Modification of Empirical Antimicrobial Regimen During the First 72 Hours of Hospitalization

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Abstract

Objective: The aims of this study were to determine the empirical antibiotic therapy used in patients admitted to the Emergency Department who were later hospitalized, and to describe the antibiotic changes during their first days of hospitalization.

Method: All 14-year-old patients admitted to the Emergency Department who were started on antibiotic therapy and subsequently were hospitalized for at least 72 hours in an in-patient hospital ward, were included in a prospective observational study. Patients underwent daily follow-up during the first 3 days of hospitalization. The type of infection, microbiological data, and empirical antibiotic therapy and its changes were registered.

Results: 225 patients were included in this study. The most frequent types of infection diagnosed were infection of the respiratory airways, pneumonia, and skin and soft-tissue infection. Amoxicillin-clavulanic acid was the most widely prescribed antibiotic followed by levofloxacin and third generation cephalosporins. Microbiological samples were taken in 80 (36%) patients. Of the 225 antimicrobial regimens started in the Emergency Department, 94 (42%) were changed during the first 72 hours of hospitalization: 37 (16%) were completely modified, 31 (14%) were discontinued and antibiotics were added or stopped from the existing regimen in 26 cases (12%). Among these 94 patients whose treatment was changed, only in 40 (42%) there was a microbiological result for aiding in the adjustment of the antibiotic therapy.

Conclusion: The frequency of early changes during inpatient hospitalization to antimicrobial regimens which were initially prescribed in the Emergency Department is high. Microbiological results were rarely used to guide these changes.

Key words: Anti-bacterial agents. Hospital emergency service. Drug use. Inpatients.

Modificación del tratamiento antibiótico empírico en las primeras 72 horas de hospitalización

Objetivo: Los objetivos del presente estudio fueron describir la modificación que se realiza de la antibioterapia empírica indicada a los pacientes ingresados desde el área de urgencias en los primeros días de estancia en la planta de hospitalización y conocer las características de dicho tratamiento antibiótico.

Método: Estudio prospectivo y observacional en el que se incluyó a pacientes mayores de 14 años que ingresaron desde el área de urgencias con al menos un antibiótico prescrito y tuvieron una hospitalización de al menos 72 h. Se realizó un seguimiento diario de cada caso durante los primeros 3 días de hospitalización, documentando el tipo de infección diagnosticada, los datos microbiológicos y la antibioterapia empírica prescrita y sus modificaciones.

Resultados: Se incluyó a 225 pacientes. Los diagnósticos más frecuentes fueron infección respiratoria, neumonía e infección de la piel y los tejidos blandos, y los antibióticos más empleados fueron amoxicilina-ácido clavulánico, levofloxacino y cefalosporinas de tercera generación. Se solicitó al menos un tipo de muestra microbiológica a 80 enfermos (36%). De las 225 pautas antibióticas prescritas en urgencias, 94 (42%) fueron modificadas durante las primeras 72 h de hospitalización: 37 (16%) pautas se cambiaron por completo, 31 (14%) se suspendieron totalmente y en 26 (12%) se añadió o suspendió algún

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antimicrobiano, aunque sólo en 40 de ellas (42%) se dispuso de cultivos para dirigir el tratamiento.

Conclusiones: La frecuencia con la que las pautas antimicrobianas prescritas en urgencias se modificaron durante los primeros días de estancia en la planta de hospitalización es elevada, y destaca la escasa utilización de los resultados microbiológicos para realizar estos cambios.

Palabras clave: Antibacterianos. Servicio de urgencias hospitalario. Utilización de fármacos. Pacientes ingresados.

