last, as we did not balance patients between groups, different baseline characteristics could influence the primary outcome. Therefore, all critical variables at baseline ($p < 0.2$) were included in a Cox proportional-hazards regression. Selected variables were included one-by-one in the multivariate analysis model and covariates were controlled by variables that had a p-value variation greater than 0.1.

All statistical analyses were conducted using SPSS v. 20.0 and considered a two-sided hypothesis test and 5% probability of a type I error. All p-values lower than 0.05 were considered statistically significant.

Ethical issues

The local Bioethics Committee, which complies with Helsinki's Declaration, approved this study and the certificate number of analysis is CAAE 26619414.2.0000.0096. Lastly, we used the STROBE Statement to write this manuscript and provide adequate reporting.[15]

Results

Patient characteristics

During the study period, pharmacists assessed more than 3000 patients and 533 had undergone clinical pharmacists DRP screening and had ADT problems. Of those, 191 received the
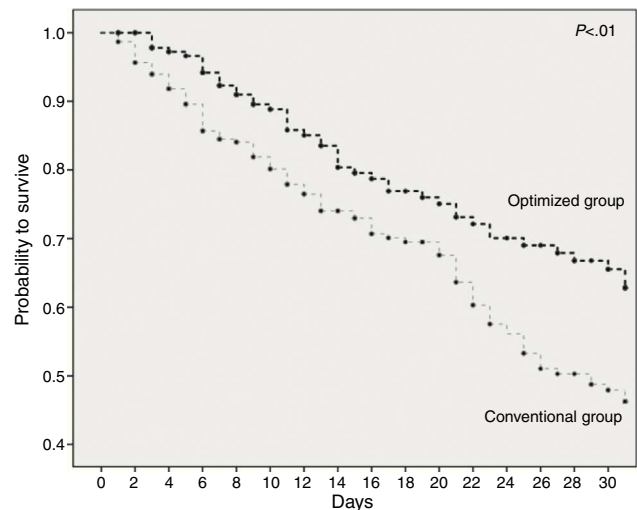

Fig. 1 – Survival curves of different ASP strategies.

bundled ASP Strategy and 300 patients received the conventional ASP. Other 42 patients did not have their drug therapy modified as suggested by the ASP team, and therefore were analyzed separately (Table 2).

In summary, there were predominantly male patients, who had a similar age (58.9 vs 55.5 years, $p = 0.17$) and CCI score (2.6 vs 2.7, $p = 0.2$). As expected, ICU patients had greater CCI scores than patients in general wards (Table 1).

The most common sites of infection in both ASP groups were, respectively, bloodstream (30.9% vs 26%, $p = 0.19$), respiratory (28.3% vs 38%, $p < 0.03$), and urinary tract infections (14.1% vs 6.7%, $p = 0.01$). Other less common sites of infection were central nervous system and ventilator-associated pneumonia (VAP).

Primary outcome: crude mortality and group comparison

In general, 166 (34%) patients experienced a fatal event and the overall 30-day mortality incidence was 1.6 deaths per 100 patient-days. There was a significant difference between group rates (1.1 vs 1.9 deaths/100 patient-days, $p = 0.002$). To calculate the incidence rate denominator, follow-up between groups ought to be statistically the same, which was confirmed with a non-significant p-value of 0.23 (Table 1).

Survival analysis showed that 30-day mortality was lower with bundled ASP ($p < 0.01$) (Fig. 1). The RR was 28% lower in the bundled ASP group (RR = 0.72, 95% CI 0.54–0.94) and we observed an absolute risk reduction of 10.7% (95% CI 2.41–19.14), which means that for every nine patients who receive ASP, one will benefit from this intervention (NNT = 9.28, 95% CI 5.22–41.54) (Fig. 2).

Secondary outcomes

The average DDD per 1000 patient-days was significantly lower in the bundled ASP group: 417 (±56.1) vs 557.2 (±10.25), $p < 0.01$.

