Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomized controlled trial

P. Lesprit, C. Landelle and C. Brun-Buisson
Université Paris EST Créteil, Unité de Contrôle, Épidémiologie et Prévention de l’Infection, Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Henri Mondor, Créteil, France

Abstract

This study aimed to determine the clinical course of patients and the quality of antibiotic use using a systematic and unsolicited post-prescription antibiotic review. Seven hundred and fifty-three adult patients receiving antibiotic therapy for 3–5 days were randomized to receive either a post-prescription review by the infectious disease physician (IDP), followed by a recommendation to the attending physician to modify the prescription when appropriate, or no systematic review of the prescription. In the intervention group, 63.3% of prescriptions prompted IDP recommendations, which were mostly followed by ward physicians (90.3%). Early antibiotic modifications were more frequent in the intervention group (57.1% vs. 25.7%, p < 0.0001), including stopping therapy, shortening duration and de-escalating broad-spectrum antibiotics. IDP intervention led to a significant reduction of the median [IQR] duration of antibiotic therapy (6 [4–9] vs. 7 days [5–9], p < 0.0001). In-hospital mortality, ICU admission and new course of antibiotic therapy rates did not differ between the two groups. Fewer patients in the intervention group were readmitted for relapsing infection (3.4% vs. 7.9%, p 0.01). There was a trend for a shorter length of hospital stay in patients suffering from community-acquired infections in the intervention group (5 days [3–10] vs. 6 days [3–14], p 0.06). This study provides clinical evidence that a post-prescription antibiotic review followed by unsolicited IDP advice is effective in reducing antibiotic exposure of patients and increasing the quality of antibiotic use, and may reduce hospital stay and relapsing infection rates, with no adverse effects on other patient outcomes.

Keywords: Antibiotic use, antimicrobial stewardship, patient outcome, re-evaluation

Patients and Methods

This was a randomized, controlled, open trial conducted over a 6-month period in an 850-bed general university hospital.
Overall hospital antibiotic consumption before starting the study was 650 DDDs/1000 hospital days, which is in the low range of antibiotic consumption among French university hospitals of the Paris area. The study was approved by the Institutional Review Board of our hospital, and patients received oral and written information regarding the study objectives and conduct. Physicians in charge of the patients were informed by mail.

Inclusion and exclusion criteria
All patients hospitalized in surgical and medical wards (650 beds) were screened daily for possible inclusion in the study using the computer-generated alert system previously described [16]. The system allows daily review (on weekdays) of all new prescriptions of any of 15 selected antibiotics of intermediate or broad spectrum (listing is given in the OLS). Medical and surgical wards represented 71% of total hospital antibiotic prescription. Antibiotics selected accounted for 47% of total antibiotic prescriptions of surgical and medical wards. To be eligible, patients had to be treated with one of the targeted antibiotics for at least 3 days (or up to 5 days if prescriptions were initiated during bank holiday periods). Patients were non-eligible if IDP advice had been requested by staff physicians within the first 3 days of initiating therapy for the infectious episode considered, if they were suffering from acute leukaemia or they had an expected survival of < 30 days. Exclusion criteria between randomization and the start of the intervention were discontinuation of any antibiotic therapy, hospital discharge, and transfer to the ICU or death.

Randomization
Eligible patients were allocated to either the intervention or the control group by using a computer-generated randomization list, which was maintained independently of the IDP. Concealment of the allocation was maintained, as the physician in charge of the patient and the IDP were involved only after randomization.

Intervention
A single IDP performed all interventions for eligible patients, after screening the patient’s computerized chart. The intervention consisted of a post-prescription review followed by direct interaction with the prescribing physician. Predefined criteria for intervention are given in the online supplementary material.

After reviewing the data the IDP provided the attending physician with an oral recommendation to modify the antibiotic regimen when deemed appropriate. When advice could not be given directly to the physician, recommendations were written in the medical chart. These could be overridden and no further attempt was made if recommendations were not followed.

No intervention was made in the control group. In this group, antibiotic management and re-evaluation was left to the ward physician. However, the physician could request advice from the IDP as needed.