INTRODUCTION

For a patient suspected of infection, the quickest possible establishment of an empirical antibiotic treatment with broad-spectrum coverage against the pathogens which most frequently cause these types of infections achieves better clinical results, and decreases hospitalization time and even mortality.[1-6] However, this clinical practice, which provides excellent individual benefits, could have collective consequences which are not so beneficial, such as the appearance and spreading of microbial resistance due to the possible abuse of broad-spectrum antibiotherapy. Currently, to avoid these possible negative consequences, it is recommended that a change be made in subsequent days from the initial empirical therapy to another according to clinical and microbiological results, and even that therapy also be suspended if the diagnosis does not concur with an infection.[7-11] This strategy may not only contribute to decreasing the spread of resistances, but may also lead to the selection of an optimal antibiotic for treating resistant microorganisms, and decrease costs and adverse effects associated with broad-spectrum antibiotherapy.[7-9]

In hospitals, the majority of empirical treatments begin in the emergency department (ED), but definitive adjustment of antibiotic treatment should be done in subsequent days by another clinical department once the patient is admitted for hospitalization. Because of this, there are very few published studies in which a follow-up—during hospitalization—of empirical therapy prescribed initially in the ED has been carried out. We have only found 2 studies in which a follow-up of all patients admitted from the ED was carried out, independent from the type of infection suspected, the antibiotic regimen prescribed, or the microbiological culture taken.[12,13] The results obtained from the study are highly disparate. In the first, Lawrence et al observed that empirical treatment was modified in a high percentage of patients, although in many cases an apparent clinical or biological indicator was not found.[12] On the other hand, in the Kumarasamy et al[13] study they found that such a change did not occur in more than half of the cases in which the microbiological result suggested therapy modification. Furthermore, we have found a few studies from Spain in which re-evaluation of empirical therapy after the first few days of treatment is described; nevertheless, these are studies which are restricted to the areas of intensive care units and to the treatment of highly specific infections such as nosocomial pneumonias.[14,15]

In light of all this, the realization of this study in our hospital was of interest to us, with the aim of describing the adjustment made in prescribed empirical antibiotherapy for patients admitted from the ED in the first few days of hospitalization and also, for knowing the characteristics of antibiotic treatment prescribed in the ED.

METHOD

Prospective and observational study carried out in a general hospital of second level of attention, between February 20 and March 28, 2005. Our centre has 520 beds, attends to a population of 360 000 residents, and has an average yearly income of 23 063.

All patients over 14 years of age who were admitted from the ED with at least 1 antibiotic prescribed, and who were hospitalized for at least 72 h were included in the study. Patients admitted to gynecology and obstetrics, and psychiatry were excluded because these, unlike others, are not seen by doctors from ED, rather directly by the specialists, just as those patients for whom the antibiotic would have been prescribed as a surgical prophylaxis.

The attendance computer program of admission services was used for the selection of patients, and from this, a daily list of patients admitted from the ED was obtained. Once patients under 14 years and those registered as previously admitted into clinical services were excluded from the list, medical records were reviewed for selecting patients with at least 1 antibiotic prescribed which was not for surgical prophylaxis.

For each case, a daily follow-up was carried out during the first 72 hours of hospitalization. The information collected on the medical record from the ED was the following:

- Demographic data: age, sex, and presence of an allergy or intolerance to any antibiotic
- Clinical data: type of infection suspected, the taking of microbiological samples, and prescribed empirical antibiotherapy (medicine, dosage, and route of administration)

Likewise, during the period of subsequent hospitalization, the following data were also collected from the medical record: clinical department to which the patient was admitted, type of infection diagnosed, microbiological results available on the record, modifications made to empirical antibiotherapy, when modifications were made (24, 48, or 72 h from being hospitalized), and the cause of this modification when it was documented in the medical record.

The following concepts and situations were defined:

- Without a change of antibiotherapy: the patient continued with the same antibiotic during the whole study period, even though dosage and route of administration were modified

- Complete suspension of the antibiotherapy: the patient remained without antibiotic treatment during the period of hospitalization studied
- Complete change of antibiotherapy: all antibiotics from initial treatment were modified
- Addition/suspension of a treatment antibiotic: at least 1 different antibiotic was added to therapy, or at least 1 of the antibiotics from the initial prescription was suspended. Those cases with treatment temporarily suspended (less than 72 h) to obtain microbiological samples have been included within this situation

No intervention was carried out by the Pharmacy service even when possible discrepancies were detected between the prescription and microbiological isolation. It was not an objective of the study to evaluate the adequacy of the prescription in the ED, as this would have required a critical assessment of patients.