There was a higher rate of resistant bacteria in the Bundled ASP group (83% vs 17%), and commonly isolated bacteria were *K. pneumonia* (either one drug resistant, carbapenemase

Table 1 – Patient characteristics.					
Characteristics	Bundled ASP	(n = 191)	Conventional ASP	(n = 300)	p-value
	No. of patients	%	No. of patients	%	
Age, in years Mean (sd)	58.9 (18.3)	55.5 (17.3)	0.38		
Sex, female	79	41.3	143	47.7	0.17[*]
General ward	54	28.3	68	22.7	0.33
Intensive care units	137	71.7	232	77.3	0.2[*]
Primary infection site					
Bloodstream site	60	31.4	78	26	0.19[*]
Central nervous system	6	3.1	6	2	0.43
Gastrointestinal	25	13.1	44	14.7	0.62
Skin and soft tissue	14	7.3	23	7.7	0.89
Respiratory tract	54	28.3	114	38	0.03[*]
Ventilation associated	5	2.6	15	5	0.19[*]
Urinary tract	27	14.2	20	6.6	0.01[*]
Charlson Comorbidity Index Mean (sd)	2.6 (2.3)	2.7 (2.4)	0.2[*]		
General ward Mean (sd)	2.6 (2.4)	2.6 (2.4)	–		
Intensive care units Mean (sd)	2.8 (1.8)	3.0 (2.3)	–		
Days of follow-up Mean (sd)	25.9 (32.7)	19.5 (21.1)	0.23		
30-Day mortality	52 (27.2)	114 (38)	<0.01		
Intensive care units	42 (21.9)	99 (33)	<0.01		
General ward	10 (5.2)	15 (5)	<0.01		

Abbreviations: sd, standard deviation; 95% CI, 95% confidence interval.
Data are *n* (%) unless otherwise stated.
[*] Considered to be included in the Cox regression.

Table 2 – Effects of non-accepting ASP intervention.		
	Bundled vs conventional ASP (total = 491 patients)	Bundled + non-accepted interventions vs observation (total = 533 patients)
ARR	10.8% (95% CI 2.4–19.1)	8.82% (95% CI 0.8–16.8)
RR	0.72 (95% CI 0.54–0.94)	0.77 (95% CI 0.6–0.98)

Fig. 2 – Interventions performed to improve Antimicrobial Drug Therapy (ADT). *Notes*: **There were 14 interventions performed by ASP after discussing laboratory preliminary results (Table 4), such as morphology, culture or biochemistry findings, whereby 8 were antimicrobial initiation, 4 escalations, and 2 de-escalations. "ADT Change" accounted for IV/PO switch and same spectrum modification (vancomycin → daptomycin).**

or extended spectrum beta-lactamase positive), followed by methicillin-resistant negative coagulase *Staphylococcus* (MR NCS) (Table 4).

There were 227 accepted interventions, which consisted in changing ADT (11%), improving dosage (39%), interruption of treatment (28%), initiation of ADT (8%), escalation or de-escalation (6% and 8%, respectively) (Table 2).

Lastly, in a subgroup analysis considering the 42 excluded patients, who had not accepted an intervention, we would have observed a 2% decrease in the efficacy of ASP (10.8% vs 8.8%) and a 6% reduction in RR (RR, 0.72–0.77) (Table 2).

Baseline characteristics and impact on 30-day mortality

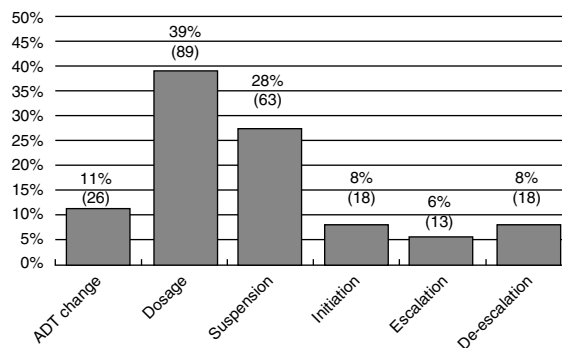Six covariates (sex, CCI, UTI, VAP, RT, and admission to ICU) were included in the multivariate model (see bivariate analysis in Table 1) to assess whether they could influence primary outcome.

Cox regression determined that two variables could independently predict the risk of death: CCI and admission to ICU

Table 3 – Independent predictors of 30-day mortality after Cox proportional-hazards regression.

