Impact of requiring re-authorization of restricted antibiotics on day 3 of therapy

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Background: Pre-authorization of restricted antibiotics is a core component of an antibiotic stewardship programme (ASP). On day 3, information about culture results and clinical status is typically available. Our objective was to compare an ASP that requires initial authorization alone with one requiring initial authorization and re-authorization on day 3 of therapy.

Methods: A single-centre, retrospective, before and after study was conducted. Randomly selected adults were eligible if receiving a restricted antibiotic for ≥ 3 days during April to June in 2012 (pre-intervention) and during the same months in 2013 (post-intervention). The target sample size was 166 patients. The intervention required re-authorization of restricted antibiotics that were continuing on day 3. The days of therapy of restricted antibiotic(s), length of hospital stay (LOS) and hospital mortality were compared between pre- and post-intervention periods.

Results: The ASP intervention was associated with a decrease in median days of therapy from 5 (4–9) to 4 (3–5) days ($P < 0.001$) for all restricted agents, from 5 (3–6) to 3 (3–5) days for broad-spectrum Gram-negative agents ($P < 0.001$) and from 6.5 (6–7) to 3 (3–4.5) days for oral vancomycin. The proportion of subjects receiving restricted agents for >4 days decreased from 57.8% to 30.1% ($P < 0.001$). LOS decreased from 8 (5–17) to 6 (5–9) days ($P = 0.005$) without a significant change in hospital mortality.

Conclusions: Requiring re-authorization of restricted antibiotics on day 3 of therapy in addition to initial authorization was associated with reduction in overall consumption of restricted antibiotics and LOS without adversely affecting hospital mortality.

Introduction

Increasing microbial resistance to antibiotics is a global problem that requires limiting and optimizing the use of antibiotics, particularly broad-spectrum agents.[1] There is an urgent need, therefore, for evidence-based strategies aimed at curbing antibiotic overuse. One core strategy of an antibiotic stewardship programme (ASP) is prior authorization of restricted antibiotics, requiring approval before therapy is initiated.[1] The strategy is based on having an infectious diseases (ID) expert to ensure appropriateness of initial antibiotics, which are usually prescribed empirically. However, culture and susceptibility results and other diagnostic results become available over the next 2–3 days providing an opportunity to revisit the therapy decisions. Either routine review or re-authorization can be performed to target this opportunity, promote de-escalation of therapy, ensure appropriateness and avoid overuse.

The antibiotic 'time out' is a strategy that has been studied and recommended by the guidelines to encourage performing routine antibiotic review by prescribers.[1] Instead, our institution required re-authorization by ID physicians in addition to prior authorization. The objective of this study was to compare restricted antibiotic utilization before and after implementation of the re-authorization requirement on day 3. We hypothesized that requiring re-authorization of antibiotics on day 3 of treatment would reduce the use of restricted antibiotics and improve appropriateness of targeted antibiotic therapy.

Methods

A retrospective study was conducted at a 267 bed academic community medical centre in Brighton (MA, USA). The ASP was established in 2007. During the study period, the ASP team consisted of one ID consultant and

one ID pharmacist as well as one pharmacy practice resident and one pharmacy student. Prior to a change in policy, prescribers of restricted antibiotics were required to obtain authorization from the centre's ID service. In February 2013, the hospital revised its ASP policy to require that in addition to receiving initial authorization, pharmacists must also refer restricted antibiotics to the ID service for re-authorization if antibiotics were administered for ≥3 days. On Monday through Friday during normal business hours, the ASP team and pharmacy generated a daily report of restricted antibiotics and determined any antibiotic orders that needed to undergo review and authorization to continue. The hospital's list of restricted antibiotics included: aciclovir intravenous (iv), amikacin iv, aztreonam iv, cefepime iv, ciprofloxacin iv, daptomycin iv, ertapenem iv, fluconazole iv, linezolid iv and oral (po), meropenem iv, micafungin iv, piperacillin/tazobactam iv, vancomycin po and voriconazole iv and po. Orders deemed to be appropriate were re-authorized to continue; however, inappropriate orders were not automatically stopped at 72 h. Instead, inappropriate prescribing initiated discussion between members of the ASP team and ordering physicians. Prospective audit and interventions comprise a major portion of ASP activities. The ASP team also reviews selected microbiology results, adjusts antibiotic doses, converts iv to po antibiotics, performs medication use evaluations to investigate potential problems with antibiotic use and participates in meetings that address policy and surveillance relating to antibiotic use and hospital-acquired infections. The review and re-authorization activity was conducted in conjunction with other ASP activities and initially was estimated to take 3–4 h/day of the whole team's time. After prescribers became familiar with the policy, the number of cases in which contact was required dropped. The following outcomes were compared before and after the change in ASP policy: restricted antibiotic use per patient as well as per antibiotic, measured by days of therapy (DOT); length of hospital stay (LOS); and hospital mortality. Because pharmacists typically contact the physicians for re-authorization on days 3–4, the proportions of patients on antibiotic therapy for >4 days was compared.