Symmetric continuous variables were expressed as average (standard deviation) and asymmetries, as median (range). Categorical variables were expressed as a number (percentage)

RESULTS

During the study period, 9878 patients older than 14 years went to the ED, of which 1498 (15%) were admitted. From these, 225 patients met the inclusion criteria, 153 (68%) males and 72 (32%) females, with a median age of 70 years (range, 16-96 years). With respect to antecedents of allergy or intolerance to any antibiotic, in 41 (18%) of included patients there was no reference to this data in the medical record. In 14 (6%), the presence of those antecedents was registered, and in 170 (76%) the absence of these was recorded.

Empirical Antibiotherapy Prescribed in the Emergency Department

The most frequently diagnosed infection in the ED was respiratory (which included upper respiratory tract infection, superinfected bronchiectasis, and superinfections in patients with chronic airflow limitation), followed by pneumonia, and skin and soft parts infection (Table 1). Seven out of 225 (3%) of patients were initially diagnosed with more than one type of infection.

In the ED, at least one type of microbiological sample was taken from 80 (36%) patients, with a total of 119 samples: in 72 (60%) no microorganisms were isolated, in 26 (22%) one was isolated, in 14 (12%) the microbiological result was not documented in the medical record, and in 7 (6%) contamination of the sample was determined. In Tables 2 and 3, the type of samples taken and results obtained are shown in detail.

A total of 284 antibiotics were prescribed (average, 1.3 antibiotics/patient), of which 247 (87%) were administered intravenously in 194 patients (86%). In the majority of cases, treatment was monotherapy (75%), while in 24% of subjects, 2 antimicrobials were prescribed and 3 drugs in 1% of the remaining.

Table 1. Diagnoses Carried Out in the Emergency Department on the 225 Included Patients

Diagnoses of Infection (n=232)	No. (%)
Respiratory[a]	73 (32)
Pneumonia	41 (18)
Skin and soft parts	30 (13)
Intraabdominal	22 (10)
Urological	17 (7)
Ocular	10 (4)
Febrile syndrome without a focus	6 (3)
Surgical wound	5 (2)
Central nervous system	4 (2)
Sepsis	4 (2)
Others	13 (6)
Non-infectious diagnosis	7 (3)

232 diagnoses were identified in 225 patients.
[a]Includes upper respiratory tract infection, superinfected bronchiectasis, and superinfections in patients with chronic airflow limitation.

Table 4 details which infections the most prescribed antibiotics (administrations/antibiotic) have been used for.

Modifications of Antibiotherapy During the First 72 h of Hospitalization

Two hundred twenty-five patients had 282 antibiotic prescriptions during the first 72 h of hospitalization, which signifies an average of 1.2 antibiotics/patient.

The clinical departments where the 225 patients were admitted are shown in Table 5.

Empirical antimicrobial therapy was modified—including complete suspension, complete change, or addition/suspension of a treatment antibiotic—during the follow-up period of 94 of 225 (42%) included patients. Table 6 shows details of the evolution of treatments according to the type of infection diagnosed.

Table 2. Results of Microbiological Samples Taken in the Emergency Department on the 225 Included Patients

Type of Microbiological Sample	Samples Taken No. (% Patients)	Samples With a Positive Result No. (% Samples)
Hemoculture	39 (17)	6 (15)
AGO	33 (15)	2 (6)
Organic fluid	16 (7)[a]	2 (12)
Urine culture	12 (5)	4 (33)
Skin-soft tissue	10 (4)	6 (60)
Sputum	9 (4)	6 (67)

AGO indicates pneumococcal and *Legionella* antigens in urine.
[a]Organic fluids: pleural (n=8), cephalorachidian (n=5), articular (n=2), and conjunctival (n=1).