Variable	p-value	aHR	95% CI
Sex	0.917	0.89	0.75–1.39
BSI	0.040	0.64	0.41–0.98
RT	0.974	1.36	0.68–1.49
UTI	0.939	1.05	0.52–1.83
VAP	0.220	0.56	0.78–2.96
Charlson Comorbidity Index[*]	0.003	1.09	1.03–1.16
Admission to ICU[*]	0.005	0.93	0.89–0.98

Abbreviations: aHR, adjusted Hazard Ratio; BSI, Blood Site Infections; RT, Respiratory Tract Infection; UTI, Urinary Tract Infection; VAP, Ventilator-Associated Pneumonia; SE, standard error; ICU; Intensive Care Unit; 95% CI, 95% confidence interval.
Intensive Care Units was changed to "Admission to ICU", to facilitate reading.

[*] Covariates with statistical significance.

(Table 3) may have influenced 30-day mortality and they were slightly higher in conventional ASP.

Discussion

Mortality reduction

This study assessed the effectiveness of a bundled ASP by using mortality and other relevant outcomes such as DDD reduction, occurrence of resistant bacteria, and interventions performed to improve ADT. The 10% absolute risk reduction between groups can be considered as an important clinical effect. Previous studies[14,16] used regression techniques or different periods to assess the effects of ASP implementation, which is different from our study design; we compared different ASP strategies.

Nonetheless, we conducted a retrospective cohort study and future prospective investigations – randomized controlled trials – would be important to answer whether different types of ASP strategies result in different outcomes. This information should be endorsed by two other findings in our study:

- The RR (0.72, 95% CI 0.54–0.94) was higher if compared to a previous research (RR = 0.57)[14] and we attribute this difference to small but important effectiveness of non-bundled strategy.
- In multivariate analysis, CCI and admission to ICU were considered risk factors and could have influenced 30-day mortality between groups. Propensity scores could not improve the balance between the two groups because all patients that received both strategies were included.

When we input patients who did not accept an intervention by bundled ASP (previously excluded from study), we observed increased mortality rates. Outcomes may be directly impacted by accepting or not ASP suggestions. Therefore, non-acceptance of an ASP intervention may be discouraged, and institutions with low rates of ASP acceptance should delineate strategies to change this risky behavior.

Lower use of antimicrobial drug therapy

Regarding DDD reduction, A-II level evidence from international guidelines[1] indicates that ASP interventions reduce unnecessary ADT prescription. Previously, a multicenter (9 hospitals) cohort study[16] showed that 206 (38%) out of 542 patients received inappropriate use of ADT. Such rate of inadequate ADT reassures why bundled strategy may have performed so many interventions to optimize antibiotics use.

In our study, renal function dose adjustments (dose reduction) and drug interruption were the most prevalent interventions and comprised almost 70% from all ADT optimizations performed by the bundled strategy. For these reasons, we believed that bundled ASP interventions were directly responsible for DDD reduction.

Although this scenario suggests less antibiotics use and cost reduction, it is important to remember that DDD decrease neither implies global cost-savings nor cost-effectiveness, as it only accounts for ADT consumption. Other variables should be addressed to assess the impact of ASP on economic outcomes – such as length of stay and human resource costs.

More bacteria identification: cause or consequence?

Interestingly, bundled ASP had more positive blood cultures than conventional ASP, both in general wards and ICU. We believe that these findings are likely to be caused by bundled ASP. In other words, local audits and continuous education to physicians may have promoted bacteria identification.

Because this study was not powered and designed for such assessment, we did not make further assessments through regression analysis, as this could lead to untrue statements. However, other hypotheses that have been brought up from these observations are: is the rate of microbial identification influenced by locally educating physicians and by better infectious disease management? Does ASP intervention lead to more cultures? Does ASP stimulate more accurate infection diagnosis or does more bacterial isolation ultimately leads to reduced mortality?

Resistant bacteria were more often identified in the bundled ASP group, like resistant *Klebsiella* spp, including carbapenemase producers, methicillin-resistant staphylococci, and resistant *Acinetobacter baumanii*. All of the aforementioned microorganisms are associated with higher death rates[17,18] and, even so, bundled ASP was associated with better outcomes.