Data collection
The following characteristics were collected from the patients’ charts by the same investigator (CL) independently of the IDP: age, sex, dates of admission to and discharge from the hospital or death (censored at 60 days after randomization), ICU admission within the first 7 days of randomization, the Charlson co-morbidity score [18], results of microbiological investigations, indication for antibiotic therapy and information on the antibiotic prescription.

The actual duration of treatment was assessed, including the duration of broad-spectrum or intermediate-spectrum antibiotics, and of intravenous or oral administration. Any new course of antibiotic therapy initiated 7 days or more after completion of the initial course of treatment was recorded. Relapse of the infection was assessed if readmission occurred within 60 days of randomization, and considered when a new course of antibiotic therapy administered for a documented or presumed infection at the same site of infection was prescribed.

Outcomes
Two series of outcomes were assessed in the study. First, we evaluated the potential clinical impact of both strategies, with regard to length of hospital stay (the primary outcome), in-hospital mortality, ICU admission, new course of antibiotic therapy, and relapse of the infection [8]. Second, we evaluated the quality of antibiotic use, which was estimated using the following criteria: rate of early antibiotic re-evaluation (defined by any change of antibiotic therapy within 24 h of randomization), duration of treatment, use of antibiotic combination, use of broad-spectrum antibiotics and oral switch [19].

Sample size
We hypothesized that the intervention might result in a 20% reduction of the duration of hospitalization. The sample size was estimated on the results of previous observations performed in our hospital showing that the mean length of hospital stay for patients treated with one of the targeted antibiotics was 15 ± 7 days. To detect a 20% reduction in the length of hospital stay in the intervention group with a type I error of 5% and a type II error of 80%, it was necessary to enrol a total of 506 patients (253 patients in each group). We also found in our previous study that 670 patients could be enrolled over 19 weeks. To account for an estimated 15% exclusion of patients receiving IDP.
advice upon the request of attending physicians during the first few days of therapy, and a further 15% loss due to secondary exclusions of randomized patients, we planned on recruiting a total of 900 subjects in a 24-week period.

Statistical analysis
Categorical variables were expressed as numbers and percentages and were compared using the Pearson \( \chi^2 \) test or the Fisher exact test, as appropriate. Continuous variables were expressed as the median with interquartile range (IQR) and were compared using the Mann–Whitney U-test. All statistical tests were two-tailed and statistical significance was set at 0.05. Analyses were performed by using the SPSS software, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results
During the study period, 1149 patients received one of the targeted antibiotics for at least 3 days (Fig. 1); 294 patients were excluded. A total of 855 patients were randomly assigned to either the intervention or the control group. The analysis was restricted to 753 patients after secondary exclusion of 102 patients.

Patients’ characteristics
At baseline, the two groups were very similar regarding demographic and clinical characteristics (Table 1). Most patients had significant but moderate co-morbidities. A large majority suffered from mild to moderately severe infection. Only 46% of the prescriptions were microbiologically documented and bacteremia was recorded in 10% or less of patients. The majority of infections were community acquired. Most prescriptions were initiated for respiratory, urinary, skin and soft tissue or digestive tract infections. There was no difference in this distribution between the two groups.

Half of the antibiotic regimens were initially prescribed intravenously by ward physicians. The majority of prescriptions were of amoxicillin clavulanate, fluoroquinolones and third-generation cephalosporins.

IDP advice and early antibiotic re-evaluation
In the intervention group, 63.3% of prescriptions prompted IDP interventions, including stopping therapy in the absence of bacterial infection, shortening the planned duration, or de-escalating broad-spectrum antibiotics (Table 2). Clinical examination of the patients was performed for 42% of the interventions. Time required, cost of the intervention and
TABLE 1. (a) Patients’ demographics and clinical characteristics of infection in patients randomized to the intervention and control groups. (b) Microbiological documentation of infection and antibiotics prescribed