Table 3. Patients With Microbiological Samples Taken According to the Type of Infection Suspected in the Emergency Department[a]

Type of Infection (No. Patients)	Patients With Some Type of Sample Taken No. (%)	Patients With Hemoculture No. (%)	Patients With Urine Culture No. (%)	Patients With AGO No. (%)	Patients With Another Type of Sample Taken No. (%)
Respiratory[b] (73)	19 (26)	7 (10)	1 (1)	9 (12)	6 (8) Sputum 3 (4) Pleural fluid
Pneumonia (41)	21 (51)	7 (17)	0	20 (49)	2 (5) Sputum 3 (7) Pleural fluid
Skin and soft parts (30)	5 (17)	2 (7)	0	0	3 (10) Skin-soft tissue 1 (3) Articular fluid
Intraabdominal (22)	7 (32)	4 (18)	1 (4)	0	3 (14) Skin and soft tissue
Urological (17)	3 (18)	1 (6)	3 (18)	0	–
Febrile syndrome without a focus (6)	4 (67)	4 (67)	1 (17)	3 (50)	1 (17) Sputum 1 (17) Cephalorachidian fluid
Central nervous system (4)	4 (100)	3 (75)	0	0	4 (100) Cephalorachidian fluid
Sepsis (4)	4 (100)	4 (100)	3 (75)	1 (25)	1 (25) Pleural fluid
Others (29)	13 (45)	7 (24)	3 (10)	0	4 (14) Skin and soft tissue 1 (3) Articular fluid 1 (3) Pleural Fluid 1 (3) Conjunctival fluid

AGO indicates pneumococcal and *Legionella* antigens in urine.
[a]In the cases where a microbiological sample has been taken from a patient diagnosed with 2 types of infection, the given patient has only been taken into account for the type of infection which prompted the taking of that sample.
[b]It includes upper respiratory tract infection, superinfected bronchiectasis, and superinfections in patients with chronic airflow limitation.

Table 4. Instructions by Antibiotic[a]

Antibiotic	Administrations of Each Antibiotic No. of Treatments (Percentage With Respect to the Total Treatments Initiated With That Antibiotic)						No. Total of Treatments Initiated With Each Antibiotic
	Respiratory[b]	Pneumonia	Skin and Soft Parts	Intraabdominal	Urological	Others	
Clavulanic acid amoxicillin	41 (47)	15 (17)	19 (22)	0	6 (7)	7 (8)	88
Levofloxacin	18 (40)	15 (33)	0	1 (2)	4 (9)	7 (16)	45
Third generation cephalosporins	4 (13)	7 (23)	2 (6)	4 (13)	2 (6)	12 (39)	31
Broad-spectrum antibiotics[c]	2 (10)	1 (5)	2 (10)	11 (55)	0	4 (20)	20
Aminoglycosides[d]	2 (11)	0	5 (28)	6 (33)	2 (11)	3 (17)	18
Anaerobicides[d]	1 (7)	1 (7)	2 (13)	10 (67)	0	1 (7)	15
Ciprofloxacin	4 (36)	0	2 (18)	0	4 (36)	1 (9)	11
Ceftacidime + vancomycin	0	0	0	0	0	10 (100)[e]	10

[a]All antibiotics prescribed in the emergency department are not included on this Table, only those prescribed the most. In the cases where an antibiotic has been prescribed to a patient diagnosed with 2 types of infections, only the main diagnosis has been taken into account.
[b]It includes upper respiratory tract infection, superinfected bronchiectasis, and superinfections in patients with chronic airflow limitation.
[c]It includes piperacillin/tazobactam and imipenem.
[d]In all cases, they were prescribed in combination with another antibiotic.
[e]In all cases, they were indicated for ocular infections.

The antibiotic treatment prescribed in the ED was completely suspended in 31 patients (14%), which occurred more frequently in patients initially diagnosed with urinary or pneumonia infections (Table 6). The main reason for this suspension was finding no signs of infections in the patient, which was observed in 25 of 29 cases (86%), for whom the cause of the suspension was documented in the medical record. In the specific case of intraabdominal infections, the carrying out of surgical intervention was not in any cases the reason for suspension of therapy.

Lastly, the antimicrobial regimen was completely modified in 37 patients (16%), with 78% of these adjustments being made in the first 24 h of admission. The reason for a complete change of antibiotherapy only showed up on the medical record of 18 patients (49%), and there were 3 justifications which were most frequent: the possibility of a different or additional infection (6/37, 16%), an adjustment to the microbiological result (4/37, 11%), and inadequacy of treatment (4/37, 11%).