Limitations

This manuscript has several limitations. Firstly, this was a retrospective study; thus, data collection and source of clinical registries are natural drawbacks for these studies including: incomplete data, censoring, and non-blinded data analysis. We preferred a cohort design instead of a clinical trial because, in this preliminary assessment, we had to investigate whether different ASP strategies could impact patient outcomes. Moreover, designing a proper randomized clinical trial for antimicrobial stewardship is rather complicated, especially for a prospective audit and feedback strategy; proper patient allocation concealment and education-feedback process may

Table 4 – Resistant bacteria isolated from blood cultures according to wards and to groups.

Bacteria	Bundled ASP		Conventional ASP	
	ICU (*n*)	Non-ICU (*n*)	ICU (*n*)	Non-ICU (*n*)
K. pneumoniae (KPC+ or ESBL)	6	–	–	–
NCS	5	1	–	2
A. baumanii (resistant)	5	–	–	–
NCS (MR)	3	–	1	–
S. aureus (MRSA)	3	–	1	1
P. aeruginosa	1	2	–	–
E. cloacae	–	1	–	1
E. faecalis	–	1	–	1
B. cepacia	1	–	–	–
C. freundii	–	1	–	–
E. faecium (VRE)	1	–	–	–
E. aerogenes	–	1	–	–
K. pneumoniae	–	1	–	–
P. aeruginosa (resistant)	1	–	–	–
S. viridans	1	–	–	–
Total (42 isolated)	27 (64%)	8 (19%)	2(5%)	5 (12%)

Abbreviations: ICU, intensive care unit; KPC+, Carbapenemase resistance; ESBL, extended spectrum beta-lactamase; NCR MR, non-coagulase methicillin-resistant *Staphylococcus*; MRSA; methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci. Resistant *A. baumanii* includes resistance to at least three drugs (cephalosporins, penicillins, aminoglycosides, or quinolones).

lead to better antibiotic prescribing practices over time.[19,20] Such method-related opportunities should be considered in future studies.

Secondly, "care bundles" of different antimicrobial stewardship interventions are often implemented concurrently (i.e., education of prescribers, formulary restriction, prospective audit, and feedback).[21] Therefore, considering also the existence of infection prevention bundles, researchers aiming to tease out the contribution of each intervention.[7] may find difficulties to isolate true clinical effects on patients' outcomes. Nevertheless, the IDSA recommend researching pragmatic and practice-oriented ASP,[1] which was our choice when designing the present study.

Furthermore, our study design did not allow for quantification of the antimicrobial stewardship effects on bacterial resistance, as it takes time for the benefits to be evident. That is why the majority of published stewardship papers adopted quasi-experimental designs: typically before and after implementation studies, where "treatment" allocation and other potential confounding factors are not controlled.[1,22–24]

We observed a significant difference between groups regarding the rate of respiratory tract and urinary tract infections. Since multivariate analysis indicated that both sites of infection were not independently associated with an increase on 30-day mortality, we believe these differences between groups were due to imbalanced patients allocation. If on one hand such statistical procedure would lead to balanced groups, on the other hand in multivariate analysis to assess whether group differences could predict primary outcome only CCI and admission to ICU played a role on 30-day mortality. Thus, future studies should strongly consider controlling for these two variables, although they were only significant after accepting a *p*-value < 0.2 in univariate analysis.

Finally, our study setting was a university hospital, where there are resident rotations, so more DRP may be found. Moreover, professionals may be more willing to accept interventions.

One should consider the external validity of our study before implementing our results in distinct services or comparing them with other investigations; this study was conducted in a Latin American country.

Final considerations

The bundled ASP proved to be an effective way to improve antimicrobial drug therapy, by reducing 30-day mortality and DDD/1000 patient-days. Moreover, CCI and admission to ICU were likely to increase mortality, so patients with these risk factors should receive more attention in future ASP studies.

