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Referents for anti-infectious agents

Factors associated with effective reassessment of antibiotic therapy on day 3

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

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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.

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 antibiothérapies 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 infectiologue 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.

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Conclusion. – La RA était associée à un séjour en réanimation, au syndrome inflammatoire et à l'absence d'amélioration clinique à j3. Ces informations devraient permettre d'améliorer la mise en œuvre du conseil en antibiothérapie.

Mots clés : Réévaluation ; Bon usage des antibiotiques ; Audit ; Bactériologie ; Microbiologie

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 antibiotherapy 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 antibiotherapy, 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 of 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,

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.
Caractéristiques épidémiologiques des patients répartis selon l'éventualité d'une réévaluation antibiotique effective, i.e. avec modification de la prescription initiale à 72 heures.

	RA without therapeutic modification $n = 120$	Effective RAs $n = 28$	P
Age (years, mean ± SD)	60 ± 28	62 ± 28	0.810
Sex-ratio (M/F)	0.87	1.33	0.317
Medical units/surgery	85/35	23/5	0.225
ICU	16 (13%)	11 (39%)	0.001
Allergy to antibiotics			
Yes/no/unknown	7/68/45	0/22/6	0.077
Severity of infection			0.545
Unknown/SIRS[a]	82/10	17/3	
Sepsis/severe sepsis or shock	17/11	3/5	
Previous antibiotherapy[b]	25 (21%)	5 (18%)	0.633
Site of infection			0.411
Pulmonary	45 (37%)	11 (39%)	
Digestive	22 (18%)	8 (28%)	
Urinary	21 (17%)	4 (14%)	
ENT	11 (9%)	0	
Bone and joint	5 (4%)	2 (7%)	
Obstetrical	6 (5%)	1 (4%)	
Others	10 (8%)	2 (4%)	
Nosocomial infections	21 (17%)	7 (25%)	0.423

[a] Systemic inflammatory response syndrome.
[b] Prescribed 3 months before hospitalization.

Table 2
Clinical and biological arguments and reassessment of antibiotic therapy on day 3.
Arguments cliniques et biologiques et réévaluation de l'antibiothérapie à 72 heures.

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

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".

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 antibiotherapy 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).

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 antibiotherapy 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

Table 3
Microbiological arguments on day 3.
Arguments microbiologiques à j3.

	RA without therapeutic modification $n=120$	Effective RAs $n=28$	*P*
Pulmonary infections	45	11	
Suspected bacterium(a) (yes)	31 (69%)	10 (91%)	0.139
Proven data at D3	13 (29%)	4 (36%)	0.234
Digestive infections	21	8	
Suspected bacterium(a) (yes)	17 (81%)	6 (75%)	0.125
Proven data at D3	8 (38%)	4 (50%)	0.560
Urinary infections	20	4	
Suspected bacterium(a) (yes)	2 (10%)	2 (50%)	0.109
Proven data at D3	16 (80%)	2 (50%)	0.205
Other infections	34	5	
Suspected bacterium(a) (yes)	25 (73%)	5 (100%)	0.189
Proven data at D3	13 (38%)	2 (40%)	0.939
Consistency between suspected and isolated bacteria[a]	42/50 (86%)	9/12 (75%)	0.368

The physicians in charge of patients were to state that bacteria were suspected and what empirical antibiotherapy had been prescribed. Proven microbiological data was defined as an undisputed result (positive non-contaminated hemoculture, samplings on normally sterile compartments, urinary and respiratory samples, detection of *Pneumococcus* or *Legionella* urinary antigens).

[a] At initiation of antibiotherapy, a bacterium responsible for the infection was reported in 114 cases (77%); proven microbiological data at D3 was available in 62 cases (42%); both pieces of information were available for 61 patients.

the antibiotic therapy; this led to underestimate the therapeutic reassessment because initially optimal antibiotherapies did not need to be modified. When considering the clinical diagnosis made and the paraclinical data collected at the time of reassessment, 81/148 antibiotherapies were initially adapted (55%), especially in digestive surgery where broad-spectrum antibiotic combinations were adequate due to a polymicrobial infection and an inappropriate oral administration.

We found that three factors were associated to an effective RA: being hospitalized in an ICU ($P=0.001$), the patient's stable or worsening clinical status ($P=0.007$), and having radiological findings supporting the clinical diagnosis ($P=0.016$). Observing an inflammatory syndrome during the initial management also tended to be associated to an effective RA ($P=0.068$).

The first factor may be explained by a greater training of ICU physicians in the reassessment of antibiotherapy, because of daily therapeutic challenges related to multiresistant bacteria.

The second factor may be explained by a more important medical effort in therapeutic management when the patient does not improve as expected. Furthermore, this may explain a longer hospitalization associated to an effective RA, altered outcome obviously delaying the patient's discharge.

The third factor may be explained by the confidence given by radiological data that gives more arguments for the diagnostic hypothesis, especially in settings of intra-abdominal surgical infections.

Finally, the normalization of inflammatory parameters could lead prescribers to be more confident, allowing de-escalation of antibiotherapy 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 benefitted from any effective RA (Table 2).

As far as we know, this clinical approach has never been used in studies on the reassessment of antibiotherapy. Manuel et al.'s study was the only one including a diagnostic evaluation of antibiotherapies 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 antibiotherapy 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.

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