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## Original article

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



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### 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.

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## Background

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

According to the Infectious Disease Society of America and Society for Healthcare Epidemiology of America,<sup>1</sup> 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 (DDD), reduction of antimicrobial resistance, and rate of *Clostridium difficile* infections.<sup>3,4</sup> ASP-related research has also reported positive effects on hospital length of stay and mortality,<sup>5,6</sup> 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.<sup>7</sup> 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.<sup>8</sup> Current research have evidenced that they play a role in reducing resistant bacteria and other undesired events.<sup>8–11</sup>

There is a demand to conduct ASP researches that illustrate what is performed during daily clinical practice. Notwithstanding, ID societies<sup>1,2</sup> endorse the need to assess whether a “bundled” ASP strategy, with as many as possible interventions, improves patients’ outcomes.<sup>2</sup>

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## 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.

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## 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)<sup>12</sup> 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.<sup>13</sup>
- 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.

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