Worldwide, ASP implementation has risen in response to the growing threat of antimicrobial resistance amidst the diminishing pipeline of new antibiotics. We believe that antimicrobial stewardship will continue to evolve in the upcoming decade, and among various interventions, prospective audit and feedback will probably be the most implemented strategy, in view of its clear advantages: particularly, lack of prescribers' opposition and prescribing behavior modification.[25]

Future researches should focus on evaluating the role and ways to improve clinical effectiveness of different bundled strategies, especially those interventions that may increase the rate of bacteria isolation, which translates into correctly selecting ADT to treat specific microorganisms. There is also an urgent need to standardize outcomes as well as develop novel study designs that can objectively assess antimicrobial stewardship interventions, despite the limitations and opportunities inherent to ASPs heterogeneous structures and process.

Funding

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

REFERENCES

1. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159–77.
2. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol. 2003;24:699–706.
3. Lawton RM, Fridkin SK, Gaynes RP, McGowan JE. Practices to improve antimicrobial use at 47 US hospitals: the status of the 1997 SHEA/IDSA position paper recommendations. Infect Control Hosp Epidemiol. 2000;21:256–9.
4. Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial *Clostridium difficile*-associated diarrhea by restricting clindamycin use. Ann Intern Med. 1994;120:272–7.
5. Yeo CL, Wu JE, Chung GWT, Chan DSG, Chen HH, Hsu LY. Antimicrobial stewardship auditing of patients reviewed by infectious diseases physicians in a tertiary university hospital. Antimicrobial Resist Infect Control. 2013;2:29.
6. Rosa RG, Goldani LZ, 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.
7. Silva BN, Andriolo RB, Atallah AN, Salomão R. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. Cochrane Database Syst Rev. 2013;3:CD007934.
8. Siegel RE, Halpern NA, Almenoff PL, Lee A, Cashin R, Greene JG. A prospective randomized study of inpatient antibiotics for community-acquired pneumonia. The optimal duration of therapy. Chest. 1996;110:965–71.
9. Shojania KG, Yokoe D, Platt R, Fiskio J, Maluf N, Bates DW. Reducing vancomycin use utilizing a computer guideline: results of a randomized controlled trial. J Am Med Inform Assoc. 1998;5:554–62.
10. Stiefel U, Paterson DL, Pultz NJ, Gordon SM, Aron DC, Donskey CJ. Effect of the increasing use of piperacillin/tazobactam on the incidence of vancomycin-resistant enterococci in four academic medical centers. Infect Control Hosp Epidemiol. 2004;25:380–3.
11. Lautenbach E, LaRosa LA, Marr AM, Nachamkin I, Bilker WB, Fishman NO. Changes in the prevalence of vancomycin-resistant enterococci in response to antimicrobial formulary interventions: impact of progressive restrictions on use of vancomycin and third-generation cephalosporins. Clin Infect Dis. 2003;36:440–6.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
13. WHO Collaborating Centre for Drug Statistics and Methodology [internet]. Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO; 2013. Available from: http://www.whocc.no/atcddd
14. Marra AR, de Almeida SM, Correa L, et al. The effect of limiting antimicrobial therapy duration on antimicrobial resistance in the critical care setting. Am J Infect Control. 2009;37:204–9.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
16. Anderson DJ, Moehring RW, Sloane R, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. PLOS ONE. 2014;9:e91713.
17. Datta R, Huang SS. Risk of infection and death due to methicillin-resistant *Staphylococcus aureus* in long-term carriers. Clin Infect Dis. 2008;47:176–81.
18. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase – producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis. 2012;55:943–50.
19. Fraser GL, Stogsdill P, Dickens JD Jr, Wennberg DE, Smith RP Jr, Prato BS. Antibiotic optimization. An evaluation of patient safety and economic outcomes. Arch Intern Med. 1997;157:1689–94.
20. Solomon DH, Van Houten L, Glynn RJ, et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Intern Med. 2001;161:1897–902, http://dx.doi.org/10.1001/archinte.161.15.1897.
21. Marwick C, Davey P. Care bundles: the holy grail of infectious risk management in hospital. Curr Opin Infect Dis. 2009;22:364–9.
22. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33:322–7.
23. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011;66:1223–30.
24. McGowan JE Jr. Antimicrobial stewardship – the state of the art in 2011: focus on outcome and methods. Infect Control Hosp Epidemiol. 2012;33:331–7.
25. Charani E, Edwards R, Sevdalis N, et al. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. Clin Infect Dis. 2011;53:651–62.