Table 5. Clinical Department to Which the 225 Included Patients Were Admitted

Clinical Departments	No. (%)
Internal medicine	62 (28)
Pneumology	58 (26)
General surgery	20 (9)
Vascular surgery	16 (7)
Infectious	12 (5)
Ophthalmology	11 (5)
Intensive medicine	11 (5)
Digestive system	10 (4)
Others	25 (11)

Modification of Antibiotherapy Based on the Microbiological Result

Of the 80 patients for whom at least one microbiological sample was taken, in 23 (29%) the result of one sample was positive (Figure). However, we were only able to document the possible adjustment of antibiotherapy in 17 patients, because in the other 6 patients, the positive result was not available in the first 72 h of hospitalization. A change in the empirical regimen was based on the microbiological result in 8 of 17 (47%) patients, and in all cases, the adjustment was appropriate based on the result and sensitivity pattern of isolated microorganisms. To the contrary, in the remaining 9 patients (53%) with a positive result, empirical therapy was not modified, although in 6 of them the isolated microorganism and its sensitivity pattern suggested de-escalation therapy. In none of these 9 cases were there antecedents of allergy or intolerance which could contraindicate a change of therapy documented in the medical record.

DISCUSSION

In our study, the empirical therapy initially prescribed for patients seen to in the ED was frequently modified (42%) during the first 3 days of hospitalization; it stands out that in 14% of cases treatment was completely suspended, reaching up to 19% (pneumonia) in some infections and up to 31% (urinary infections).

This result is higher than those studies we have found with a design similar to ours. In the study published by Lawrence et al,[12] in which a follow-up of empirical treatment prescribed from the ED during the first 72 h of hospitalization is also carried out, antimicrobial therapy was suspended in only 6 of 119 (5%) patients included in the study. Likewise, Kumarasamy et al[13] carried out a descriptive study on antibiotic prescription in the ED and its evolution during hospital admission, in which, 8% of antibiotic regimens prescribed were suspended during admission. On the

Table 6. Modifications During Hospitalization of Empirical Antibiotherapy Prescribed in the Emergency Department According to the Type of Infection Diagnosed[a]

	Modifications of Antibiotherapy During Hospitalization According to the Type of Infection Diagnosed No. of Patients (Percentage With Respect to Patients With That Type of Infection)						
	Respiratory[b]	Pneumonia	Skin and Soft Parts	Intraabdominal	Urological	Other Diagnoses	Total
Without a change of antibiotherapy	42 (57)	18 (44)	26 (87)	17 (77)	6 (38)	22 (51)	131 (58)
Complete suspension of antibiotherapy	7 (10)	8 (19)	0	4 (18)	5 (31)	7 (16)	31 (14)
Complete change of antibiotherapy	15 (21)	11 (27)	3 (10)	0	4 (25)	4 (10)	37 (16)
Addition/suspension of an antibiotic	9 (12)	4 (10)	1 (3)	1 (5)	1 (6)	10 (23)	26 (12)

[a]The 225 patients from the study are included, and in the cases of patients diagnosed with 2 types of infection, only the main diagnosis has been taken into account.
[b]It includes upper respiratory tract infection, superinfected bronchiectasis, and superinfections in patients with chronic airflow limitation.

