Factors associated with effective reassessment of antibiotic therapy on day 3

Facteurs associés à une réévaluation effective de l’antibiothérapie à 72 heures


* Service d’infectiologie, hôpital de l’Archet 1, centre hospitalier universitaire de Nice, BP 3079, 06202 Nice cedex 3, France
\^b Pharmacie, centre hospitalier régional de Draguignan, Draguignan, France
\^c Réanimation polyvalente, centre hospitalier régional de Draguignan, Draguignan, France
\^d Laboratoire de biologie polyvalente, centre hospitalier régional de Draguignan, Draguignan, France
\^e Département d’information médicale, centre hospitalier régional de Draguignan, Draguignan, France

Received 1st May 2012; received in revised form 23 August 2012; accepted 7 December 2012
Available online 19 February 2013

Abstract

Reassessment of antibiotic therapy (RA) after 3 days is constitutive of French antibiotic stewardship. This delay is required because of the need for clinical reappraisal and for obtaining microbiological data. Our aim was to determine the factors associated with an effective RA.

 Patients and method. – A prospective study was made in a 350-bed general hospital in which all prescriptions are computerized and validated daily by prescribers. All curative antibiotic therapies were reassessed during 4 weeks. RA was defined as effective if the initial antibiotic treatment was modified. All clinical, biological, and radiological data having contributed to the initial prescription and to RA were recorded during bedside visit with the prescribers, two hospital physicians and one infectious diseases specialist.

 Results. – In one month, 148 antibiotic treatments were reassessed. Pulmonary, digestive, and urinary infections accounted for two thirds of the cases. An effective RA was recorded in 28 cases (19%) and associated with hospitalization in the ICU (P=0.001), imaging supporting the diagnosis (P=0.016), and persistence or aggravation of clinical signs (P=0.007). Microbiological findings were not contributive to an effective RA.

 Conclusion. – RA was associated to hospitalization in the ICU, to an inflammatory syndrome, and to the clinical outcome after 3 days. These results should help to improve the implementation of infectious diseases advice.

 © 2013 Elsevier Masson SAS. All rights reserved.

Keywords: Reassessment; Antibiotic stewardship; Audit; Bacteriology; Microbiology

Résumé

La réévaluation de l’antibiothérapie (RA) à 72 heures est constitutive de la politique du bon usage des antibiotiques. Ce délai est sous-tendu par la nécessité du recul clinique et l’obtention des données microbiologiques. Notre objectif était de déterminer les éléments associés à la mise en œuvre effective de la RA.

 Patients et méthode. – Il s’agissait d’une étude prospective menée dans un centre hospitalier où les prescriptions sont informatisées et validées quotidiennement par les prescripteurs. Toutes les antibiot thérapies curatives étaient réévaluées durant quatre semaines. Une RA effective était définie par une modification de l’antibiothérapie initiale. Les données participant à l’initiation thérapeutique et à la RA étaient répertoriées au cours d’une visite confraternelle de deux médecins de l’établissement et d’un infectologue auprès des médecins prescripteurs.

 Résultats. – En un mois, 148 antibiothérapies étaient réévaluées. Les infections pulmonaires, digestives et urinaires constituaient les deux tiers des cas. Une RA effective était observée dans 28 cas (19 %), et était associée à une hospitalisation en réanimation (p=0.001), à une imagerie constitutive du diagnostic (p=0.016) et à la persistance des signes cliniques ou leur aggravation (p=0.007). Les données microbiologiques ne contribuaient pas à une RA effective.

* Corresponding author.

E-mail address: roger.pm@chu-nice.fr (P.-M. Roger)
1. Introduction

The inadequate use of antibiotics, with its deleterious consequences on bacterial resistance and costs, led to implement a national policy for antibiotic stewardship [1,2]. The ICATB score (Composite index for antibiotic stewardship) assesses the results of this policy, with the need for hospitals to prove its implementation [3]. The ICATB is made on eight items, including assessment of antimicrobial therapy and reassessing antibiotic prescriptions at 48 to 72 hours [3,4].

For several years, the Infectious Diseases unit of Nice Teaching hospital has been collaborating with general hospitals members of the Infectious Diseases Network of the South-East French region (Reso-Infectio-PACA-East) to help implement this antibiotic stewardship policy [5,6].

The Draguignan hospital is a 350-bed institution having rapidly implemented the main measures indicated in the ICATB, except for evaluation and reassessment at 72 hours. We began this evaluation by considering antibiotic combinations [5]. The results suggested that contradictory discussion was an important element of antibiotic reassessment. This result fully justifies reassessment of treatment at the 3rd day of antimicrobial therapy, when clinical and microbiological data may help optimize the treatment [1]. But, the elements effectively contributing to antibiotic adaptation were not systematically studied. We actually tried to determine factors associated to an effective RA.

2. Patients and method

The Draguignan regional hospital center has implemented the policy for antibiotic stewardship: the prescriptions are computerized, allowing an easy calculation of antibiotic consumption; the prophylactic and curative antibiotherapy protocols are available on the hospital’s computer network, there is a list of restricted use broad-spectrum antibiotics issued by the drug and sterile medical devices committee (French acronym COMEDIMS); and a referent infectious disease specialist was appointed by the hospital director.