### TABLE 1

<table>
<thead>
<tr>
<th>Ward</th>
<th>Surgical</th>
<th>Medical</th>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Charlson score, median (IQR)</th>
<th>Charlson score, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>126 (33.4)</td>
<td>129 (34.3)</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>66 (53–78)</td>
<td>67 (54–78)</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>237 (62.9)</td>
<td>226 (60.1)</td>
<td>0.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson score, median (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>6 (1.6)</td>
<td>8 (2.2)</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired infection</td>
<td>113 (31)</td>
<td>127 (33.9)</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Antibiotic Modification

- **Any change:** 97 (25.7) 215 (57.1) <0.0001
- **Stopping therapy:** 15 (0.4) 59 (15.6) <0.0001
- **Shortening duration:** 24 (6.3) 65 (17.2) <0.0001
- **De-escalating:** 9 (0.2) 72 (19.1) <0.0001
- **Oral switch:** 47 (12.6) 48 (24.1) 0.90
- **Other:** 47 (12.6) 30 (7.9) 0.39

---

### TABLE 2

Rates of infectious disease physician (IDP) advice and actual early (days 3–5) antibiotic modification prescribed by ward physicians in the two study groups

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Control group N = 377</th>
<th>Intervention group N = 376</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>Solicited IDP advice</td>
<td>30 (8.0)</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>No. (%)</td>
<td>Unsolicited IDP review</td>
<td>0 (0.0)</td>
<td>315 (83.6)</td>
</tr>
<tr>
<td>No. (%)</td>
<td>Antibiotic modification</td>
<td>97 (25.7)</td>
<td>215 (57.1)</td>
</tr>
</tbody>
</table>

---

### TABLE 3

Duration of antibiotic therapy in the two study groups, overall and for the antibiotic regimen subgroups

<table>
<thead>
<tr>
<th>Median duration, days (IQR)</th>
<th>Control group N = 377</th>
<th>Intervention group N = 376</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total antibiotic course</td>
<td>7 (5–9)</td>
<td>6 (4–9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Broad-spectrum antibiotic³</td>
<td>4 (0–7)</td>
<td>2 (0–5)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Narrow to intermediate spectrum antibiotic³</td>
<td>4 (0–8)</td>
<td>5 (0–7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Intravenous administration</td>
<td>3 (0–6)</td>
<td>3 (0–6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Oral therapy</td>
<td>4 (0–7)</td>
<td>4 (0–7)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

---

### TABLE 4

Clinical outcomes of patients in the two study groups

<table>
<thead>
<tr>
<th>Control group N = 377</th>
<th>Intervention group N = 376</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>60 days in-hospital mortality, n (%)</td>
<td>38 (10.1)</td>
</tr>
<tr>
<td>ICU admission within 7 days of randomization, n (%)</td>
<td>6 (1.6)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>New course of antibiotic therapy, n (%)</td>
<td>25 (6.6)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Antibiotic treatment for relapsing infection, n (%)</td>
<td>30 (7.9)</td>
<td>13 (3.4)</td>
</tr>
<tr>
<td>Length of stay, days (median, IQR)</td>
<td>Overall population 15 (9–27)</td>
<td>15 (9–25)</td>
</tr>
<tr>
<td>Community-acquired infection 6 (3–14)³</td>
<td>5 (3–10)³</td>
<td>0.06</td>
</tr>
</tbody>
</table>

---

**Notes:**
1. Patients were non-eligible if IDP advice had been requested by staff physicians within the first 3 days of initiating therapy for the infectious episode considered.
2. Rate of compliance with IDP advice was 85.0%.
3. Including reducing antibiotic spectrum and antibiotic combination.
4. Antibiotic spectrum was classified as narrow to intermediate (amoxicillin/clavulanate or amoxicillin and clavulanate) or broad spectrum (third-generation cephalosporins, piperacillin/tazobactam, imipenem or fluoroquinolones).

---

**Antibiotic Expenditures:** Antibiotic expenditures are given in the OLS. Most (90.3%) IDP recommendations were adopted by ward physicians. In contrast, IDP advice was rarely solicited by physicians (8% of prescriptions) in the control group. Accordingly, most prescriptions were left unchanged. Significant differences were observed between the two groups with regard to the rates of stopping therapy, reducing the planned duration or de-escalating therapy. However, switching to the oral route was not more frequent in the intervention group.