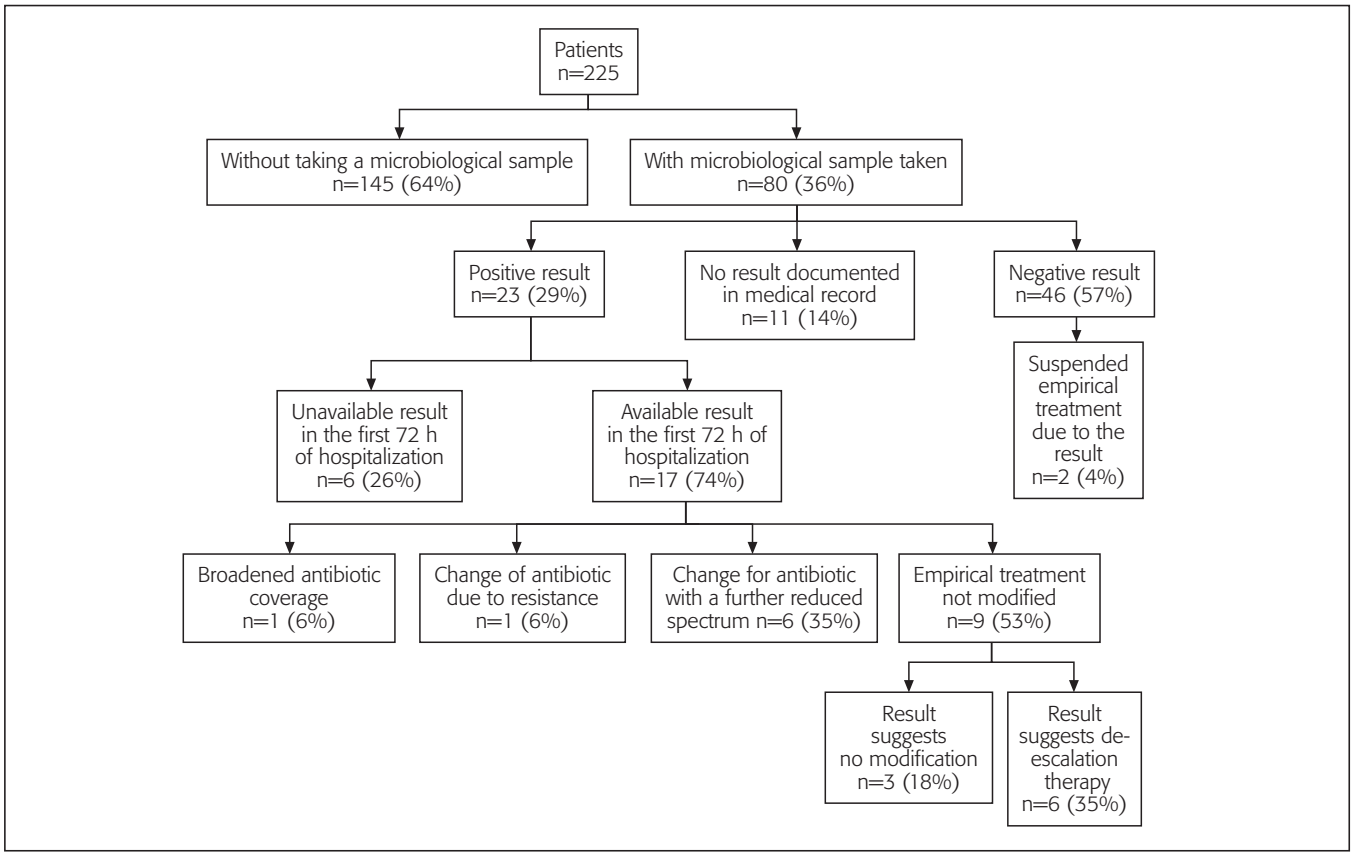

Figure. *Modification of empirical therapy guided by microbiological result.*

other hand, it is also of interest to us to point out that, in our study, the main reason for suspension was the absence of signs or symptoms of infection in the patient.

This high percentage of antibiotherapy suspension during the first days of hospitalization indicates a probable overuse of antimicrobials in the ED of our hospital. Considering this, one of the key points for achieving a rational use of antibiotics is the preparation and establishment of clinical guidelines which advise on diagnosis and pharmacotherapy of the most frequent types of infection. With this, a decrease in treatment failures, length of hospital stay, health costs, and even, mortality have been accomplished.[16,17] Nevertheless, even though we have at our disposal specific guidelines for particular infectious diseases in our hospital, we consider the appropriate establishment of these in certain areas of the centre as a part of the antibiotic policy for improving rational use of antibiotics a priority.[7-9,18]