We made a 4-week prospective study during which all curative antibiotherapy prescriptions were systematically reassessed. This RA was recorded during a bedside visit with the prescribing physicians, plus two hospital physicians, and the referent infectious disease specialist, at the initiation of antibiotic therapy and on Day 3.

During this bedside visit, the prescribing physician recorded useful data by filling out a questionnaire.

The reassessment of antibiotic therapy (RA) period was announced to all the hospital’s medical staff by e-mail, after collegial decision taken by the COMEDIMS.

Our objective was to determine the factors associated to implementation of antibiotic prescription reassessment by prescribers; the investigators were present only for data collection and did not participate in the RA.

An effective RA was defined as a modification of the antibiotic and/or the administration mode, and/or of the dose.

The anamnestic, clinical, biological, microbiological and radiological data leading the physician in charge of the patient to prescribe the antibiotic therapy were identified. The same factors were also required for the RA at D3. The prescribers had to mention their clinical diagnosis, the arguments supporting the diagnosis, and the suspected bacteria. The data used for the diagnosis were quantified, without any qualitative analysis as to their adequacy. A proven diagnosis was defined by the observation of three clinical signs or more, associated to fever, supporting the diagnosis; these signs had to be reported by the physician in charge of the patient.

The severity of the patient’s status was assessed according to previous international definition conference [7]. The physicians had to classify their patients as presenting with a systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock.

The antibiotherapy was considered as probabilistic when supported by a clinical diagnosis of infection, or was empirical without the diagnosis. It was considered documented when based on bacteriological identification and when an antibiogram was available.

The duration of hospitalization and the outcome (cure or death) were documented by the Medical computer science department.

3. Statistical analysis

Data collection and statistical analyses were performed with Stat view 5.1 software. The associations in qualitative data were identified with the $\chi^2$ test for populations superior to 5. We used Fisher’s exact test when populations were inferior to 5. The comparison of averages was made with Mann and Whitney’s non-parametric test. Differences were considered significant when $p$ was inferior or equal to 0.05.

4. Results

One hundred and fifty-one curative antibiotherapies were prescribed during the 4-week study. Useful data was collected in 148 cases, allowing reassessing of 98% of antibiotherapies at D3.

RA was effective in 28 cases (19%). It was switching from parenteral to oral intake in seven cases, narrowing the antibiotic spectrum after microbiological documentation in six cases,
empirical therapy de-escalation in five cases, broadening the antibiotic spectrum in three cases, and an other cause in seven cases.

The epidemiological and clinical data of 148 patients is listed in Table 1, distributed according to whether the RA was effective or not. Pulmonary, digestive, and urinary infections accounted for two thirds of the cases; 32 patients presented with severe sepsis or septic shock (22%), and 27 with nosocomial infections (18%).

The only epidemiological feature that was different for patients benefiting or not from an effective RA was being hospitalized in an ICU (P = 0.001, Table 1).

The diagnostic, clinical, biological, and imaging features are listed in Table 2. A proven clinical diagnosis was reported in 53 cases (36%). These cases were distributed as 14 cases (50%) with effective RA, and 39 cases (32%) without any therapeutic modification after RA (P = 0.08).

Concerning biological data, biological inflammation criteria tended to be mentioned more often in the effective RA group compared to patients not benefitting from an effective RA.

Radiological data, whatever the technique used, was used to support a diagnosis in 55 cases (37%); it was more frequently mentioned in case of effective RA (P = 0.016).

The antibiotic therapy was probabilistic in 115 cases (78%), documented in 22 cases (15%), and empirical in 11 cases (7%). An effective RA was reported in respectively 24, one, and three cases (P not significant).

Table 1: Epidemiological data of patients distributed according to a possible effective reassessment of antibiotic therapy (with modification of the initial prescription) on day 3.

<table>
<thead>
<tr>
<th>Age (years, mean ± SD)</th>
<th>RA without therapeutic modification n = 120</th>
<th>Effective RA n = 28</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 ± 28</td>
<td>62 ± 28</td>
<td>0.810</td>
<td></td>
</tr>
<tr>
<td>Sex-ratio (M/F)</td>
<td>0.87</td>
<td>1.33</td>
<td>0.317</td>
</tr>
<tr>
<td>Medical units/surgery</td>
<td>85/35</td>
<td>23/5</td>
<td>0.225</td>
</tr>
<tr>
<td>ICU</td>
<td>16 (15%)</td>
<td>11 (39%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Allergy to antibiotics</td>
<td>7/68/45</td>
<td>0/22/6</td>
<td>0.077</td>
</tr>
<tr>
<td>Severity of infection</td>
<td></td>
<td></td>
<td>0.545</td>
</tr>
<tr>
<td>Unknown/SIRS</td>
<td>82/10</td>
<td>17/3</td>
<td></td>
</tr>
<tr>
<td>Sepsis/severe sepsis or shock</td>
<td>17/11</td>
<td>3/5</td>
<td></td>
</tr>
<tr>
<td>Previous antibiotherapy</td>
<td>25 (21%)</td>
<td>5 (18%)</td>
<td>0.633</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
<td>0.411</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>45 (37%)</td>
<td>11 (39%)</td>
<td></td>
</tr>
<tr>
<td>Digestive</td>
<td>22 (18%)</td>
<td>8 (28%)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>21 (17%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>ENT</td>
<td>11 (9%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bone and joint</td>
<td>5 (4%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Obstetrical</td>
<td>6 (5%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>10 (8%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>21 (17%)</td>
<td>7 (25%)</td>
<td>0.423</td>
</tr>
</tbody>
</table>

Table 2: Clinical and biological arguments and reassessment of antibiotic therapy on day 3.