Hospitalized patients 18 years of age or older who received restricted antibiotic treatment for ≥3 days were included; patients who were re-admitted or who received antibiotics for <3 days or for prophylaxis were excluded. A computerized random number generator was used to identify patients on any restricted antibiotic during April–June 2012 (pre-intervention phase) and April–June 2013 (post-intervention phase). The same months of the 2 years were chosen to control for seasonal changes. We are not aware of any particular change that might have happened over the two study periods that could confound our findings, including changes to the restricted antibiotic list or ID consultants doing the authorization. Institutional Review Board authorization was obtained from the hospital.

A total of 166 patients (83 in each period) was required to detect a 45% assumed reduction in DOT of restricted antibiotics per patient, with 80% power for a two-tailed alpha at 0.05. This assumed reduction in DOT was based on the authors' opinion, as no previous studies evaluating the same intervention were found. Differences between the study groups were compared using a two-tailed Mann–Whitney U-test for non-normally distributed continuous variables and a Fisher's exact or χ^2 test for categorical variables. Statistical analyses were performed with SPSS software, version 23 (IBM, Armonk, NY, USA).

Results

During the pre-intervention and post-intervention periods, 926 and 939 subjects, respectively, were screened. Nine patients were excluded due to receiving antibiotics for <3 days, 6 were excluded due to readmission and 11 were excluded due to receiving antibiotics for prophylaxis. Of the screened patients, 83 were randomly selected from each period. The median age of selected patients was ~71 years in both groups and there were no significant differences in baseline characteristics between the study groups (Table 1).

Significant changes in the measured outcomes were observed following the change in ASP policy. Considering all restricted antibiotics, the median (IQR) DOT decreased from 5 (4–9) to 4 (3–5) days ($P<0.001$) and the percentage of patients receiving restricted

Table 1. Patient characteristics and study outcomes

	Pre-intervention ($N = 83$)	Post-intervention ($N = 83$)	P
Patient characteristics			
age (years), median (IQR)	71.5 (59.25–83)	71 (60–81)	0.656
male, *n* (%)	40 (48.2)	48 (57.8)	0.180
diagnosis, *n* (%)[a]			
pneumonia	18 (21.7)	25 (30.1)	0.066
intra-abdominal infection	16 (19.3)	18 (21.7)	0.359
urinary tract infection	17 (20.5)	11 (13.3)	0.452
skin and soft tissue infection	12 (14.5)	13 (15.7)	0.507
miscellaneous[b]	9 (10.8)	5 (6.0)	0.430
C. difficile infection	6 (7.2)	7 (8.4)	0.548
febrile neutropenia	5 (6.0)	3 (3.6)	0.729
bloodstream infection	4 (4.8)	2 (2.4)	0.689
Patient outcomes			
restricted antibiotics DOT, median (IQR)	5 (4–8.75)	4 (3–5)	<0.001
restricted antibiotic therapy >4 days, *n* (%)	48 (57.8)	25 (30.1)	<0.001
LOS (days), median (IQR)	8 (5–17)	6 (5–9)	0.005
hospital mortality, *n* (%)	8 (9.6)	2 (2.4)	0.057

[a]No statistically significant difference.
[b]Miscellaneous: bone and joint infection, CNS infection, sinusitis, oesophagitis, laryngitis, epididymitis/orchitis, herpes labialis, herpes zoster, fever and leucocytosis.