The taking of microbiological cultures before beginning empirical therapy allows for the subsequent carrying out of a precise microbiological diagnosis and guided antibiotic treatment. This is why it is considered to be an essential previous step for the subsequent re-evaluation of the given therapy. In fact, in clinical practice, this strategy is widely recommended and is also considered a quality indicator in treatment of patients suspected of infection.[11,19-22] However, in our study there were only microbiological samples taken in 36% of patients, a figure which we consider really low and for which improvement, we believe, should be a prioritized objective for our hospital. Furthermore, this figure is considerably less than those described in other studies similar to ours, where samples were taken from 77%-94% of patients.[12,13,23] Specifically, the low percentage of patients with hemocultures taken (17%) is striking, much lower than figures described by other authors (52%-94%).[12,24,25] It is important to clarify that, in some of these studies, the authors do not ensure that the hemocultures have been taken before the beginning of antibiotherapy, for which, if they only took into account those taken adequately, these elevated percentages could decrease. However, we have to specify that in our study we also cannot ensure whether the taking of samples was done before the beginning of therapy. Again, we believe that the availability of protocols specifically aimed at the treatment of patients suspected of infection which include recommendations regarding which samples should be taken and when to take them, could contribute to improving these results. In this manner, in various studies it has been demonstrated that the establishment of these types of treatment protocols in the ED is one of the educational and organizational interventions which manages to increase the

percentage of patients from which cultures are taken when prescribed.[26,27]

Likewise, we analyzed the influence of the microbiological result in modifications which were made in empirical treatment. In the first place and maybe most importantly, it is fitting to highlight that in at least 64% of patients, these modifications were not made based on a microbiological result, because they had not obtained the given samples. Secondly, we emphasize that only 11% of those with changes of antibiotherapy were done based on the microbiological result, including positive and negative results; the given percentage decreases to 8.5% if we only take into account the changes made with a positive culture. This last fact, although we believe it is noticeably improvable, it is similar to that published by Lawrence et al[12] in the previously mentioned study, in which, of the total of modified treatments, only 8% were adjusted based on the result of a positive culture. Thirdly, if we only take into account the cases in which there was a positive microbiological result at the moment of re-evaluation of therapy, for 47% of these patients treatment was adjusted adequately, and in 18% the result suggested to not modify the initial therapy, this being done. These data concur with those published in other studies, in which the percentage of patients with positive cultures where treatment was adequately modified varied from 30% to 58%.[13,24,28,29] If we take into account all of these data, we believe that the problem in our case was the limited taking of microbiological samples in the ED, considering that most of the times when they were available they were used in the re-evaluation of empirical therapy.

Finally, in relation to the prescribed antibiotic regimens in the ED, we should highlight the high usefulness of the intravenous route. Even though our study was not designed to evaluate the adequacy of the route of administration, there are some data which indicate that the oral route could have been prescribed with greater frequency. In the first place, our hospital's antibiotic policy guideline recommends using the oral route of administration in empirical treatment for the majority of diagnosed infections in our series, except for those which are serious. In the present study, only 4 of the 194 (2%) patients with intravenous therapy were diagnosed with sepsis and 8 (4%) had serious symptomatic factors which prompted their admission into the intensive care unit. Secondly, the appropriate bioavailability by oral route of some of the most prescribed antibiotics (amoxicillin/clavulanic acid and quinolones) would also justify higher use of the oral route. In spite of these data, we believe it necessary to establish a study with an appropriate design for evaluating if the increased use of the intravenous route of administration in the ED of our hospital is actually justifiable.

One of the possible limitations of our study would be that of not establishing evaluation of clinical objectives, which would have allowed for an assessment to be made of the effectiveness of biotherapy in each patient, such as the possible influence of changes of therapy in the clinical evolution of each patient. Nevertheless, these were not the initial objectives of the study, a reason why it would be interesting to analyze them in the future.

In conclusion, the frequency with which prescribed antibiotic regimens in the ED were modified is elevated, and the percentage of complete suspension of treatment is high. Furthermore, the use of microbiological results for making these changes in initial empirical therapy was rare. The carrying out and dissemination in our hospital of specific diagnostic and treatment protocols for the main infectious diseases seen to in the ED, along with the recommended prescriptions for taking microbiological samples in these cases, is a strategy which should be considered for accomplishing an improvement in the use of antibiotics in the ED of our hospital.

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