<table>
<thead>
<tr>
<th>Number of arguments per site of infection</th>
<th>RA without therapeutic modification n = 120</th>
<th>Effective RA n = 28</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical arguments</td>
<td></td>
<td></td>
<td>0.354</td>
</tr>
<tr>
<td>0</td>
<td>34 (28%)</td>
<td>5 (18%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (24%)</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 (15%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Proven diagnosis</td>
<td>39 (33%)</td>
<td>14 (50%)</td>
<td></td>
</tr>
<tr>
<td>Biological arguments</td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>0</td>
<td>87 (72%)</td>
<td>14 (50%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14 (12%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (2%)</td>
<td>7 (2%)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory syndrome</td>
<td>17 (14%)</td>
<td>8 (29%)</td>
<td></td>
</tr>
<tr>
<td>Imaging used for the diagnosis</td>
<td>39 (32.5%)</td>
<td>16 (57%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Clinical arguments at D3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>65 (54%)</td>
<td>17 (61%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Clinical persistence or degradation</td>
<td>9 (8%)</td>
<td>7 (25%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Information not available</td>
<td>46 (38%)</td>
<td>4 (14%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

The physicians in charge of patients were to collect biological data used for every antibiotic prescription. Some summed up the biological data by using the global term of “inflammatory syndrome”.

The microbiological examinations allowed isolating one or several bacteria in 62 cases (42%), The isolation of a bacterium responsible for the infection was not associated to an effective modification of antibiotic therapy during RA (Table 3).

During RA, the initial diagnosis was confirmed in 120 cases (81%), a different diagnosis was made 16 times (11%), and the absence of infection was reported in two cases. Physicians did not make any diagnosis in 10 cases (7%).

RA with an effective modification of the ongoing treatment was associated to a significant longer hospitalization with an average 15 versus 11 days (P = 0.03), and a favorable outcome was observed in respectively 96 and 89% (P = 0.23).

5. Discussion

Several authors have reported that RA was rarely done [8,9], and mentioned how to improve its practice, especially by support from the referent ID specialist, and using feedback after the assessment [10–15]. We had for objective to determine the characteristics of effective RAs.

Prescribers were questioned by pairs in our prospective study, and the rate of effective RA was 19%. This rate may seem weak considering the reported need for therapeutic adaptations, often superior to 50% of antibiotic treatment initiations [16]. But the methods used by authors varied significantly, sometimes focusing on broad-spectrum antibiotics [10], on a switch after parenteral antibiotic therapy [11], or restricted to one or two departments and excluding the others [12,13]. We also defined an effective RA as one leading to a modification of
Finally, the normalization of inflammatory parameters could lead prescribers to be more confident, allowing de-escalation of antibiotic therapy at 48 to 72 hours. Correlated to this, prescribing physicians did not document a number of clinical items, resulting in a great number of non-proven diagnoses not having benefited from any effective RA (Table 2).

As far as we know, this clinical approach has never been used in studies on the reassessment of antibiotic therapy. Manuel et al.’s study was the only one including a diagnostic evaluation of antibiotic therapies reassessed at 72 hours, but the clinical and paraclinical arguments were not recorded systematically [13].

It was surprising that microbiological data did not influence the rate of effective RA. This could be explained by the frequency of diseases for which the contribution of bacteriological sampling is not proved. Thus, in community-acquired pulmonary infections, first cause of infection in our study, the opportunity for microbiological adaptation is rare, and systematic investigations may not be considered as contributive [17]. Likewise, in intra-abdominal surgical infections, second cause of infection in our study, therapeutic adaptation at 48 to 72 hours is rare for the reasons mentioned above.

The limitations of our study are related to the difficulties to understand the relative value of each parameter leading to a medical decision. We made only one quantitative evaluation of parameters used by prescribers. It is evident that the relative value of these parameters may vary significantly. Experience shows that CRP is still widely used despite studies proving its weak predictive value, and weak contribution to follow-up under treatment [18,19]. Thus, the diagnostic activity in infectious diseases, often based on the analysis of several parameters with different values, cannot be assessed with the analytic method we used.

6. Conclusion

An effective antibiotic reassessment relies on the prescriber’s experience, on the association of convergent clinical and paraclinical elements, as well as on the patient’s outcome. Microbiological data does not seem to have any impact on RA, even though it justifies waiting between 48 and 72 hours before reassessment. Knowing about these elements used by physicians for the reassessment of antibiotic therapy should contribute to improving counseling by the ID specialist.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