**Duration of Antibiotic Therapy:** Consistent with the higher rates of stopping therapy or reducing its planned duration, the IDP intervention led to a significant reduction of the median duration of antibiotic therapy (Table 3). Of interest, a reduction was also observed for the duration of intravenous administration and of broad-spectrum antibiotics.

**Clinical Endpoints:** The duration of hospitalization did not differ between the two groups (median, 15 days). However, there was a trend for a shorter duration of hospital stay for patients admitted with community-acquired infections in the intervention group (Table 4). No apparent detrimental effect was found associ-
ated with the lower antibiotic exposure of patients: in-hospital mortality and ICU admission rates did not differ between the two groups. Similarly, new courses of antibiotic therapy prescribed 7 days or more after completion of the first treatment course were not more frequent in the intervention group. Of note, more patients in the control group were readmitted with relapsing infection within the 2 months following randomization. Rate of secondary infection and/or colonization due to multidrug-resistant bacteria did not differ between the two groups (see the OLS). Clinical outcomes of patients according to the adoption of the IDP advice in the intervention group are shown in the OLS.

Discussion

In this randomized controlled study evaluating the impact of an ASP on the outcomes of patients, we found that the intervention resulted in reduced overall antibiotic exposure of patients without apparent adverse effects, and a suggestion of a better outcome with a lower rate of readmissions with relapsing infection. There was, however, no effect of the intervention on the primary outcome selected (length of hospital stay) or on mortality rate, although the former tended to this finding, it was reassuring to find that the in-hospital death rate was not higher in the intervention group, consistent with previous findings [20,21,24,31]. Furthermore, we assessed the relapse rate of infection. Indeed, in one study, a programme aimed at discontinuing intravenous antibiotics was associated with a significantly higher readmission rate, albeit not considered as infection related by the authors; other studies did not report an increased risk of hospital readmission [20,21,26,27]. In contrast, we found that patients randomized to the IDP intervention group were less frequently readmitted with relapsing infection.

We were unable to show a reduction in length of hospital stay associated with the intervention. Whether interventions aimed at reducing patients’ antibiotic exposure may also reduce the length of hospital stay is controversial. Previous studies evaluating interventions directed at reducing intravenous antibiotic use have shown variable results, including a significant effect, a trend toward a shorter length of stay or no effect at all [21,24,31]. In this study, we did not observe a reduction in the length of hospital stay in the intervention group, similar to the findings by Salomon et al. [20]. There can be several explanations for these findings: first, intravenous antibiotics accounted for only 55% of the prescriptions at the time of the intervention; second, the rate of early oral switch was not higher in the intervention group; and third, our patient population included a mix of patients with both community-acquired (68%) and hospital-acquired (32%) infections, in whom infection may not be the sole reason for hospitalization. Finally, length of stay is not
an ideal endpoint, as it can be influenced by several factors other than management of infection, such as co-morbidities and availability of outpatient care. Nevertheless, there was a trend toward a shorter length of stay for patients hospitalized with community-acquired infections in the intervention group (p = 0.06), but our study lacked the power to detect a significant difference regarding this outcome.

Strengths of our study include its randomized and controlled design and the assessment of a number of clinical outcomes, but some limitations should be considered. First, it was performed in a single institution by the same IDP and the results may not be applicable to other hospitals. Because we did not randomize treating physicians, contamination occurring between the intervention and control groups may have diminished the effects of the intervention. Finally, we did not find an ecological benefit of the intervention as suggested by others [3,12,24,31]. As patients were not followed-up after hospital discharge, we may not have captured all potential relapses of infection, and these were only assessed at time of readmission in patients readmitted within 60 days of discharge.

In summary, our study provides evidence in the clinical setting that a post-prescription antibiotic review followed by unsolicited IDP advice can be successfully implemented in hospitals, is not associated with adverse effects, and may actually have beneficial effects on outcomes of patients. Our results support the contention that this strategy should be integrated into ASPs wherever possible.

Transparency Declaration

None to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Impact of unsolicited antibiotic review: supplementary data.

References