antibiotics for >4 days declined from 57.8% to 30.1% ($P < 0.001$). Considering only restricted broad-spectrum Gram-negative agents (amikacin, aztreonam, cefepime, ertapenem, meropenem and piperacillin/tazobactam), the median (IQR) DOT decreased from 5 (3–6) to 3 (3–5) days ($P < 0.001$) and DOT declined for each of these antibiotics, though the decrease was statistically significant only for cefepime [decreased from 6 (5–10.25) to 3 (3–5), $P = 0.018$] and piperacillin/tazobactam [decreased from 5 (4–7) to 4 (3–5), $P = 0.002$]. Considering vancomycin po, DOT decreased from a median (IQR) of 6.5 (6–7) to 3 (3–4.5) days, but this decrease was not correlated with fewer cases of *Clostridium difficile* infection. Considering all restricted antibiotics, the LOS significantly decreased from a median (IQR) of 8 (5–17) to 6 (5–9) days ($P = 0.005$), while hospital mortality did not change significantly, decreasing from 8 (9.6%) to 2 (2.4%) ($P = 0.057$).

Discussion

To our knowledge, our study is the first to evaluate the impact of requiring ID re-authorization on day 3 of restricted antibiotic therapy in addition to prior authorization. A significant positive impact was demonstrated on restricted antibiotic consumption and LOS. Furthermore, a significant reduction in the use of broad-spectrum Gram-negative agents, in particular cefepime and piperacillin/tazobactam, was accomplished. It is important to note that restricted Gram-positive agents were not used extensively enough in this study to allow assessment. Vancomycin iv was not included in the hospital's list of restricted antibiotics that required initial authorization; however, future studies should be conducted to determine if authorization for continuation on day 3 could reduce vancomycin iv use. Our study detected a significant reduction in vancomycin po use despite no reduction in cases of *C. difficile* infection. This is likely explained by earlier discontinuation of empirical therapy in patients with negative laboratory findings.

Requiring prior authorization can either have a larger or smaller impact on reducing antibiotic overuse and LOS than prospective audit and feedback.[2,3] Though requiring pre-authorization of restricted antibiotic use has disadvantages, such as loss of prescriber autonomy, it has been found to be associated with a significant reduction in the use of and resistance to the restricted antibiotics.[4–8] The prior authorization process has to be timely or allow antibiotic administration to proceed until the evaluation by ID occurs. Our study demonstrates further benefits of requiring authorization of restricted antibiotic use on day 3.

A recently published set of guidelines for ASP has discussed the advantages of both prior authorization and prospective audit and feedback;[1] therefore, we add insight by highlighting the advantages of requiring authorization on day 3. While prior authorization can reduce initiation of unnecessary or inappropriate antibiotics (mostly empirical therapy), authorization on day 3 can reduce continuation of antibiotics that are deemed unnecessary and result in de-escalation and switching to more appropriate alternatives according to culture results and other findings that are not available at initiation. Authorization on day 3 addresses definitive antibiotic therapy and can better address duration of therapy than can prior authorization.

Our study has several limitations. Adherence to the revised ASP policy was not verified and this could have lessened the magnitude of reduced antibiotic consumption. The process of re-authorization is resource intensive; therefore, a cost-effectiveness study is needed to determine whether benefits outweigh the costs of maintaining the review process. A retrospective study worth mentioning incorporated the handshake approach and was successful.[9] On the other hand, our ASP had a mixture of this approach via the ward pharmacist and ASP team as well as paging or calling prescribers. Pharmacists and physicians have not been formally surveyed to determine their perception of the re-approval process. However, this policy has been continued now for several years. The workload has been manageable and is distributed across the ASP team and unit pharmacists. Further studies are needed to define whether the target population can be refined, whether the candidate antibiotics should be narrowed or expanded, which interventions are most effective and whether the impact on antibiotic consumption can be sustained. This study focused on restricted antibiotics and did not quantify all antibiotic use. It is possible that the interventions may reduce overall antibiotic exposure and perhaps affect antibiotic resistance in a positive way. Finally, retrospective before and after studies carry a risk of unmeasured confounders; therefore, this study found an association not causality, which is best assessed by randomized controlled trials. All of these factors should be considered by future researchers. Nonetheless, this study is an initial attempt to examine a re-authorization requirement on day 3 of antibiotic therapy.

In conclusion, requiring re-authorization of restricted antibiotics on day 3 of therapy reduced the overall consumption of restricted antibiotics, particularly vancomycin po and antibiotics targeting Gram-negative infections. In addition, this intervention was associated with decreased LOS without adversely affecting hospital mortality.

Transparency declarations

None to declare.

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